RESPIRATORY MANAGEMENT OF EXTREMELY PRETERM INFANTS

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RESPIRATORY MANAGEMENT OF EXTREMELY PRETERM INFANTS

Topic Editors:
Hasan Özkan, Dokuz Eylül University, Turkey
Saadet Arsan, Ankara University, Turkey
Yuan Shi, Children's Hospital of Chongqing Medical University, China

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Table of Contents

05 ***Editorial: Respiratory Management of Extremely Preterm Infants***
Hasan Özkan, Saadet Arsan and Yuan Shi

08 ***Fine Tuning Non-invasive Respiratory Support to Prevent Lung Injury in the Extremely Premature Infant***
Kirsten Glaser, Christian P. Speer and Clyde J. Wright

16 ***Systematic Reviews in Neonatal Respiratory Care: Are Some Conclusions Misleading?***
Andres Maturana, Fernando Moya and Steven M. Donn

21 ***Volume Targeted Ventilation and High Frequency Ventilation as the Primary Modes of Respiratory Support for ELBW Babies: What Does the Evidence Say?***
Abhrajit Ganguly, Abhishek Makkar and Krishnamurthy Sekar

29 ***Clinical Study of Different Modes of Non-invasive Ventilation Treatment in Preterm Infants With Respiratory Distress Syndrome After Extubation***
Fei Ding, Jingling Zhang, Wenya Zhang, Qian Zhao, Zimei Cheng, Yang Wang, Tao Bo and Hui Wu

35 ***Caffeine Citrate for Apnea of Prematurity: A Prospective, Open-Label, Single-Arm Study in Chinese Neonates***
Lizhong Du, Xiaomei Tong, Chao Chen, Xirong Gao, Alessandra Gagnatelli, Jingyang Li, Debora Santoro, Sara Nicolardi and Laura Fabbri for the Peyona Chinese Study Group

42 ***Light or Deep Pressure: Medical Staff Members Differ Extensively in Their Tactile Stimulation During Preterm Apnea***
Sven Martin, Ulrich Herbert Thome, Martin Grunwald and Stephanie Margarete Mueller

48 ***Study on the Relationship Between Respiratory Distress Syndrome and* SP-A1 *(rs1059057) Gene Polymorphism in Mongolian Very Premature Infants***
Xiaoli Wang, Yuheng Zhang, Hua Mei, Caiyan An, Chunzhi Liu, Yayu Zhang, Yanbo Zhang and Chun Xin

53 ***Application of Neurally Adjusted Ventilatory Assist in Premature Neonates Less Than 1,500 Grams With Established or Evolving Bronchopulmonary Dysplasia***
Xiao Rong, Feng Liang, Yuan-Jing Li, Hong Liang, Xiao-Peng Zhao, Hong-Mei Zou, Wei-Neng Lu, Hui Shi, Jing-Hua Zhang, Rui-Lian Guan, Yi Sun and Huayan Zhang

59 ***Volume Guarantee High-Frequency Oscillatory Ventilation in Preterm Infants With RDS: Tidal Volume and DCO_2 Levels for Optimal Ventilation Using Open-Lung Strategies***
Funda Tuzun, Burak Deliloglu, Merve Meryem Cengiz, Burcin Iscan, Nuray Duman and Hasan Ozkan

65 *Use of Autologous Cord Blood Mononuclear Cells Infusion for the Prevention of Bronchopulmonary Dysplasia in Extremely Preterm Neonates: A Study Protocol for a Placebo-Controlled Randomized Multicenter Trial [NCT03053076]*
Zhuxiao Ren, Xu Fang, Qi Zhang, Y. G. Mai, X. Y. Tang, Q. Q. Wang, C. H. Lai, W. H. Mo, Y. H. Dai, Q. Meng, Jing Wu, Z. Z. Ao, H. Q. Jiang, Yong Yang, L. H. Qu, C. B. Deng, Wei Wei, Yongsheng Li, QI Wang and Jie Yang

73 *Endotracheal Surfactant Combined With Budesonide for Neonatal ARDS*
Burak Deliloglu, Funda Tuzun, Merve Meryem Cengiz, Hasan Ozkan and Nuray Duman

78 *Minimally Invasive Surfactant Administration for the Treatment of Neonatal Respiratory Distress Syndrome: A Multicenter Randomized Study in China*
Tongyan Han, Huiqiang Liu, Hui Zhang, Ming Guo, Xuefeng Zhang, Yang Duan, Fuqiang Sun, Xinjian Liu, Xiang Zhang, Mingtao Zhang, Fang Liu, Lisha Bao, Min Xiao, Weili Liu, Rui Jiang, Jun Zheng, Xiuying Tian, Qi Gao, Wanxian Zhang, Wei Guo, Ling Li and Xiaomei Tong

90 *A Review on Non-invasive Respiratory Support for Management of Respiratory Distress in Extremely Preterm Infants*
Yuan Shi, Hemananda Muniraman, Manoj Biniwale and Rangasamy Ramanathan

107 *The Comparison of HHHFNC and NCPAP in Extremely Low-Birth-Weight Preterm Infants After Extubation: A Single-Center Randomized Controlled Trial*
Jia Chen, Yingyi Lin, Lanlan Du, Mengmeng Kang, Xiufang Chi, Zhu Wang, Ying Liu, Weiwei Gao, Jie Yang and Yunbin Chen

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EDITORIAL
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Editorial: Respiratory Management of Extremely Preterm Infants

Hasan Özkan[1]*, *Saadet Arsan*[2] *and Yuan Shi*[3]

[1] Department of Neonatology, Dokuz Eylül University, Izmir, Turkey, [2] Department of Neonatology, Ankara University, Ankara, Turkey, [3] Department of Neonatology, Chongqing Medical University, Chongqing, China

Keywords: extremely preterm infant, apnea of prematurity, lung protective ventilation, high frequency ventilation, volume guarantee ventilation, non-invasive ventilation, neurally adjusted ventilation assist, acute respiratory distress sendrom

Editorial on the Research Topic

Respiratory Management of Extremely Preterm Infants

The USA Neonatal Research Network reports that 82% of extremely preterm infants receive mechanical ventilation during their NICU stay (1). The lungs of extremely preterm infants are structurally and biochemically immature and extremely vulnerable and susceptible to ventilator-induced lung injury (2). A variety of respiratory support techniques, ventilation modes, and strategies such as non-invasive respiratory support, volume targeted ventilation, high frequency ventilation with lung recruitment maneuvers and neurally adjusted ventilatory assist (NAVA) have been studied in preterm infants but high-quality evidence for respiratory management of extremely preterm infants from well-designed clinical studies are very scares (3–6). With this Research Topic, we aim to reach more scientific evidence for optimizing respiratory management of ELBW infants. We present a special collection of 14 articles contributing sound evidence for the key concepts outlined.

First of all, Maturana et al. emphasizes the importance of careful interpretation of the conclusions of systemic reviews. They point out the potential sources of bias such as, heterogeneity in included populations, interventions, control groups and outcomes which might not be detected by the statistical analyses used in very well-known systematic reviews. We agree with the authors and find their approach applaudable.

Premature infants experience frequent apneas and intermittent hypoxemia episodes due to their respiratory instability. There are two articles on preterm apnea in this collection. Du et al. once more present the efficacy and safety of caffeine citrate in the treatment of intermittent hypoxia and bradycardia episodes in preterm infants in their multicentric, prospective longitudinal open-label, single-arm study. On the other hand, Martin et al. present an interesting *in-vitro* study to analyze the necessary pressure intensity and frequency of various models of tactile stimulation applied to terminate preterm apnea episodes.

Respiratory distress syndrome is the leading cause of respiratory failure in preterm infants. Two major underlying pathophysiologic mechanisms are surfactant deficiency and structural immaturity of their lungs. There is limited evidence for genetic susceptibility for the development of RDS in preterm infants (7). Wang et al. have investigated the relationship between rs1059057 gene polymorphism of *SP-A1* and RDS in Mongolian very premature infants. Their findings do not support a relation between the gene polymorphism of *SP-A1* and the incidence of RDS.

In recent years, minimal invasive surfactant administration is a promising new therapy for extremely preterm infants with respiratory distress syndrome. Han et al. have conducted a multicentric randomized study in China and demonstrated that minimal invasive surfactant administration was not superior concerning the incidence of bronchopulmonary dysplasia, but it

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Edited and reviewed by:
Arjan Te Pas,
Leiden University, Netherlands

***Correspondence:**
Hasan Özkan
hasanozkan1958@gmail.com

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was associated with benefits in reducing the incidence of patent ductus arteriosus, which suggests less hemodynamic interference to the extremely/very low birth weight infants during the critical transition phase of physiological adaptation soon after birth.

Evidence from clinical trials indicates non-invasive ventilation has been shown to decrease the need for mechanical ventilation and reduce the risk of bronchopulmonary dysplasia. Shi et al. provide a comprehensive review of the non-invasive respiratory support for management of respiratory distress in extremely preterm infants. This article reviews respiratory management with current NIV support strategies in extremely preterm infants both in delivery room as well as in the NICU and discusses the evidence to support commonly used NIV modes including nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), bi-level positive pressure (BI-PAP), high flow nasal cannula (HFNC) and newer NIV strategies currently being studied including, nasal high frequency ventilation (NHFV) and non-invasive neutrally adjusted ventilatory assist (NIV-NAVA).

Ding et al. have compared the clinical effects of three ventilation modes, NCPAP, SNIPPV and sequential SNIPPV/NCPAP in the treatment of preterm infants with severe RDS after extubation. They demonstrate that compared to NCPAP alone, the sequential treatment reduces the failure rate of extubation and increases the success rate of withdrawal of non-invasive ventilation within 1 week without increasing the risk of developing complications such as BPD and ROP. In another study Chen et al. compare the clinical efficacy of heated, humidified high-flow nasal cannula (HHHFNC) and nasal continuous positive airway pressure Their study show that HHHFNC not only shortens the oxygen exposure time but also effectively reduces the incidence of nasal injury and NEC. Additionally, HHHFNC achieves a significant advance in the time to reach full enteral feeding and reduces the days of hospitalization.

Glaser et al. provide a fantastic mini-review including many recent trials focusing the evolution and success of non-invasive ventilatory support, alternative means of delivering surfactant, and sustained lung inflation.

Despite best efforts to maximize non-invasive support, most of extremely preterm infants still need mechanical ventilation (1, 6). The use of volume targeted ventilation (VTV), high-frequency ventilation (HFV) and lung protective strategies in extremely preterm infants have gained popularity in recent years because of their potential to improve outcomes (4, 5). Ganguly et al. present a review of the existing literature including systematic reviews and meta-analysis for these popular modes of ventilation. They conclude that the evidence support the use of volume targeted and high frequency ventilation to reduce ventilator-induced lung injury but existing studies are not powered to determine significant reductions in mortality or morbidity in ELBW babies. Tüzün et al. evaluates the optimal high frequency oscillatory ventilation with volume-guarantee (HFOV-VG) settings in premature infants with respiratory distress syndrome, using the open-lung strategy. Their findings indicate that optimal levels are dynamic and change instantly and individually. Rong et al. demonstrate a similar efficacy of neurally adjusted ventilatory assist ventilation (NAVA) to conventional ventilation in respiratory outcomes of very low birth weight preterms with evolving or established BPD.

Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by acute diffuse inflammatory lung injury and surfactant catabolism leading to severe hypoxemia. The management of ARDS in newborns consist of lung-protective ventilation strategies and therapeutic agents to improve gas exchange (8). Deliloglu et al. report two preterms diagnosed as neonatal ARDS according to the Montreux criteria, who benefitted from intratracheal surfactant plus budesonide treatment.

In recent years, both preclinical and clinical research have proven the efficacy and safety of stem cells in treating and preventing lung injury (9). However, there are currently no randomized clinical trials (RCTs) investigating the use of autologous cord blood mononuclear cells (ACBMNC) for the prevention of BPD in premature infants. Ren et al. present their placebo-controlled randomized multricentric study protocol to evaluate the efficacy of ACBMNC infusion in prevention of BPD.

Although the evidence to guide respiratory support strategies remains incomplete, the evidence available from this collection may provide an opportunity for a better approach to respiratory management and may provide additional clues for minimizing the adverse respiratory outcomes in extremely preterm infants requiring respiratory support.

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MINI REVIEW
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Fine Tuning Non-invasive Respiratory Support to Prevent Lung Injury in the Extremely Premature Infant

Kirsten Glaser[1], Christian P. Speer[1] and Clyde J. Wright[2]*

[1] University Children's Hospital, University of Würzburg, Würzburg, Germany, [2] Section of Neonatology, Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO, United States

Within the last decades, therapeutic advances, such as antenatal corticosteroids, surfactant replacement, monitored administration of supplemental oxygen, and sophisticated ventilatory support have significantly improved the survival of extremely premature infants. In contrast, the incidence of some neonatal morbidities has not declined. Rates of bronchopulmonary dysplasia (BPD) remain high and have prompted neonatologists to seek effective strategies of non-invasive respiratory support in high risk infants in order to avoid harmful effects associated with invasive mechanical ventilation. There has been a stepwise replacement of invasive mechanical ventilation by early continuous positive airway pressure (CPAP) as the preferred strategy for initial stabilization and for early respiratory support of the premature infant and management of respiratory distress syndrome. However, the vast majority of high risk babies are mechanically ventilated at least once during their NICU stay. Adjunctive therapies aiming at the prevention of CPAP failure and the support of functional residual capacity have been introduced into clinical practice, including alternative techniques of administering surfactant as well as non-invasive ventilation approaches. In contrast, the strategy of applying sustained lung inflations in the delivery room has recently been abandoned due to evidence of higher rates of death within the first 48 h of life.

Keywords: preterm infant, respiratory distress syndrome (RDS), lung injury, bronchopulmonary dysplasia (BPD), non-invasive ventilation, non-invasive respiratory support, continuous positive airway pressure (CPAP), sustained lung inflation (SLI)

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Edited by:
Saadet Arsan, Ankara University, Turkey

Reviewed by:
David Gordon Sweet, Belfast Health and Social Care Trust, United Kingdom
Ömer Erdeve, Ankara University Medical School, Turkey

****Correspondence:***
Kirsten Glaser
Glaser_K@ukw.de

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most prevalent complication related to prematurity. It is associated with an increased risk of mortality, as well as multiple in-hospital and post-discharge morbidities (1, 2). Considerable advances in neonatal strategies and corresponding improvements in survival from respiratory distress syndrome (RDS) have altered the nature of BPD, but have not changed its incidence in extremely premature preterm infants (3). Apparently, practice change to prevent neonatal lung injury has not been effective or has not evolved quickly enough in this population of infants. The pathogenesis of BPD is multifactorial, and involvement of various underlying mechanisms affecting immature airway structures leads to inflammation, apoptosis and extensive extracellular matrix remodeling, culminating in pathologic alveolarization and angiogenesis. It is well-established that exposure to and duration of invasive mechanical ventilation (IMV) and the resulting volutrauma, barotrauma, atelectrauma, rheotrauma, and biotrauma are

major contributing factors (4–6). This causal relationship was first noted in the 1970's (7, 8). Unfortunately, episodes of IMV often cannot be avoided for the highest risk babies, and exposure to IMV may even remain the rule rather than the exception in some countries. In the United States based NICHD Neonatal Research Network, in 2012, 82% of all infants who were born between 22 and 28 weeks' gestation and survived more than 12 h were mechanically ventilated during their NICU stay (3). While refinements in ventilators and modes of ventilation have been introduced to minimize lung injury, no data exist that definitely prove any one mode of ventilation or any one ventilator beneficial (9–11).

CPAP AND THE PHYSIOLOGIC BASIS FOR SUPPORTING FUNCTIONAL RESIDUAL CAPACITY AS A MEANS TO PREVENT MECHANICAL VENTILATION

Successful transition to postnatal life requires the opening and aeration of the lung. This process is impaired in many extremely preterm infants (12). Multiple unique physiologic and anatomic features put the tiny baby at risk of having a low functional residual capacity (FRC). Any degree of surfactant deficiency will bias the lung toward atelectasis. The structural immaturity and increased compliance of the chest wall dictate impaired stability of those structures needed for adequate aeration. Limited lung volume, increased airway resistance, and decreased compliance result in and add to increased work of breathing, predisposing to respiratory failure. These factors act to limit FRC, and the physiologic implications have been recognized in premature neonates for over half a century. Early reports included vivid descriptions of the increased work of breathing observed in the premature infant with RDS (13). Multiple solutions were proposed to stabilize the chest wall. Many of these are no longer in use today, including negative pressure ventilators (14) and continuous negative pressure boxes (15), or sternal traction (13). In 1971, Gregory reported that continuous positive airway pressure (CPAP) via endotracheal tube or head box increased survival in spontaneously breathing neonates with RDS (16). Innovative ways to deliver CPAP were reported, including face mask, face chamber, pneumask, and nasal prongs (17, 18). The use of CPAP became so extensively studied, that it was claimed that "no new technique in the treatment of hyaline membrane disease has so thoroughly been researched and evaluated as CPAP" (19). However, many limitations of non-invasive support were noted, including air leak (e.g., pneumothorax), need for escalation of support (CPAP failure), and an inability to treat apnea. The combination of these limitations and the advent of ventilators specifically designed for neonates, led to increased use of IMV to treat RDS (19, 20). However, even in this climate, clinical data supported the use of NIV to prevent lung injury in high risk neonates. In 1987, it was reported that very low birth weight infants treated at Columbia University had significantly lower rates of BPD when compared to seven other similar centers in the US (21). Many potential reasons of this finding were considered, including the early and aggressive use of CPAP at this institution. Although no data from randomized trials existed, other clinical reports supported the hypothesis that routine use of NIV decreased the risk of developing BPD (4, 22). Despite these data, studies directly comparing CPAP to IMV as primary support for preterm neonates were not performed until relatively recently.

ADVENT OF EXOGENOUS SURFACTANT AND ITS IMPACT ON THE PRACTICE OF RESPIRATORY SUPPORT

It can be argued that the advent of exogenous surfactant in RDS treatment delayed significant refinements in the use of NIV for the early respiratory support of the premature infant. Beginning in the late 1980s, investigators began reporting the results from randomized trials that convincingly demonstrated that the use of "early rescue surfactant" decreased air leak and improved survival in preterm infants with RDS (23). Practice evolved, and results from multiple randomized-controlled trials (RCTs) further refined surfactant therapy. Strategies referred to as "prophylactic surfactant use" or "early rescue surfactant" were proved to reduce air leak and mortality in infants at highest risk of developing RDS (24–26). Thereby, "rescue treatment" was generally defined as surfactant given to intubated patients after RDS had been diagnosed, whereas "prophylactic surfactant" was defined as surfactant given during the initial resuscitation. Findings led to the adoption of these practices as the standard of care for the prevention and treatment of RDS in the US and Europe from the 1990s onward (27).

A "NEW GENERATION" OF PRETERM INFANTS AND THEIR SPECIAL NEED FOR RESPIRATORY SUPPORT

In 2020, preterm infants at highest risk of BPD are different from those enrolled in the surfactant trials in the 1980s and early 1990s. Data collected at the NICHD Neonatal Research Network centers on 34,636 infants between 22 and 28 weeks' gestation between 1993 and 2012 showed that survival increased in those born at 23, 24, 25, and 27 weeks' gestation (3). Data from this same registry demonstrated that rates of BPD seemed to increase in the same population, with rates ranging from ∼40 to 90% (3). Thus, it appears that the most vulnerable babies are surviving at rates higher than ever before, but with significant morbidities. It is likely that a major contributor to this improved survival is the enhanced use of antenatal corticosteroids (ACS), having been increased from 24% in 1993 to 87% in 2010 (3).

Both increased survival of the most premature, most vulnerable infants and the increased use of ACS make application of the findings of surfactant trials published in the late 1980s and early 1990s difficult. The infants enrolled in these trials were more mature. For example, the babies enrolled in the surfactant replacement therapy for severe RDS by the Collaborative European Multicenter Study Group were on average 28.5 weeks' gestation (28). ACS exposure was not reported (28). Meta-analyses revealed that babies enrolled in

RCTs evaluating the use of prophylactic surfactant were ∼27 weeks of gestational age (GA), and ACS exposure was low (∼30–40%) (25). Of note, one trial comparing prophylactic vs. rescue surfactant did report a protective effect in the subgroup of babies <26 weeks' gestation; however, ACS exposure was ∼30% (29). Undoubtedly, these trials demonstrated that with true surfactant deficiency, preterm neonates need, and respond to exogenous surfactant.

Meanwhile, increased survival of infants at highest risk of BPD and the standardized exposure of these neonates to ACS have driven new clinical questions. Specifically, could it be hypothesized that the respiratory instability demonstrated by this patient population has less to do with primary surfactant deficiency, but more to do with chest wall instability and the inability to recruit, and maintain FRC (30)? And if that were true, should the approach to managing these high risk patients further evolve? Three RCTs comparing routine use of early nasal CPAP with routine intubation and surfactant have been performed: COIN (31), SUPPORT (32), and the *Vermont Oxford Network Delivery Room Management Trial* (VON-DRM) (33). Direct comparison of early CPAP and prophylactic surfactant was only done in the SUPPORT and VON-DRM trials (32, 33), while babies randomized to intubation did not routinely receive surfactant in the COIN trial (31). Importantly because these trials recruited patients antenatally the use of ACS was high (>90%) in both studies. Routine use of CPAP has been shown to be superior to routine intubation and prophylactic surfactant in preventing the combined outcome of BPD or death (10). Other meta-analyses that include a control group not limited to strictly routine intubation and prophylactic surfactant have been published (34, 35). Data from multiple meta-analyses point to a protective signal with routine use of early CPAP preventing lung injury in high risk infants, with a number needed to treat of 17.7 (10), 25 (35), and 35 (34). Current European and US American guidelines recommend prophylactic CPAP and early selective surfactant over primary intubation, prophylactic surfactant and subsequent IMV in preterm infants with RDS (36, 37).

NON-INVASIVE SUPPORT FAILURE AND STRATEGIES TO PREVENT IT

Knowing that exposure to IMV is as major contributing factor to neonatal lung injury, it is somewhat disappointing that routine use of non-invasive support does not result in a larger treatment effect. One possible explanation may be given by the high rate of CPAP failure (10, 38). Data from both RCTs and observational reports demonstrate that within the first week of life, ∼50% of infants initially supported with CPAP require IMV (31–33). Moreover, data suggest that a huge number of infants fail early, within the first 8 h of life (31, 39, 40). GA appears to be a strong predictor of failure, with the most immature neonates failing at the highest rates (31, 40, 41). Based on these observations, multiple interventions aiming at optimizing primary non-invasive respiratory support have been studied.

Sustained Lung Inflation

The first respiratory efforts of term infants deliver a sustained pressure (30–35 cm H_2O) over a long inspiratory time (4–5 s) to the lung, resulting in the clearance of lung fluid and the establishment of FRC (42, 43). These initial efforts are blunted in the extremely premature infant whose initial course may be complicated by respiratory depression, decreased respiratory muscle strength, and/or surfactant deficiency. Thus, it has been proposed that providing positive pressure (∼20–25 cm H_2O) for a sustained amount of time (5–20 s) may help to clear lung fluid, establish FRC, and prevent NIV failure (43). This approach has been named "sustained lung inflation" (SLI). Several small RCTs in preterm infants have been published examining different SLI levels and durations (44), demonstrating a decreased need for IMV at 72 h (45–47). However, a meta-analysis of four studies found no difference in the rates of BPD, death, or the composite outcome among those infants treated with SLI compared to standard (44). Moreover, in these studies, SLI did not decrease rates of surfactant replacement therapy for RDS (45–47). Recently, the results from the largest RCT performed to date examining the safety and efficacy of SLI in very immature babies born at 23–26 weeks' gestation, the *Sustained Aeration of Infant Lungs* (SAIL) trial, were published (48). This trial was stopped early, after recruitment of 426 of the calculated 600 infants, due to higher rates of death within the first 48 h of life in the SLI group (48). Of note, SLI compared with standard IMV did not reduce the risk of the primary outcome death or BPD (48). The SAIL trial concluded that SLI maneuver should not be performed in extremely premature infants (48).

Minimally Invasive Surfactant Therapy

Surfactant deficiency has been assumed one major cause of CPAP failure. Alternative techniques of surfactant administration without using an endotracheal tube have been developed, including nasopharyngeal instillation, laryngeal mask placement and aerolization (49, 50). While none of these methods is ready for clinical application, two promising strategies have evolved, combining the positive effects of surfactant and early CPAP: the INtubation-SURfactant-Extubation (INSURE) procedure and less invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST), respectively (38, 51–54). Using sedation and a short period of IMV, INSURE comprises intubation, intratracheal surfactant administration, and immediate extubation to CPAP (38, 49, 52). During LISA, a fine catheter or feeding tube is inserted into the trachea of a preterm infant spontaneously breathing on CPAP, and surfactant is administered slowly over several minutes (51, 53, 54). The very similar MIST approach positions a more rigid vascular catheter via direct laryngoscopy but without using a Magill's forceps (55). A meta-analysis of RCTs comparing INSURE with standard intubation followed by surfactant and IMV, reported a reduced need of IMV and reduced risk of BPD in INSURE cohorts (52). Studies comparing prophylactic INSURE with early CPAP found no benefit of INSURE over CPAP (33, 39). Two meta-analyses documented that prophylactic INSURE did not result in higher survival without BPD (26, 56). Of note, in a retrospective cohort study in 322 preterm infants <32 weeks' gestation who had

undergone INSURE, 60% of study infants could not be extubated within 2 h after the procedure (57).

LISA procedure was first described in the early 1990s and was rediscovered about 10 years later (51, 58). It has been widely used in Germany and increasing parts of Europe meanwhile, and is the most intensively studied method of less invasive surfactant therapy (49, 53, 54, 59). The first RCT of the German Neonatal Network including 220 preterm infants born at 26–28 weeks' gestation demonstrated a reduced need of IMV at any time and reduced median days on IMV in the LISA cohort (60). A multi-center study from the same Network in 1,103 neonates <32 weeks' gestation found lower rates of IMV and BPD following LISA (61). So far, seven RCTs have evaluated the efficacy and safety of LISA, with four trials comparing LISA with INSURE (62–64), and three trials comparing LISA with intubation and standard surfactant (60, 65, 66). Two meta-analyses covering these RCTs found a reduction in CPAP failure, need of IMV at any time and a reduction in death or BPD in LISA cohorts (67, 68). It is worth mentioning that the studies included in these meta-analyses were quite heterogeneous. Some of the included trials compared LISA to INSURE (meaning study groups differed solely in the technique of surfactant administration), while some trials compared LISA to standard intubation and subsequent IMV (meaning study groups differed in the approach of both surfactant administration and respiratory support). A more recent meta-analysis attempted to control for study heterogeneity by performing two analyses: one strictly comparing LISA and INSURE, and another comparing LISA to standard intubation and subsequent IMV. LISA was not found to be superior for decreasing BPD or the combined outcome of BPD or death (59). Of note, all RCTs evaluated are small, with only ∼450 preterm infants included across all studies. They further differ in risk of bias assessment and study cohorts, ranging from very immature preterm infants in two studies (60, 65) to moderate (63, 64) and late preterm infants in other trials (62, 66). Of note, a comprehensive meta-analysis comprising 30 trials and ∼5,600 preterm infants <33 weeks' GA evaluated the effect of different NIV strategies, including CPAP, INSURE, LISA, and nasal intermittent positive-pressure ventilation (NIPPV) vs. IMV on the avoidance of death or BPD (50). The use of LISA was associated with the lowest risk of the latter (50). Recently, the largest cohort study comparing LISA with standard surfactant, so far, has been published by the German Neonatal Network, reporting data on 7,533 preterm infants ≤28 weeks' gestation and of whom 1,214 infants had been managed with LISA (69). LISA was associated with reduced risk of mortality and BPD and reduced risk of secondary outcome measures, except for focal intestinal perforation (69).

Nasal Intermittent Positive Pressure Ventilation

NIPPV has been proposed as an alternative approach of non-invasive support, adding time-cycled positive-pressure inflations to a background support of CPAP (70). A recent Cochrane review comparing primary NIPPV to CPAP concluded that NIPPV prevented intubation in preterm infants (71). However, every trial evaluated in this review, except for one (72), stipulated a diagnosis of RDS for inclusion. Thus, whether NIPPV is superior to CPAP to prevent failure of non-invasive respiratory support for the very tiny baby at high risk of lung injury is unknown. A very recent sub-analysis in the subset of extremely low birth weight infants without RDS found that NIPPV did not decrease failure of primary non-invasive support in these high risk infants (73). A Cochrane meta-analysis found NIPPV was superior to CPAP in preventing extubation failure (74). BPD rates did not differ between both study groups except for those infants who had synchronized NIPPV delivered by a mechanical ventilator (74). This raises the question as to whether NIPPV delivered by neurally adjusted ventilator assistance would be superior to other modes.

Nasal High-Flow Therapy

Nasal high-flow therapy (nHF) constitutes an additional strategy of nasal breathing support in preterm infants at high risk of lung injury. Heated, humidified, blended air and oxygen are delivered via thin nasal cannulae (75). Perceived benefits include increased comfort and reduced nasal trauma. There are some studies describing the use of nHF as primary respiratory support of preterm infants (76). However, a Cochrane review on nHF vs. CPAP for respiratory support in preterm infants reported that zero infants <28 weeks had been randomized to nHF as primary support, thus making any conclusions in this group impossible (77). Since that time, other RCTs evaluating the same issue have been completed, but none of these trials enrolled neonates born <28 weeks' GA (78–80). It can be safely concluded that there are no data supporting superiority of nHF over CPAP for primary support of very premature babies. In fact, there are data indicating that nHF is inferior to CPAP for this indication. Roberts and colleagues enrolled 564 neonates > 28 weeks' GA with RDS to determine if nHF was non-inferior to CPAP in preventing treatment failure evaluated at 72 h (79). The trial was stopped early due to increased treatment failure in the nHF group. Although the subjects enrolled in this trial are not those at highest risk of lung injury, there is little data to suggest that nHF would perform better in a more premature population. Manley and colleagues randomized 303 preterm infants <32 weeks' GA at first extubation attempt to determine if nHF was non-inferior to CPAP in preventing treatment failure evaluated at 7 days post-extubation (81). nHF was reported "non-inferior" even though treatment failure occurred in 34.2% of infants randomized to nHF vs. 25.8% in the CPAP group. Finally, data guiding the use of nHF as a "weaning modality" from CPAP or directing the reduction and escalation of gas flows are lacking.

Caffeine

The *Caffeine for Apnea of Prematurity* (CAP) trial established that in high risk premature infants, caffeine reduces the risk of BPD and improves long-term developmental outcomes (82, 83). This protective effect could be largely attributed to a significant reduction in the duration of IMV (82, 83). Importantly, the beneficial effects of caffeine were affected by the timing of

initiation of therapy. Subgroup analysis of the CAP trial showed that early (<3 days) compared to later (>3 days) initiation of therapy was associated with a greater reduction in the time on ventilation (84). Additional studies have supported the finding that early caffeine reduces the duration of IMV and enhances the protective effect on BPD (85).

Despite its association with reduced exposure to IMV (37), it cannot be definitely concluded that early caffeine improves the success of NIV. A large observational study showed that early (day of birth) compared to late (after the day of birth) initiation of caffeine did not improve rates of CPAP failure (86). Of note, the average GA of infants in this study was 29–30 weeks, and the rate of CPAP failure was ∼20%, suggesting that this conclusion may not apply to the more premature neonate at very high risk of failing non-invasive support. Smaller pilot trials have demonstrated that early administration of caffeine induces demonstrable physiologic effects in this cohort. Administration of caffeine in the delivery room improves respiratory effort, and administration <2 h of age results in hemodynamic benefits (87). The longer-term implications are unknown. Data from adequately powered RCTs are needed to determine whether very early caffeine is safe and improves success rates of non-invasive respiratory support (37).

ASSOCIATION OF NIV WITH OUTCOME MEASURES OTHER THAN BPD AND LONG-TERM PULMONARY OUTCOME

Respiratory support of very premature infants cannot be evaluated solely for the prevention of BPD. Other outcome measures, including high-grade intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus, severe retinopathy of prematurity, and postnatal corticosteroid treatment, were assessed in the COIN, SUPPORT and VON-DRM trial (31–33). Infants treated with early CPAP compared with infants managed with elective intubation and IMV did not significantly differ in any of these outcomes (31–33).

There is growing evidence of persistent pulmonary morbidity in BPD survivors even in the post-surfactant era (2, 88, 89). However, BPD diagnosis does not necessarily predict long-term lung function (89–91). Vice versa, a high incidence of respiratory morbidity has been described in children born preterm, even in the absence of BPD (89, 90). Recent longitudinal cohort data found similar or worse lung function at 8 years follow-up in children born preterm in 2005 compared with cohorts born in 1991 and 1997 (88). Given the increasingly established use of NIV in the more recent cohort of infants, this finding raises the question of long-term effects of NIV. So far, this issue has been addressed in only few prospective studies. The *Breathing Outcomes Study*, follow-up study of the SUPPORT trial, found fewer episodes of wheezing, acute respiratory illnesses and physician or emergency room visits for breathing problems in the CPAP group as compared to the intubation/surfactant group at 18–22 months corrected age (90). Improved lung mechanics and decreased work of breathing at 8 weeks corrected age were reported in a subcohort study of the COIN trial (92).

CONCLUSION AND OUTLOOK

Non-invasive respiratory support of very immature preterm infants constitutes a paradigm shift—aiming at the prevention of BPD. Current data suggest that composite measures including (i) initiation of CPAP within the first minutes of life, (ii) its continuous delivery at safe and appropriate levels as well as, (iii) targeted surfactant therapy in the spontaneously breathing infant identified with surfactant deficiency may be key to improved success of primary NIV in this cohort. However, published trials have several limitations and future RCTs are necessary. In terms of LISA, the total number of infants covered in existing RCTs is small, and potential adverse side effects still need to be critically reviewed. Further studies are needed to determine the cohort of preterm infants that might benefit most from LISA. NIPPV may offer advantages over CPAP in terms of intubation rates. Scarce data, so far, do not sufficiently back superiority of NIPPV over CPAP and do not support its routine use in very premature preterm infants. Minimal data exist to support the use of nHF as primary mode of support in preterm infants <28 weeks. Evidence of beneficial effects of advanced NIV strategies, such as synchronized modes of NIPPV or nasal high frequency oscillatory ventilation mainly derive from small, single-center studies, differing in patient population, ventilator settings and mode of synchronization, and need to be further studied. Attention needs to be paid to the complex interplay of NIV with other morbidities of prematurity. Given the shortcomings of BPD as a surrogate for long-term pulmonary dysfunction, long-term follow-up, and longitudinal assessment of pulmonary morbidity is required to conclusively determine the impact of NIV on pulmonary outcome later in life.

Future approaches, most likely, will represent a bundle of procedures supporting spontaneous breathing in the very immature preterm neonate. In this context, early initiation of caffeine and optimized caffeine therapy may be vital as adjunctive therapy to prevent apnea and non-invasive support failure.

AUTHOR CONTRIBUTIONS

KG and CW wrote the first draft of the manuscript. KG, CS, and CW wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Systematic Reviews in Neonatal Respiratory Care: Are Some Conclusions Misleading?

Andres Maturana[1,2]*, *Fernando Moya*[3] *and Steven M. Donn*[4]

[1] Neonatology, Clinica Alemana, Department of Pediatrics, Santiago, Chile, [2] Faculty of Medicine, Centro de Desarrollo Educacional, Universidad del Desarrollo, Santiago, Chile, [3] Betty Cameron Children's Hospital, Coastal Carolina Neonatology, Coastal Children's Services, PLLC, Wilmington, NC, United States, [4] Division of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, Michigan Medicine, Ann Arbor, MI, United States

An increasing amount of information is currently available in neonatal respiratory care. Systematic reviews are an important tool for clinical decision-making. The challenge is to combine studies that address a specific clinical question and have similar characteristics in terms of populations, interventions, comparators, and outcomes, so that their combined results provide a more precise estimate of the effect that can be validly extrapolated into clinical practice. The concept of heterogeneity is reviewed, emphasizing that it should be considered in a wider perspective and not just as a mere statistical test. A case is made of how well-designed studies of the neonatal respiratory literature, when equivocally combined, can provide very precise but potentially biased results. Systematic reviews in this field and others should be rigorously peer-reviewed before publication to avoid misleading readers to potentially biased conclusions.

Keywords: neonatal respiratory care, meta-analysis, systematic reviews, clinical decision-making, infant-newborn

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***Correspondence:**
Andres Maturana
amaturana@alemana.cl

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INTRODUCTION

We are currently confronted with an overwhelming amount of information in all medical disciplines, and neonatal care is no exception (1, 2). A systematic review of the current literature can provide information that may be combined, thus increasing statistical power and providing a quantitative estimate of the effect in a meta-analysis (3). Although systematic reviews addressing a specific clinical question can help clinicians appraise in a summarized format all or most of the existing research pertaining to that topic and aid in bedside decision-making, they have recognized limitations (4, 5). Clinicians are sometimes confronted with systematic reviews that claim results based on combining studies that differ in substantial ways and therefore yield conclusions that are very difficult to interpret (6). Most of us would agree that almost any respiratory outcome in premature infants could be significantly influenced by antenatal steroid exposure and gestational age. Nevertheless, systematic reviews combining study populations with significant differences in these relevant variables have been published (**Table 2**).

The purpose of this review is to raise awareness of the importance of adequately appraising systematic reviews, using examples from the neonatal respiratory literature that, in our view, can sometimes lead to misleading conclusions. **Table 1** summarizes the definitions of terms that will be used.

TABLE 1 | Terms used in this review.

Term	Definition (*)
Systematic Review	The identification, selection, appraisal, and summary of primary studies that address a focused clinical question using methods to reduce the likelihood of bias.
Meta-Analysis	A statistical technique for quantitatively combining the results of multiple studies that measure the same outcome into a pooled or summary estimate.
Heterogeneity	Differences among individual studies included in a systematic review. These differences can refer to study characteristics or study results.
I^2 Statistic	The I^2 statistic is a test of heterogeneity. The results range from 0 to a 100% indicating no heterogeneity to high heterogeneity, respectively.
Bias	Systematic deviation from the truth because of a feature of the design or conduct of a research study. This can skew the outcome in a certain direction.
Selection Bias	Occurs when the population that is selected for a study is not representative of the general population addressed by the question the study intends to answer. This has the consequence that study results although not necessarily biased may not be applicable to the general population.

**Definitions adapted from Users' Guides to the Medical Literature: Essentials of Evidence-Based Clinical Practice, Third Edition (7).*

THE CONCEPT OF HETEROGENEITY

A systematic review summarizes the existing research that addresses a specific clinical question in a systematic and reproducible way. For the purpose of this review, we will refer to systematic reviews addressing the effect of therapeutic interventions in randomized clinical trials. In some cases, the studies found in the review process can be combined using meta-analysis, so as to provide a single more precise estimate of the effect (3). This entails some assumptions about the studies included in the analysis. First, the magnitude and direction of the treatment effect across the different studies should be relatively similar and that there are no significant variations in the results that could be explained by relevant differences among the studies. The studies should be combined only if they lack significant bias, if they answer the same specific question, if they include similar populations, and if they attempt to compare similar interventions and measure equivalent outcomes, so that a pooled effect of the results from individual studies yields a more precise and representative estimate of the treatment effect (6). The challenge is how much difference (heterogeneity) we are willing to tolerate in these parameters among the different studies without compromising the confidence of the pooled estimate. The usual approach to this conundrum is to evaluate heterogeneity in a statistical manner. Any of the tests used for this purpose are only providing information about differences between study results and telling us how likely the differences in individual trial results are from chance alone (9). A frequently used test for evaluating heterogeneity is the I^2 statistic that estimates the heterogeneity as the magnitude of variability. It is easily interpreted as the percentage of heterogeneity in the point estimates from individual studies. When it approaches 0%, the reader can be relatively confident that any differences between the individual point estimates of the included studies is explained merely by chance and, therefore, the summary estimate of the treatment effect is credible. When this percentage approaches 100% the probability that only chance explains these differences is substantially less likely and, therefore, a summary effect is more difficult to interpret (10). The problem is that sometimes we can be confronted with differences in study design that make any pooled estimate of the effect difficult to interpret or even meaningless, and are not necessarily detected by any statistical test for heterogeneity. Therefore, heterogeneity between studies in a meta-analysis needs to be examined as much more than a simple statistical test, and clearly, one more relevant issue when critically appraising a systematic review.

HETEROGENEITY IN INCLUDED POPULATIONS, INTERVENTIONS, CONTROL GROUPS, AND OUTCOMES

If we are considering therapeutic interventions, a certain homogeneity in the populations included in the different studies considered in a systematic review can be a very relevant issue. We should not feel comfortable drawing any conclusions from a meta-analysis within a systematic review that combines studies including populations that differ in characteristics that could potentially influence the magnitude or direction in the effect of the intervention being studied.

A systematic review by Ferguson et al. addressing the question of interventions to improve rates of successful extubation in preterm infants can help exemplify this point (8). If we review the comparison between high flow nasal cannula and nasal continuous positive airway pressure (CPAP) on the outcome respiratory failure, three studies are included in this analysis (**Table 2**) (11–13). As an example, the populations in the study by Yoder include more mature infants (>28 weeks) and with a significantly lower percentage of antenatal steroid receipt (<35%) than the other two included studies, and these are two well-recognized prognostic factors for respiratory failure. Fortunately, in this case we are alerted by an I^2 of 55%, suggesting that chance does not adequately explain the variability between the point estimates. Regretfully, this is not always the case.

An intervention will have an effect that will reflect a magnitude and a direction. Evidently, this is dependent upon the comparative intervention. It would not be correct to claim a certain magnitude of effect of a certain intervention if it is being compared to anything different than the standard of care for the control group, since this could potentially overestimate the real effect of the intervention. It would not make much sense to combine studies that have different comparators in a meta-analysis. A recently published systematic review by Wu et al. addresses the outcomes of surfactant administration in a minimally invasive way (via thin endotracheal catheter) to spontaneously breathing infants (14). In this review, four studies are included for the outcome of requiring mechanical ventilation within the first 72 h of life (15–18). The trial by

TABLE 2 | Heterogeneity in populations included in the Meta-Analysis by Ferguson et al. (8).

Trial	Mean gestational Age (treated/controls)	% of Antenatal Steroids (treated/controls)	% of Caffeine use (treated/controls)
Yoder et al. (11)	33.5 ± 3.6/33.2 ± 3.2	38/32	27.0/30.0
Manley et al. (12)	27.7 ± 2.1/27.5 ± 1.9	93.4/94.7	99.3/98.0
Collins et al. (13)	27.9 ± 1.9/27.6 ± 1.9	88.0/89.0	100.0/100.0

Göpel compared a less invasively administered surfactant (LISA) to intubation and rescue surfactant via endotracheal tube in the control group, while Kanmas and Bao compared LISA with the Intubation-Surfactant-Extubate (INSURE) procedure in the control group. In these studies, specific criteria for respiratory failure where defined in the protocols. The included study by Kribs used LISA and compared this to surfactant administration with mechanical ventilation. In this last case, indications for mechanical ventilation were defined by protocol for the control group and, in fact, only one infant was not mechanically ventilated. For this analysis, the I^2 statistic shows 0% heterogeneity, suggesting that the summary point estimate is not biased by any relevant differences between the studies. Nevertheless, it is obvious that these studies are completely different and probably should not have been combined for this outcome.

When evaluating the impact of an intervention on a specific outcome across different studies, an important assumption is that the outcome in each of the studies was similarly defined, so as to render the combined effect in a meta-analysis interpretable. This is particularly relevant when considering physician-driven outcomes, which are those that depend upon the treating physician and therefore rely on how every protocol in each study defined the criteria for this outcome. An example of such an outcome in neonatal practice is nasal CPAP failure or intubation for mechanical ventilation. We can expect differences in clinical practice among different centers and even within a single center among different clinicians. When one performs a systematic review, one forgoes the ability to conduct logistic regression analysis using center effect as a variable. The problem arises when we try to interpret combined results of studies that have, for instance, significant differences in the criteria for intubation, especially if it is not defined *a priori* in the various studies included in the systematic review.

Another example of this is the recently published review by Conte that addresses the comparison of high flow nasal cannula and nasal CPAP as the initial strategy to treat RDS in preterm infants (19). In this review, six studies are included in the analysis for the outcome of respiratory failure, but only five of them contribute with outcomes (11, 20–23). If we look at the I^2 statistic, it shows that there is relatively little heterogeneity (17%) within the included studies for this outcome and, therefore, we should be fairly confident in interpreting this summary estimate of the treatment effect. Unfortunately, this statistic can only detect the mathematical heterogeneity in the individual point estimates of the effect but will not reflect relevant differences within the studies. In this example, three of the studies (20, 22, 23) have intubation thresholds utilizing an FiO_2 of 0.4, whereas Nair and Karna (21) and Yoder et al. (11) have significantly higher thresholds for intubation (0.6 and 0.7, respectively). These differences will evidently bias the results toward a lower difference between the groups for this outcome, since fewer patients will meet the threshold. If we exclude these two studies, the analysis yields a significantly greater magnitude in the point estimate against using high flow nasal cannula as the initial support strategy (1.72 vs. 1.57).

LIMITATIONS IN GENERALIZABILITY

When examining the conclusions of any trial, including those conducted under high standards, they can only provide an answer to a clinical question that generally is fairly specific (primary outcome), and applicable to the population studied. Good examples of this paradigm are those studies that compared CPAP at or soon after birth vs. intubation with or without surfactant administration. For instance, the COIN trial enrolled preterm infants of a minimum gestational age of 25 weeks or more, who were spontaneously breathing at 5 min of life (24). Therefore, their findings *do not* apply to all infants born at 25 weeks or more, but obviously more to those who were in apparently better status immediately after delivery. Furthermore, their findings *do not* apply at all to preterm infants below 25 weeks. In fact, in the systematic review of Schmolzer et al. comparing CPAP to intubation (usually plus surfactant), only one trial enrolled infants <25 weeks' gestation (SUPPORT) (25, 26). In this large trial, essentially all extremely preterm infants for whom informed consent had been obtained antenatally were enrolled. This is an important difference compared to the other trials included in this systematic review, where a more select population of preterm infants was enrolled. The critical nature of this potential source of bias is clearly demonstrated by Rich et al. who reported outcomes of all infants that were eligible for the SUPPORT trial but *were not enrolled* (27). Undoubtedly, essentially all meaningful outcomes were worse among those infants, signaling a clear selection bias, albeit smaller than in other trials of this systematic review.

A PLAUSIBLE EXPLANATION FOR STATISTICAL ASSOCIATIONS

When interpreting the pooled results of a systematic review, we should not accept the results without considering some logical explanation behind them. An example of this point can

be made in relation to a recently published systematic review by King and colleagues (28). In this review, two interfaces to deliver nasal CPAP were compared and a total of seven studies met the inclusion criteria; however, only six of them were considered for the outcomes of nasal CPAP failure and bronchopulmonary dysplasia (BPD) (29–33). When we look at the pooled results for nasal CPAP failure within 72 h after initiation, we see a marginally significant result in favor of nasal mask vs. binasal prongs (Risk ratio 0.72, 95%. CI 0.53–0.97) without considerable heterogeneity (I^2 of 16%). What is more promising is the fact that there is a significant difference again in favor of the nasal mask interface with a reduction in moderate to severe BPD, this time with moderate heterogeneity (I^2 of 30%). Nevertheless, if we try to find a plausible explanation for this difference based on better effectiveness and less failure with the nasal mask, the results do not support this. The study by Say et al. is the major contributor to the difference observed in moderate to severe BPD, but it shows no difference in the failure rate between the compared nasal CPAP interfaces (33). This strongly suggests that this observed association probably occurred by chance and is not related to the intervention.

CONCLUSIONS

Systematic reviews are in great demand and remain a significant contribution for clinical decision-making and effectively provide an updated and informative perspective of the current state of the literature in a specific topic but their results should be interpreted with care. The Cochrane Library, which in many ways has set the standards for systematic reviews in therapeutic interventions, has not been always able to keep the published reviews updated with sufficient promptness, thus creating a valid space for alternate versions of already published topics.

We have shown how well-designed studies can be equivocally combined in a meta-analysis and lead to biased summary point estimates of the effect. Heterogeneity among studies is a potential source of bias and may not always be detected by statistical tests. The latter aim to detect variability between study results but cannot detect relevant differences in design that could result in a meaningless conclusion from the combination of very different studies. This problem should be better described in the existing literature. Publication requirements for systematic reviews should be strengthened, following currently existing guidelines and undergo a rigorous peer-review process that considers some of the issues discussed previously. Clinicians should definitely be more aware of potential sources of bias when reading published systematic reviews to avoid being misled by only interpreting their conclusions.

AUTHOR CONTRIBUTIONS

AM: substantial contributions to the conception, analysis, and interpretation of the work. Drafting and revising the manuscript critically for important intellectual content. Agrees to be accountable for all aspects for all aspects of the work in ensuring that questions related to the accuracy of any part are appropriately resolved. FM and SD: substantial contribution to the analysis and interpretation of the work. Drafting and revising the manuscript critically for important intellectual content.

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Volume Targeted Ventilation and High Frequency Ventilation as the Primary Modes of Respiratory Support for ELBW Babies: What Does the Evidence Say?

*Abhrajit Ganguly, Abhishek Makkar and Krishnamurthy Sekar**

Section of Neonatal-Perinatal Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Respiratory management of the extremely low birth weight (ELBW) newborn has evolved over time. Although non-invasive ventilation is being increasingly used for respiratory support in these ELBW infants, invasive ventilation still remains the primary mode in this population. Current ventilators are microprocessor driven and have revolutionized the respiratory support for these neonates synchronizing the baby's breath to ventilator breaths. High frequency ventilators with the delivery of tidal volumes less than the dead space have been introduced to minimize barotrauma and chronic lung disease. Despite these advances, the incidence of chronic lung disease has not decreased. There is still controversy regarding which mode is ideal as the primary mode of ventilation in ELBW infants. The most common modes seem to be pressure targeted conventional ventilation, volume targeted conventional ventilation and high frequency ventilation which includes high frequency oscillatory ventilation, high frequency jet ventilation and high frequency flow interrupter. In recent years, several randomized controlled trials and meta-analyses have compared volume vs. pressure targeted ventilation and high frequency ventilation. While volume targeted ventilation and high frequency ventilation does show promise, substantial practice variability among different centers persists. In this review, we weighed the evidence for each mode and evaluated which modes show promise as the primary support of ventilation in ELBW babies.

Keywords: ELBW, ventilation strategies, high frequency ventilation, volume targeted ventilation, extremely premature infants

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****Correspondence:***
Krishnamurthy Sekar
krishnamurthy-sekar@ouhsc.edu

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INTRODUCTION

The rate of preterm birth (<37 weeks) in the USA has decreased between 2007 and 2014 by 8% (1). Extremely low birth weight (ELBW) babies occupy a large portion of the current population of preterm infants with gestational ages ranging from 22 to 28 weeks. With significant advances in the care of newborns, the high mortality among the ELBW population has been replaced by increased survival but with significant long-term morbidity. Several collaborative improvement projects and network studies have been undertaken between countries and centers with the evaluation of outcomes among the ELBW population. These major network studies have been published reporting these outcomes over time (2–5). While some reports show minimal improvement in

certain outcome measures, others show worsening results. Given that major pulmonary morbidity and bronchopulmonary dysplasia (BPD) remain some of the most important outcome measures in this population, a lot of research has been done trying to optimize the respiratory management of ELBW babies. The principal components of respiratory management in ELBW babies include conventional ventilation (pressure or volume targeted), high frequency ventilation (HFV), non-invasive ventilation [nasal continuous positive airway pressure or nCPAP, nasal intermittent mandatory ventilation or NIMV, high flow or low flow cannula, non-invasive high frequency oscillatory ventilation or nHFOV and neurally adjusted ventilatory assistance or NAVA], use of surfactant and nitric oxide (3, 6, 7). While non-invasive ventilation could be an effective way of establishing functional residual capacity immediately after birth without the adverse effects of positive pressure ventilation, its use is limited to babies who are >25 weeks gestation (8). A majority of ELBW infants, however, require invasive ventilation. In 2012, The Neonatal Research Network found that 82% of the babies born before 29 weeks of gestation ended up needing invasive ventilation (3). These infants are also at the greatest risk of developing ventilation-induced lung injury (VILI) and BPD. While many recent advances have been made in neonatal ventilation strategies, the rate of BPD has either remained stable or increased depending on the region and centers (3, 9). An important reason for the increased prevalence of BPD is the increased survival especially at extreme gestational ages (22–24 weeks). The definition of BPD has evolved over the years with the most recent definitions including aspects, such as the gestational age, the total time on supplemental oxygen and the use of nasal CPAP or positive pressure ventilation (PPV) in addition to the dependence on oxygen at 36 weeks corrected gestational age (10). It is a well-established fact that lung injury secondary to invasive ventilation in addition to exposure to high oxygen plays an important role in the development of BPD. This is especially true in ELBW babies who tend to require invasive ventilation for a prolonged period. Ideally, it is beneficial for preterm babies to quickly transition from invasive to non-invasive modes of ventilation in order to minimize VILI. Bjorklund et al. found that even a few high tidal volume positive pressure breaths (35–40 ml/kg) shortly after birth was enough to initiate lung injury and minimize the effectiveness of later surfactant administration (11).

As our understanding of the different mechanisms of lung injury has improved along with the technological advancement of neonatal care, the mortality rate in the ELBW population has come down significantly. Early mortality in this age group at present is related more to sepsis, pulmonary hemorrhage, severe intracranial hemorrhage among others rather than acute respiratory failure (12). More babies in the ELBW population are surviving until discharge and as a result, decreasing later morbidity has become the focus for further research. Thus, we have seen large follow-up studies published in the last several years focusing on BPD and later pulmonary morbidities (13). Given the cascade of BPD is set into motion shortly after or even before the birth of the baby (14–16), proper respiratory management in the immediate post-natal period has become the focus of importance to reduce later morbidity. While the pathogenesis of BPD in ELBW babies may be multifactorial, ventilation is a component that is potentially modifiable (17). Therefore, it is of utmost importance to practice ventilation strategies that minimize lung injuries and in turn long-term morbidity and mortality. The use of volume targeted ventilation (VTV) and high-frequency ventilation (HFV) in extremely preterm infants have gained a lot of momentum in the last few decades because of their potential to minimize VILI (18, 19). This has resulted in some well-designed studies and meta-analysis being published which included ELBW babies (birth weight < 1,000 g) (20–23). However, an international survey showed that the acceptance of these modes in the NICUs around the world is not consistent and carries significant practice variability (24). We have reviewed the existing literature including systematic reviews and meta-analysis for these popular modes of ventilation and explored whether a clear recommendation could be made regarding the primary modes of ventilatory management for ELBW infants.

CONVENTIONAL VENTILATION IN ELBW INFANTS

Conventional ventilation (CV) is a frequently used mode of invasive ventilation in ELBW babies (3). It is used in ELBW babies primarily for acute respiratory failure, which causes CO_2 retention. Invasive mechanical ventilation can be administered in two different ways: pressure limited ventilation (PLV) and VTV. In PLV, a preset peak inspiratory pressure (PIP) is dialed above the positive end-expiratory pressure (PEEP) along with the rate and inspiratory time. The delivered tidal volume is variable depending on the change in lung compliance. As ventilation is based on constantly delivered tidal volume to the lung, PLV is not the ideal respiratory support for ELBW infants. VTV is based on the principle of targeting a specific tidal volume consistently during each breath. The tidal volume and respiratory rate set in the ventilator determine how efficiently the retained CO_2 will be removed.

It is important to distinguish the concept of "volume targeted" ventilation from "volume control" ventilation in the context of neonatal respiratory management. These two terms have been used interchangeably by many authors over the years. Volume control ventilation is typically used in the adult and larger pediatric population. In this modality, a specific tidal volume (chosen by the user) is set and calculated at the ventilator machine itself and then administered through the circuit and finally to the patient (25). Thus, the pressure in the circuit rises throughout the breath and reaches the PIP just before expiration. In this mode, the pressure is a dependent variable to the set tidal volume. The rate of pressure rise also depends on the compliance of the lung and the resistance of the circuit. Additionally, because of the use of cuffed endotracheal tubes in this population, the amount of air-leak around the ETT is negligible. As a result, there is a good correlation between the calculated tidal volume at the ventilator and the administered tidal volume to the patient. This system would not work in the ELBW population because of the very low tidal volume required (∼2–5 ml in babies <1,000 g)

and the lost volume secondary to compression in the circuit. The situation is further complicated by the fact that air-leak around the ETT is variable between breaths thus making the correlation between the targeted tidal volume and the administered tidal volume very poor (26). This was a problem several years back when the ventilators were not sensitive enough to deliver small tidal volumes consistently with each breath (27). Earlier ventilators used to have flow sensors located in the main body of the ventilator (many ventilators still do) (26). Modern ventilators are equipped with a microprocessor that can detect small changes in tidal volumes as low as 0.5 ml (28, 29). The volume guarantee mode also makes these ventilators "self-weaning" in which inspiratory pressures are adjusted based on measured exhaled tidal volume, in response to changing lung compliance and respiratory effort (30, 31). This is especially helpful for preterm babies with respiratory distress syndrome who have received surfactant. The self-weaning features of these ventilators decrease the risk of volutrauma and unintended hyperventilation in these babies. Compared to PLV, VTV is associated with less variability in tidal volume and stable $PaCO_2$ levels (31). Whereas, avoiding high tidal volume prevents volutrauma, avoiding lower than physiological tidal volume reduces the risk of atelectrauma and CO_2 retention (32). Furthermore, avoiding both hypo and hypercarbia, prevent rapid changes in the cerebral blood flow thus decreasing the risk of intracranial bleeds, which is a major cause of morbidity and mortality in ELBW babies (33).

In VTV, the user-set tidal volume is measured at the airway opening (most commonly at the Y-piece between the ventilator circuit and the ETT) through a flow sensor, which makes it more accurate and sensitive in detecting changes in volume (28). The ventilator automatically adjusts the PIP on each administered breath to reach the preset tidal volume measured at the Y-piece. In essence, volume targeted ventilation is a "pressure control" mode of ventilation where tidal volume is a dependent variable to changes in pressure. Depending on the ventilator design or mode of VTV, the tidal volume may be measured at the flow sensor either during inspiration or during expiration or both. Expired tidal volume is generally considered more accurate as it is not affected by the air-leak around the ETT unless the leak is very high (>50%) (34). Nonetheless, volume control ventilation is still being used in many NICUs and Singh et al. showed that volume control ventilation can be used safely in extremely preterm infants when an additional flow sensor is used near the ETT which helps to adjust the volume according to the targeted tidal volume (35).

VOLUME TARGETED (VTV) VS. PRESSURE LIMITED VENTILATION (PLV) IN ELBW INFANTS

Numerous studies have been published comparing VTV and PLV in the neonatal population (36–39). However, there is very little data specifically on ELBW babies. A Cochrane meta-analysis was published in 2017 which included 16 parallel and 4 cross-over studies (20). Data from 977 infants were included in the analysis and the authors found that VTV offered multiple benefits when compared to PLV. VTV was found to significantly decrease rates of death and/or BPD, mean duration on ventilation, air leaks, hypocarbia, and severe intraventricular hemorrhage (IVH). Additionally, there was no significant difference in patent ductus arteriosus (PDA) and inspired oxygen concentration between the two groups. However, there were considerable differences between studies in regard to the diagnostic criteria for PDA and oxygen targeting strategies. The authors, however, report the quality of evidence for these outcome measures is moderate to low due to the use of different ventilators and modes between studies, differing ventilator strategies and differing methods for measuring and targeting tidal volume. While some of the studies included in the meta-analysis reported a separate subgroup analysis for ELBW or extremely preterm infants (32, 35), others did not. The authors utilized supplementary data from studies to get a total of 247 ELBW babies in the meta-analysis which did not have the power to identify significant differences between the VTV and PLV group (20). Indeed, there were no significant differences in major outcomes noted between VTV and PLV for ELBW babies (**Table 1**).

While we wait for RCTs specifically designed for ELBW infants to be published, it is worth discussing some of the interesting studies related to this topic. Polimeni et al. performed a study with ELBW babies studying the importance of maintaining stable tidal volume from breath to breath (42). The group compared the hypoxemic episodes in VTV vs. PLV group in these babies and showed that while there was no difference in the number of hypoxemic episodes in the two groups, the duration of those hypoxemic episodes was significantly reduced in the VTV group. This was a significant finding as an automatic reaction to these hypoxemic episodes in ELBW babies is to increase the fraction of inspired oxygen (FiO_2). Frequently these babies would stay on the increased FiO_2 for some time before the oxygen is titrated down, even though they have recovered from the hypoxemic event. This leads to more oxidative stress for the baby and an increased risk of future lung and eye disease. VTV could partially solve this problem by decreasing the duration of these hypoxemic episodes.

Lista et al. showed that VTV was associated with lower levels of inflammatory cytokines [interleukin 6 (IL−6), interleukin 8 (IL−8), and tumor necrosis factor-alpha (TNFα)] in the tracheal aspirate fluid compared to PLV among preterm infants with respiratory distress syndrome (43). This could be explained by the avoidance of volutrauma and atelectrauma by maintaining a consistent tidal volume over time.

A recently published study by Wong et al. showed that there was a good correlation of measured expired tidal volume through a flow sensor between ELBW babies (<1,000 g) and VLBW babies (1,000–1,500 g) (44). This is a significant finding because VTV relies heavily upon the accurate measurement of expired tidal volume. Indeed, newer ventilators have flow sensors that are very sensitive up to tidal volumes of 5 ml (29). This would encompass a big portion of the tidal volume range seen in ELBW babies weighing <1,000 g. This is supported by the study published by Keszler et al. that a tidal volume of ∼5 ml/kg is needed to maintain stable $PaCO_2$ in babies weighing <800 g (12).

TABLE 1 | Characteristics and outcome measures of studies with different ventilation strategies in ELBW infants.

References	Design	Group	Mortality	BPD	Time on ventilation	Hypocarbia	Amount of inspired oxygen	IVH or PVL	Air leak
Klingenberg et al. (20) (VTV vs. PLV)	Cochrane review (16 parallel and 4 cross-over studies)	All babies	Reduced in VTV group*	Reduced in VTV group*	Reduced in VTV group*	Reduced in VTV group*	No significant difference	Reduced incidence of severe IVH in VTV group*	Reduced in VTV group*
		ELBW subgroup	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
Bhuta and Henderson-Smart (40) (Elective HFJV vs. CV)	Cochrane review (3 RCTs)	All babies	No significant difference	Reduced in HFJV group*	Higher in HFJV group	NR	Fewer days on oxygen in HFJV group	Increased risk of PVL in HFJV group	NR
		ELBW subgroup	NR	NR	NR	NR	NR	NR	NR
Cools et al. (22) (Elective HFOV vs. CV)	Cochrane review (19 RCTs)	All babies	Reduced in HFOV group*[a]	Reduced in HFOV group*	Meta-analysis not done due to variability	NR	Meta-analysis not done due to variability	Increased risk in 2 trials but not in overall meta-analysis	Increased risk in HFOV group*
		ELBW subgroup	NR	NR	NR	NR	NR	NR	NR
Craft et al. (21) (Elective HFFI vs. CV)	Sy-fi study group (RCT)	ELBW babies	No significant difference	No significant difference	No significant difference	NR	No significant difference	No significant difference	No significant difference
Rojas-Reyes and Orrego-Rojas (41) (Rescue HFJV vs. CV)	Cochrane review (1 RCT)	All babies	No significant difference	No significant difference	NR	NR	NR	Reduced incidence of new IVH in HFJV group	NR
		ELBW subgroup	NR	NR	NR	NR	NR	NR	NR

*NR, not reported; VTV, volume targeted ventilation; PLV, pressure limited ventilation; HFJV, high frequency jet ventilation; CV, conventional ventilation; HFOV, high frequency oscillatory ventilation; HFFI, high frequency flow interrupter; ELBW, extremely low birth weight – defined as birth weight ≤ 1000gms; Mortality is defined as death before hospital discharge; BPD, bronchopulmonary dysplasia – need for oxygen or ventilatory support at 28 days or 36 weeks postmenstrual age; Hypocarbia defined as CO_2 tension in arterial blood < 40torr; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; *denotes statistically significant difference between two groups ($p < 0.05$); a denotes combined death and BPD.*

One concern with VTV for ELBW babies would be the dead space in the flow sensor. While this does not affect ventilation much in larger babies it could be a concern for babies <1,000 g. A study published in 2009 showed that adequate alveolar ventilation was achieved using VTV in babies <800 g in spite of the flow sensor dead space (45). Interestingly, another study with VTV which measured arterial CO_2 in newborn infants showed that a higher amount of tidal volume was needed to maintain normocapnia in the smallest babies (<500 g) (32). This finding would mean that the extra dead space in the flow sensor may indeed play some role in the smallest micro-preemie population. However, this small disadvantage should not preclude the use of flow sensors in the smallest babies given the multiple advantages it confers, such as measuring accurate tidal volume and flow triggering (46).

HIGH FREQUENCY VENTILATION IN ELBW INFANTS

The goal of high frequency ventilation is to maintain optimal lung expansion while reducing the risk of lung injury by avoiding high or rapid changes in tidal volume (47). Several animal studies have been published over the years demonstrating the advantages of high frequency ventilation over conventional ventilation in immature and/or injured lungs (48, 49). McCulloch et al. showed that maintaining a sustained alveolar expansion through high frequency ventilation prevented lung injury in the atelectasis-prone immature lungs (50). Three forms of high frequency ventilation have been widely used for respiratory management of preterm infants: high frequency oscillatory ventilation (HFOV), high frequency flow interrupter (HFFI) and high frequency jet ventilation (HFJV). Of these three HFOV and HFJV are the two popular modes when compared to HFFI. There are differences in the mechanism between the three modes but the target is the same, that is, to produce optimal gas exchange while minimizing peak and mean airway pressures (51). In HFOV, a piston-like mechanism is used to generate small tidal volumes at the rate of 5–15 Hz (300–900 cycles per minute) which are then transmitted through a rigid circuit, ETT and finally through the tracheobronchial tree to reach the alveoli resulting in gas exchange. The user sets the mean airway pressure (MAP), amplitude and the amount of inspired oxygen based on the need of the patient. In HFOV both inspiration and expiration are

active processes (52). HFJV, which is commonly used as a parallel connection with a conventional ventilator, functions differently. The jet ventilator is attached to the ETT through a special 3-way cannula. It generates gas pulses at a high frequency (4–11 Hz or 240–660 cycles per minute) and propels it through one of the ports of the three-way cannula while the conventional ventilator maintains an optimum lung expansion with a stable PEEP (53). HFFI is a recent advancement in some conventional ventilators which offer both conventional and high frequency modes (18). They function similar to the HFJV. A high-pressure system delivers gas into the ventilation-endotracheal tube circuit and a valve system is used to interrupt the flow and produce high frequency breaths. The valve system is controlled either mechanically or through a microprocessor in the ventilator. The operator selects the parameters including the frequency (6–20 Hz or 360–1,200 cycles per minute), PIP and PEEP. While inspiration is an active process in HFJV and HFFI, expiration is passive secondary to lung recoil. Boros et al. performed a study in cats comparing HFOV and HFJV to look at differences in peak and mean airway pressures for similar pH and $PaCO_2$ levels (54). They found that HFJV was able to produce better gas exchange compared to HFOV at lower peak and mean airway pressures. This benefit may partly be due to the passive expiration seen in HFJV. While none of the clinical studies have proved one to be better than the other, HFJV is theoretically considered better for non-homogenous lung pathologies and air leak syndromes (55). Both HFOV and HFJV have been used either electively (i.e., as the primary mode of respiratory treatment shortly after birth) or as a rescue (i.e., after the failure of conventional ventilation or a complication from conventional ventilation) in preterm infants (40, 41, 56). It is important to note that Ethawi et al. attempted to perform a Cochrane review comparing HFJV and HFOV for acute pulmonary dysfunction in preterm infants (57). However, they did not find any randomized controlled trials (RCT) or quasi-RCTs that met the inclusion criteria.

CONVENTIONAL VENTILATION VS. HIGH FREQUENCY VENTILATION IN ELBW INFANTS

There has been much debate regarding the use of conventional ventilation or high frequency ventilation in ELBW babies. Unfortunately, there is not much evidence to suggest that one is superior to the other. As with many other aspects of neonatology, significant practice variability exists among different centers. Bhuta and Henderson-Smart (40) performed a systematic review in 1998 comparing elective HFJV (i.e., starting soon after initiation of mechanical ventilation or shortly after birth) and conventional ventilation in babies <2,000 g or <34 weeks with RDS. While the group did not specifically target the ELBW babies, it is still worth discussing the results. Overall, three trials were included in the review. Of these, one of the trials used both a high (defined as increasing the PEEP by ≥1 cm H_2O from pre-HFJV baseline and/or using PEEP ≥7 cm H_2O) and low airway pressure strategy while using HFJV (58) and the other two trials used a low airway pressure strategy (59, 60). The primary outcome was a decreased rate of chronic lung disease without serious adverse effects. The meta-analysis found a reduction in the rate of BPD at 36 weeks corrected age in the HFJV group [Relative risk (RR) 0.58, 95% CI 0.34–0.98]. There were no significant differences in mortality, the overall incidence of IVH or severe IVH (grades 3 and 4), air leaks although the number of ventilator days saw a non-significant increase in the HFJV group (**Table 1**). There was a non-significant decrease in the number of days on oxygen in favor of the HFJV group. There was no reported data on PDA or hypocarbia. However, one of the trials (60) which used the low airway pressure strategy showed a significantly increased risk for periventricular leukomalacia (PVL) in the HFJV group (RR 5.0, 95% CI 1.19–21.04). The trial that used high mean airway pressure strategy did not show an increased risk of acute brain injuries (58). The authors concluded that HFJV might have an advantage as a primary mode over conventional ventilation in preterm infants but given the adverse effects of HFJV being unclear, more research is needed before clear recommendations can be made.

In 2016, a Cochrane review comparing elective HFOV and CV in preterm infants was published (22). Overall, 19 RCTs between 1989 and 2014 were included. The HFOV group showed a small reduction in the risk of BPD (RR 0.86, 95% CI 0.78–0.96) and combined death or BPD (RR 0.90, 95% CI 0.84–0.97) at 36 weeks corrected age compared to CV. However, the outcomes were variable across different studies. Additionally, the HFOV group had an increased risk of air leak (RR 1.19, 95% CI 1.05–1.34), which may balance out the slight advantage of HFOV in reducing the rate of BPD. Even though two of the included trials reported significantly increased risk of severe IVH in the HFOV group (61, 62), the overall meta-analysis did not find a significant difference between the two groups. There was no statistically significant difference in mortality, the overall incidence of IVH or PVL. Meta-analysis was not done for total ventilator days, duration of oxygen therapy because of high variability between studies (**Table 1**). Data regarding PDA and hypocarbia were not reported. The sy-fi trial was one of the RCTs included in the review (21). This trial used HFFI as the high frequency mode of ventilation. Interestingly, the sy-fi study was the only RCT with babies <1,000 g. For the purpose of this review, we have discussed this study separately below.

There have been a number of studies over the years comparing the effects of these two modes of ventilation on lung inflammation. Generally, HFV is considered to be less traumatic to the preterm developing lungs when compared to CV. However, the evidence is contradictory. Thome et al. compared levels of numerous inflammatory markers (IL-8, leukotriene B4) in the tracheal aspirates of babies either ventilated with CV and HFOV (63). There was no significant difference in the levels of the inflammatory markers at 10 days of life between the two groups. Lista et al. did a study in 2008 comparing the effect primary VTV and primary HFOV would have on lung inflammation in infants between 25 and 32 weeks gestational age (64). The levels of inflammatory markers (IL-6, IL-8, and TNFα) were measured in the tracheal aspirate on the first, third, and seventh day of life. IL-6 levels were significantly higher in the HFOV group after 3 days. The HFOV group also was found to

have longer oxygen dependence. In a similar study published in 2011, the investigators measured the serum levels of Clara cell 16 kD protein (CC16) and IL-6 in babies <30 weeks of gestation age ventilated with either CV or HFOV (65). CC16 and IL6 are considered as biomarkers for alveolar inflammation and leakage. The levels were comparable between the two groups at the third and fourteenth day of life, and at 36 weeks post-menstrual age.

A meta-analysis performed in 2015 by Rojas-Reyes and Orrego-Rojas compared conventional ventilation and rescue HFJV (i.e., after the failure of conventional ventilation mostly after 24 h of life) in babies <35 weeks who had severe pulmonary dysfunction (41). Only one study by Keszler et al. (66) met the inclusion criteria. This study was a multi-center RCT performed between 1987 and 1989 comparing HFJV with conventional ventilation in 144 babies weighing ≥750 g who had developed pulmonary interstitial emphysema (PIE) with the primary outcomes being an improvement of PIE. There was no statistically significant difference in chronic lung disease (RR 0.77, 95% CI 0.54–1.07) or overall mortality (RR 1.03, 95% CI 0.64–1.66) between the two groups. There was no difference between groups regarding air leaks or severe IVH (**Table 1**). There was a trend toward the decreased incidence of "new" IVH in the HFJV group but it was not statistically significant (RR 0.49, 95% CI 0.19–1.24). Data regarding total ventilator days, PDA, PVL or hypocarbia were not reported and there was no subgroup analysis for babies <1,000 g. Overall, the level of evidence from this study was assessed to be low in quality as the study was performed before the era of surfactant and antenatal steroids making interpretation of the results difficult.

The sy-fi study group performed a RCT between 1999 and 2000 comparing HFFI and conventional ventilation in ELBW babies (21). Forty-six infants were enrolled in the study from two separate centers. There was no significant difference in the incidence of BPD or oxygen requirement at 36 weeks post-menstrual age. The total number of days on a ventilator was similar between the two groups. The study did not find any difference in mortality, duration of oxygen therapy, air leak, severe IVH or PDA between the HFFI and CV in ELBW babies (**Table 1**). Data on hypocarbia was not reported. A previous study was published by Thome et al. comparing elective HFFI and CV (within 6 h of birth) in preterm infants (67). The study, however, was not specifically done on ELBW babies. There was no significant difference between the two groups for BPD at 30 days (88 vs. 88%) or at 36 weeks post-menstrual age (25 vs. 23%). An even earlier study published in 1993 also used the HFFI in babies <1,800 g with RDS (68). While there was a trend of decreased BPD in the HFFI group compared to the CV group (63 vs. 80% at 28 days, 25 vs. 40% at 36 weeks), the result was not statistically significant.

A meta-regression analysis published by Bollen et al. in 2007 analyzed 15 RCTs performed over the years comparing HFV and conventional ventilation in infants with RDS (69). They found comparable pulmonary outcomes in both groups when they adjusted for the integration of lung-protective ventilation strategies (i.e., avoiding overdistension or atelectasis, surfactant administration, controlled oxygen use) during conventional ventilation over the years and the types of ventilator used. There is a general belief that prolonged time spent on CV before switching to HFV diminishes the benefits of HFV. However, the results of this study were not compatible with that hypothesis. Consequently, at present, making a clear recommendation between HFV and CV especially for ELBW babies is difficult and clinical judgment should be used while deciding between one or the other.

CONCLUSION

In conclusion, there is a lot of variations in practice that exist when it comes to the ventilator management of extremely preterm infants. This is due to evolving technology in ventilator modes, performance and its use supporting ELBW infants. At present, no single ventilator has been shown to be superior to others. There is no clear consensus as to which ventilator mode is preferable as the primary mode in ELBW babies with respiratory failure. The several studies discussed in this review illustrate the difficulty in making any clear recommendations. While VTV and HFJV do show some promise in some studies, these studies were not powered to determine significant reductions in mortality or morbidity in ELBW babies. Therefore, larger studies comparing the outcomes of different modes of ventilation as primary support are needed specifically targeting ELBW population.

AUTHOR CONTRIBUTIONS

AG and AM wrote the first draft of the manuscript. KS edited and revised the manuscript. All authors approved the final manuscript for submission.

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Clinical Study of Different Modes of Non-invasive Ventilation Treatment in Preterm Infants With Respiratory Distress Syndrome After Extubation

Fei Ding[1], *Jingling Zhang*[1], *Wenya Zhang*[1], *Qian Zhao*[1], *Zimei Cheng*[1], *Yang Wang*[1]*, *Tao Bo*[2]* and *Hui Wu*[3]*

[1] Department of Pediatrics, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [2] Department of Pediatrics, Second Xiangya Hospital, Central South University, Changsha, China, [3] Department of Pediatrics, First Hospital of Jilin University, Changchun, China

Objective: This study aimed to investigate the clinical efficacy and safety of different non-invasive respiratory support methods in preterm infants with respiratory distress syndrome (RDS) after extubation.

Methods: From Oct 2017 to 2018, 120 preterm infants were recruited from the NICUs of three hospitals. They were diagnosed with RDS and required mechanical ventilation. After extubation from mechanical ventilation, these infants were divided into NCPAP group, SNIPPV group and SNIPPV + NCPAP group. The time of non-invasive ventilation, reintubation rate within 72 h, success rate of non-invasive ventilation within 1 week, duration of oxygen therapy, hospital stay and incidence of complications were recorded and compared.

Results: Compared with the NCPAP group, the SNIPPV group and the SNIPPV + NCPAP group had significantly higher rate of successful extubation and removal from non-invasive ventilation within 1 week ($P < 0.05$). There were no significant differences among three groups in the time of non-invasive ventilation, time of oxygen therapy, hospital stay or incidence of complications ($P > 0.05$).

Conclusion: SNIPPV + NCPAP after mechanical ventilation is a relatively safe and effective ventilation strategy for preterm infants with severe RDS. The use of NCPAP facilitates the turnover of SNIPPV ventilators in developing countries.

Keywords: preterm infants, respiratory distress syndrome, synchronized nasal intermittent positive pressure ventilation, nasal continuous positive airway pressure ventilation, extubation

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Yuan Shi,
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Camilla Gizzi,
Ospedale San Carlo, Italy
Li Wang,
Daping Hospital, China

***Correspondence:**
Yang Wang
w.yang126@126.com
Tao Bo
boily@yeah.net
Hui Wu
wuhui97@126.com

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INTRODUCTION

With the development of perinatal medicine, the survival rate of preterm infants with extremely/ultra-low birth weight has increased yearly, and the incidence of respiratory distress syndrome (RDS) has also increased over year. Mechanical ventilation can quickly and effectively improve the clinical symptoms of preterm infants with severe RDS, but long-term invasive ventilation may increase the risks for ventilator-associated lung injury and infection. Therefore, the mechanical ventilation in preterm infants with severe RDS should be switched to

non-invasive respiratory support as soon as their spontaneous breathing becomes stable and symptoms are improved.

Nasal continuous positive airway pressure ventilation (NCPAP) is most commonly used in clinical practice. However, reintubation is needed in some infants undergoing NCPAP, mainly due to the frequent apnea or severe carbon dioxide (CO_2) retention. In recent years, synchronized nasal intermittent positive pressure ventilation (SNIPPV) has been increasingly used in China as an enhanced mode of NCPAP. It has been shown that the success rate of extubation after SNIPPV is higher than after traditional NCPAP (1). However, SNIPPV is costly and has not been popularized (2). Theoretically, it is possible to reduce the time of SNIPPV in RDS infants and ease the burden without increasing the failure rate of extubation if the infants are initially administered with respiratory support by SNIPPV after the weaning of mechanical ventilation and then with NCPAP. The present study aimed to explore the efficacy and safety of sequential application of SNIPPV and NCPAP in extubated preterm infants with RDS.

MATERIALS AND METHODS

Study Subjects

Preterm infants who met the inclusion criteria and were born between Oct 2017 and 2018 were recruited from the Departments of Obstetrics of three newborn intensive care units (NICUs). These infants received treatment within half hour after birth. After extubation, the enrolled infants were divided into SNIPPV group, NCPAP group and sequential SNIPPV and NCPAP group (sequential treatment group) ($n = 40$ per group).

The inclusion criteria were as follows: (1) The gestational age was <32 weeks and the birth weight was <1,500 g. (2) The infant met the diagnostic criteria for RDS according to the "Practical Neonatology (4th Edition)" (3). (3) The infant underwent tracheal intubation-mechanical ventilation immediately after being transferred to the NICU. In addition, the infant received non-invasive respiratory support after the withdrawal of mechanical ventilation. (4) Their parents signed the informed consent form before study.

The exclusion criteria were as follows: (1) The infant had congenital malformations of vital organs, birth defects, or genetic/metabolic diseases. (2) The duration of premature membrane rupture was longer than 72 h and there was concomitant intrauterine infection. (3) severe perinatal asphyxia was present. (4) no inform ed consent was obtained before study.

Methods

NCPAP was performed using the CareFusion TF5000 ventilator, while SNIPPV using the Comen nv8 ventilator. In Comen nv8 ventilator, there is a signal acquisition probe which is connected to the abdomen of infants. The respiratory signals are collected via the probe based on the muscular contraction during the respiration, leading to the synchronous NIPPV.

Non-invasive Ventilation Parameter Settings

Extubation was performed when the PIP $\leq$ 18 cmH_2O, PEEP at 2–4 cmH_2O, RR $\leq$10 breaths/min, $FiO_2 \leq 0.4$ and normal results on arterial blood gas analysis were present simultaneously. After the withdrawal of mechanical ventilation: (1) In the NCPAP group, the positive end-expiratory pressure (PEEP) was 6 cm H_2O, and the lowest fraction of inspired oxygen (FiO_2) was used to achieve a target oxygen saturation of 90–95% (4). NCPAP noninvasive ventilation was weaned when the PEEP was <4 cmH_2O, FiO_2 was <0.21 and the results of blood gas analysis were within the acceptable range. (2) In the SNIPPV group, the peak inspiratory pressure (PIP) was 15–25 cmH_2O, the PEEP was 4–6 cmH_2O, the respiratory rate (RR) was 15–50 breaths/min, and the lowest FiO_2 was used to achieve a target oxygen saturation of 90–95%. SNIPPV non-invasive ventilation was weaned when the following conditions were present: a. the PIP was <14 cmH_2O, PEEP was <4 cmH_2O, FiO_2 was <0.3, and RR was <15 breaths/min; b. the infants did not experience apnea and bradycardia; c. the results of arterial blood gas analysis were within the acceptable range (5). (3) In the sequential treatment group, The starting parameters of SNIPPV were the same as in the SNIPPV group, than we shifted to NCPAP when FiO2 < 0.35, PIP < 20 cmH_2O and PEEP < 6 cmH_2O were present simultaneously, and then we started the following NCPAP with the same starting parameters of the NCPAP group and considered for weaning the same weaning parameters of the NCPAP group.

An infant was administered with SNIPPV support again if she/he experienced phenomena such as apnea and significant fluctuation in oxygen saturation after weaning of NCPAP or SNIPPV and inhalation of air-oxygen mixture. The time of ventilation was included in the total time of non-invasive ventilation. An infant was administered with endotracheal intubation-mechanical ventilation if she/he still experienced one of the following conditions: (1) progressive dyspnea or frequent apnea with the requirement for balloon-mask positive pressure ventilation; (2) inhaled $FiO_2 > 60\%$ and percutaneous oxygen saturation < 85% or blood $PaO_2 < 50$ mmHg; (3) $PaCO_2 > 60$ mmHg with concomitant persistent acidosis (pH<7.20–7.25); (4) no improvement and the presence of pulmonary hemorrhage and tension pneumothorax on chest X-ray examination (6).

Observations

The observations included: (1) rate of reintubation within 72 h after extubation, success rate of weaning from non-invasive ventilation within 1 week and time of non-invasive ventilation; (2) time of oxygen therapy and time to total enteral nutrition; (3) incidence of complications, including neonatal hypoxic-ischemic encephalopathy (HIE), neonatal feeding intolerance, neonatal pneumonia, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and patent ductus arteriosus (PDA); (4) hospital stay and medical cost.

Statistical Methods

Statistical analysis was performed using the SPSS version 23.0 (Statistical Product and Service Solutions, NY, USA). Data were subjected to normality test. The normally distributed data are expressed as mean ± standard deviation ($\bar{x} \pm s$), and compared with one way analysis of variance (ANOVA) among three groups, followed by Student-Newman-Keuls (SNK)-q test. Data with abnormal distribution were compared with the non-parametric

test. Qualitative data are expressed as number or percentage, and rates were compared using the χ^2 test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of Infants in Three Groups

As shown in **Tables 1**, **2**, there were no significant differences among three groups in the sex, gestational age, birth weight, use of pulmonary surfactants, time of mechanical ventilation, and age at breastfeeding initiation ($P > 0.05$).

Time of Non-invasive Ventilation, Rate of Reintubation Within 72 h, and Success Rate of Weaning From Non-invasive Ventilation Within One Week

The rate of reintubation within 72 h was significantly lower in the SNIPPV group and sequential treatment group as compared to the NCPAP group, whereas the success rate of weaning from non-invasive ventilation within 1 week was markedly higher in the SNIPPV group and sequential treatment group as compared to the NCPAP group ($P < 0.05$). In addition, no significant difference was noted in the time of non-invasive ventilation among three groups ($P > 0.05$) (**Table 3**).

Incidence of Complications and Mortality

There were no significant differences among three groups in the incidences of HIE, neonatal feeding intolerance, neonatal pneumonia, PDA, BPD and ROP, and mortality ($P > 0.05$) (**Table 4**).

Time of Oxygen Therapy, Time to Total Enteral Feeding, Hospital Stay, and Medical Cost

As shown in **Table 5**, there were no statistically significant differences among 3 groups in the time of oxygen therapy, time to total enteral feeding, hospital stay, and medical cost ($P > 0.05$).

DISCUSSION

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome (2019) recommend non-invasive ventilation as the best respiratory support for preterm infants with RDS (7). However, approximately half of extremely preterm infants are unable to maintain stable oxygenation under non-invasive ventilation and require endotracheal intubation-mechanical ventilation. The lung of preterm infants is still immature and highly susceptible to external disturbances. Such disturbances may affect the normal development, causing lung diseases (8). To decrease the risk for complications (such as ventilator-associated pneumonia and BPD) and reduce

TABLE 1 | Baseline characteristics of infants in three groups (part 1).

Group	*n*	Sex (*M*/*F*, *n*)	Gestational age ($\bar{x} \pm s$, week)	Birth weight ($\bar{x} \pm s$, *g*)	Small for gestational age [*n* (%)]	Twins [*n* (%)]	Mode of delivery (cesarean section/vaginal delivery)	Premature rupture of membranes [*n* (%)]
NCPAP	40	22/18	29.9 ± 1.4	1.1 ± 0.2	8 (20)	10 (25)	30/10	6 (15)
SNIPPV	40	26/14	29.7 ± 2.3	1.3 ± 0.2	6 (15)	12 (30)	24/16	7 (17.5)
Sequential treatment	40	26/14	29.3 ± 1.8	1.2 ± 0.2	7 (17.5)	8 (20)	26/14	6 (15)
$F(\chi^2)$		1.128	0.418	1.803	0.346	1.067	2.100	0.125
P		0.597	0.661	0.176	0.954	0.628	0.400	0.939

P refers to three groups of comparison: NCPAP, SNIPPV and Sequetial treatment. The comparison was conducted among the three groups. If P < 0.05, a pairwise comparison was further performed between every two groups. If P > 0.05, it means that there was no statistical difference among them, so no further pairwise comparison would be performed.

TABLE 2 | Baseline characteristics of infants in three groups of infants (part 2).

Group	*n*	*In vitro* fertilization [*n* (%)]	Mother with pregnancy-induced hypertension [*n* (%)]	Prenatal use of hormones [*n* (%)]	Use of PS* [*n* (%)]	Duration of mechanical ventilation ($\bar{x} \pm s$, day)	Age at breast feeding initiation ($\bar{x} \pm s$, day)
NCPAP	40	8 (20)	12 (30)	38 (95)	38 (95)	7 ± 5	2.9 ± 1.2
SNIPPV	40	10 (25)	14 (35)	39 (97.5)	37 (93.5)	7 ± 5	3.5 ± 1.0
Sequential treatment	40	14 (35)	20 (50)	39 (97.5)	38 (95)	8 ± 5	3.0 ± 1.2
$F(\chi^2)$		2.386	3.666	0.517	0.303	0.411	0.915
P		0.352	0.164	0.772	0.859	0.665	0.410

**PS, Pulmonary surfactants. P refers to three groups of comparison: NCPAP, SNIPPV and Sequetial treatment. The comparison was conducted among the three groups. If P < 0.05, a pairwise comparison was further performed between every two groups. If P > 0.05, it means that there was no statistical difference among them, so no further pairwise comparison would be performed.*

the possibility of long-term oral intubation-induced upper jaw deformity and effects on the tooth development (4), early switching from the mechanical ventilation to the non-invasive ventilation has been advocated, even for extremely preterm infants (9). Therefore, it is of great clinical value to determine the optimal mode for the assisted respiratory support after extubation.

NCPAP is the first mode of non-invasive ventilation used for neonatal respiratory support. It provides a positive airway pressure for infants with spontaneous breathing through a continuous air flow, which enhances the functional residual capacity, reduces the work of breathing, maintains lung expansion, prevents end-expiratory alveolar collapse, and prepares for successful extubation. However, infants who receive NCPAP as the respiratory support after extubation sometimes require reintubation and repeat mechanical ventilation due to some conditions such as apnea, which is usually accompanied by increased risk for complications and elevated medical cost and affects the quality of life of these infants.

Nasal intermittent positive pressure ventilation (NIPPV) provides an intermittent positive-pressure respiratory support at set intervals on the basis of NCPAP. NIPPV provides infants with stable PIP and PEEP and offers stronger respiratory support than NCPAP. NIPPV is a transitional assisted ventilation after extubation, and its efficacy has been confirmed in some randomized controlled studies (10). Xia et al. showed that, compared with NCPAP, NIPPV effectively improved the pulmonary oxygenation, shortened the duration of assisted ventilation, increased the extubation rate, and reduced the incidence of frequent apnea and BPD (11). Lemyre et al. analyzed the results of 10 randomized and semi-randomized trials (12). Their results showed that NIPPV was more effective than NCPAP in reducing the need for reintubation within a week. However, NIPPV had no effect on the chronic lung diseases and mortality. In a retrospective analysis, Bhandari et al. found that NIPPV was more helpful for the weaning from ventilation than NCPAP, and SNIPPV seemed to be as effective as NIPPV (13).

SNIPPV is achieved by adding a synchronous sensor to NIPPV, which renders breathing more suitable to the physiological state of infants. Theoretically, this synchronized mode allows air to efficiently enter the lower respiratory tract and reach the lungs during assisted ventilation. Therefore, SNIPPV has a stronger biological effect than NIPPV. Aghai et al. indicated that SNIPPV could decrease work of breathing (WOB) compared with NCPAP, because SNIPPV can provide positive inspiratory pressure intermittently. The NIPPV mode often causes desynchrony between the ventilator and the infant's

TABLE 3 | Reintubation rate within 72 h, success rate of weaning from noninvasive ventilation within one week, and time of noninvasive ventilation in three groups.

Group	*n*	Reintubation rate within 72 h [*n* (%)]	Success rate of withdrawal of non-invasive ventilation within one week [*n* (%)]	Duration of non-invasive ventilation ($\bar{x} \pm s$, day)
NCPAP	40	10 (25)	16 (40)	6.5 ± 5.9
SNIPPV	40	2 (5)	28 (70)	4.0 ± 1.35
Sequential treatment	40	2 (5)	30 (75)	4.6 ± 1.93
$F(\chi^2)$		10.350	12.127	1.329
P		0.007[a]	0.002[a]	0.278[b]

[a]*Fisher's exact probability method; a refers to two groups of comparison: NCPAP and SNIPPV.*

[b]*Refers to three groups of comparison: NCPAP, SNIPPV, and Sequetial treatment. The comparison was conducted among the three groups. If P < 0.05, a pairwise comparison was further performed between every two groups. If P > 0.05, it means that there was no statistical difference among them, so no further pairwise comparison would be performed.*

TABLE 5 | Time of oxygen therapy, time to total enteral feeding, hospital stay and medical cost in three groups.

Group	Time of oxygen therapy ($\bar{x} \pm s$, day)	Time to total enteral feeding ($\bar{x} \pm s$, day)	Hospital stay ($\bar{x} \pm s$, day)	Medical cost ($\bar{x} \pm s$, yuan)
NCPAP	26.6 ± 11.6	36.2 ± 8.1	44.0 ± 7.9	69945.1 ± 13362.6
SNIPPV	22.8 ± 11.7	37.4 ± 14.8	37.4 ± 14.7	64954.0 ± 16677.5
Sequential treatment	20.9 ± 6.0	36.0 ± 10.3	39.5 ± 11.3	62193.1 ± 16360.1
F	1.986	0.015	0.088	1.914
P	0.370	0.993	0.784	0.384

P refers to three groups of comparison: NCPAP, SNIPPV, and Sequetial treatment. The comparison was conducted among the three groups. If P < 0.05, a pairwise comparison was further performed between every two groups. If P > 0.05, it means that there was no statistical difference among them, so no further pairwise comparison would be performed.

TABLE 4 | Incidence of complications and mortality in three groups [*n* (%)].

Group	HIE	Neonatal feeding intolerance	Neonatal pneumonia	PDA	BPD	ROP	Mortality
NCPAP	10 (25)	14 (35)	12 (30)	4 (10)	7 (17.5)	6 (15)	4 (10)
SNIPPV	8 (20)	10 (25)	13 (32.5)	3 (7.5)	4 (10)	4 (10)	2 (5)
Sequential treatment	6 (15)	12 (30)	10 (25)	6 (15)	6 (15)	5 (12.5)	2 (5)
χ^2	1.250	0.952	0.656	1.208	0.959	0.457	1.071
P	0.581	0.660	0.882	0.665	0.719	0.940	0.728

BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; P refers to three groups of comparison: NCPAP, SNIPPV, and Sequetial treatment. The comparison was conducted among the three groups. If P < 0.05, a pairwise comparison was further performed between every two groups. If P > 0.05, it means that there was no statistical difference among them, so no further pairwise comparison would be performed.

spontaneous breathing, which may increase the ventilator-related adverse events, such as apnea and fluctuations of oxygen saturation in infants (14), because asynchronous breaths may induce laryngeal closure, inhibit inspiration, increase abdominal distention, have detrimental effects on blood pressure and cerebral blood flow, and increase WOB. The SNIPPV mode solves the problem of desynchrony. Research from Gizziet et al. showed that SNIPPV could reduce the occurrence of apnea in preterm infants compared with NIPPV and NCPAP (15). Chen et al. found that, as compared to NCPAP, SNIPPV enhanced the success rate of weaning from ventilation, reduced the incidences of apnea and BPD, and shortened the time of oxygen exposure and hospital stay (16).

The Chinese "Expert Consensus on Nasal Intermittent Positive Pressure Ventilation in Preterm Infants (2018)" recommends that NIPPV transition is preferred after extubation of endotracheal tube. After weaning from the NIPPV, infants should be administered with NCPAP, high-flow nasal cannula (HFNC) or nasal cannula oxygen inhalation depending on the disease condition (5). A sequential SNIPPV/NCPAP mode that continued to provide low-parameter NCPAP support after weaning from SNIPPV was established in the present study. Theoretically, this sequential mode may decrease the failure rate of extubation and reduce the risk from ventilator-related lung injury in preterm infants with RDS.

In the present study, the clinical efficacy of three ventilation modes (NCPAP, SNIPPV and sequential SNIPPV/NCPAP) was compared in the treatment of preterm infants with severe RDS after extubation. The results showed that sequential SNIPPV and NCPAP treatment achieved an efficacy similar to SNIPPV alone. Compared with NCPAP alone, the sequential treatment reduced the failure rate of extubation and increased the success rate of weaning from the non-invasive ventilation within 1 week without increasing the risk for complications such as BPD and ROP. There was no significant difference in the time of non-invasive ventilation between SNIPPV group and sequential treatment group. However, the time of SNIPPV was reduced in the sequential treatment group when compared with the SNIPPV group, which reduced the medical cost to a certain extent. Although the medical cost was comparable between two groups, the medical cost was slightly lower in the sequential treatment group than in the SNIPPV group. Compared with the other two groups, the time of oxygen therapy and the time to total enteral nutrition were reduced in the sequential treatment group, although no significant differences were observed. This might be related to the small sample size. Our results should be confirmed by multicenter clinical trials with large sample size. In addition, no patients were followed up, so the short-term/long-term prognosis (such as long-term lung function and neurodevelopmental outcome) was unclear.

In summary, the sequential SNIPPV/NCPAP mode can safely and effectively facilitate the weaning from invasive mechanical ventilation in preterm infants with RDS without increasing the risk for complications and medical cost.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical medical research ethics committee of The First Affiliated Hospital of Anhui Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YW, TB, and HW contributed to the conception and design of this study. FD, JZ, and WZ organized the data. QZ and ZC performed the statistical analysis. FD, JZ, and WZ drafted the manuscript. QZ and ZC wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Caffeine Citrate for Apnea of Prematurity: A Prospective, Open-Label, Single-Arm Study in Chinese Neonates

Lizhong Du[1], Xiaomei Tong[2], Chao Chen[3], Xirong Gao[4], Alessandra Gagnatelli[5], Jingyang Li[6], Debora Santoro[5], Sara Nicolardi[5] and Laura Fabbri[5] for the Peyona Chinese Study Group*

[1] Neonatal Intensive Care Unit, Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China, [2] Peking University Third Hospital, Beijing, China, [3] Fudan University Children's Hospital, Shanghai, China, [4] Hunan Children's Hospital, Changsha, China, [5] Research & Development – Neonatology, Chiesi Farmaceutici SpA, Parma, Italy, [6] Chiesi Pharmaceutical (Shanghai) Co., Ltd., Shanghai, China

Background: Caffeine citrate has been approved in China for the management of apnea of prematurity. This clinical trial was conducted as a condition of regulatory approval. The aim was to confirm the efficacy of caffeine citrate in the treatment of recurrent intermittent hypoxia and bradycardia in preterm newborns with primary apnea.

Objectives: The primary outcome was the change from baseline in the number of apnea events after loading dose administration of caffeine citrate. Secondary efficacy outcomes included the change from baseline in apnea events after 2 and 4 weeks of maintenance doses.

Methods: This was a multicenter, prospective longitudinal open-label, single-arm study. Neonates who had experienced at least four apnea events during a 24 h period received a loading dose of caffeine citrate 20 mg/kg; those who required additional maintenance doses received 5 mg/kg/day (titrated up to 10 mg/kg/day in case of insufficient response). The number of apnea events was recorded for 6–12 h prior to the loading dose (baseline), and for 12 h post-dose, following the loading dose and at Weeks 2 and 4 (during maintenance).

Results: A total of 247 neonates received the loading dose, who had a significant reduction from baseline of 3.9 events ($p < 0.001$) in the mean number of apnea events. The subset of neonates who required maintenance doses also had significant reductions in the number of events at all visits ($p < 0.001$ for all). A total of 79.4% of participants had at least one adverse event, but only one non-serious and no serious events were considered related to treatment.

Conclusions: In this large, prospective, open-label study, premature infants with a history of apnea who received caffeine citrate were significantly less likely to experience further apnea events.

Keywords: infant, newborn, drug therapy, bodyweight, apnea

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***Correspondence:**
Laura Fabbri
l.fabbri@chiesi.com

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INTRODUCTION

The incidence of apnea of prematurity increases as gestational age decreases, from 7% of neonates born at 34–35 weeks to nearly 100% of those born before 29 weeks (1). This contributes substantially to the length of hospitalization (2). Severe apnea (lasting longer than 20 s) is usually associated with bradycardia or desaturation, which may in turn lead to disturbances of cerebral hemodynamics, subsequently impacting neurodevelopment (1). Furthermore, in a *post-hoc* analysis of data from extremely preterm neonates, prolonged hypoxemic episodes during the first 3 months after birth were associated with a range of adverse outcomes, including increased mortality after 36 weeks, motor impairment, cognitive or language delay, severe hearing loss, and bilateral blindness (3).

Methylxanthine therapy is the mainstay of pharmacologic therapy for apnea of prematurity (4, 5). Two forms are predominantly used, caffeine citrate and theophylline, both of which have similar efficacy, although caffeine citrate is associated with a better safety profile and a lower incidence of adverse events (6, 7). Further, compared with theophylline, caffeine citrate has a longer half-life and does not require drug-level monitoring, and is therefore described in guidelines as generally preferred (4). However, most of the data supporting these treatment guidelines are from relatively small, old studies (8–11), with only one large, long-term follow-up study (12, 13).

Although caffeine citrate has been used for the management of apnea of prematurity in Europe and the US for decades, it was approved in China in December 2012. As a condition of the regulatory approval, the manufacturer was asked to conduct a clinical trial to evaluate the efficacy and possible side-effects of caffeine citrate in neonates who were experiencing apnea and who were being managed under current best clinical practice. The aim was to confirm the efficacy of caffeine citrate in the treatment of recurrent intermittent hypoxia and bradycardia in preterm newborns with primary apnea.

METHODS

Trial Design

This was a multicenter, prospective longitudinal open-label, single-arm study that included five visits (**Figure 1**). At a screening visit (Visit 1), after parents or legal guardians provided written informed consent, neonates who met the inclusion/exclusion criteria had their demographic and medical history collected, and their baseline bodyweight recorded. Baseline apnea data were collected between Visits 1 and 2, including related pulse-oximetry for transcutaneous oxygen saturation (SpO_2) and cardiopulmonary monitoring using chest electrodes to record heart rate and respiratory rate/apnea. At Visit 2, neonates received a loading dose of caffeine citrate and were then observed for a further 12 h. Between Visits 2 and 4, neonates received maintenance caffeine citrate, continuing until they reached an age of 37 weeks or had 5–7 days without significant apnea events (where significant apnea events were those accompanied by desaturation <80% SpO_2 and/or bradycardia <100 bpm). Visits 3 and 4 took place 2 and 4 weeks after Visit 2, respectively, and commenced 12 h prior to dosing with caffeine citrate, running until 12 h post-dose. Visit 5 was a follow-up visit, taking place 5 days after discontinuation of caffeine citrate therapy.

The study was approved by the independent ethics committee at each institution (see **Supplementary Material**), and was performed in accordance with the principles of the Declaration of Helsinki, and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95). The protocol was amended twice after commencement of recruitment, mainly to match the inclusion/exclusion criteria to standard clinical practice in the study sites, to reduce the number of apnea events required for inclusion. The only criterion added was to exclude neonates with any condition that, in the opinion of the investigator, made them unsuitable for participation in the study. In response to requests from ethics committees and study sites the baseline observation period was shortened to commence a minimum of 6 h prior to loading dose administration, rather than 12 h pre-dose. The study is registered at www.chinadrugtrials.org.cn (CTR20140706).

Participants

Eligible patients were male or female, gestational age 28–33 weeks, with a first apnea event resulting in breathing cessation for ≥20 s, or accompanied by bradycardia (heart rate <100 bpm) or oxygen desaturation (SpO_2 <80%), and that occurred more than 12 h after birth. Furthermore, eligible neonates had at least three other apnea events within 24 h after the first occurrence. The main reasons for exclusion were: hematocrit >65% or <40% in room air; clinical suspicion or proven sepsis; blood urea nitrogen >20 mg/dL or urine output <1 mL/kg/h; body temperature <36.0 or >38.5C; hemodynamically significant patent ductus arteriosus confirmed by cardiac ultrasound; suspected or confirmed necrotizing enterocolitis; or confirmed intraventricular hemorrhage above Grade 2. Full inclusion and exclusion criteria are listed in the **Supplementary Material**.

Intervention

Caffeine citrate (Peyona®, Chiesi Farmaceutici SpA) was administered at Visit 2 in a loading dose of 20 mg/kg bodyweight via controlled intravenous infusion over 30 min, using a syringe infusion pump. The maintenance dose was 5 mg/kg bodyweight every 24 h, orally or by intravenous infusion. This maintenance dose could be titrated by the investigator up to 10 mg/kg/day if the neonate responded poorly. The protocol did not mandate whether continuous positive airway pressure or non-invasive positive-pressure ventilation should be used and did not prevent switching from one to the other.

Outcomes

The primary objective was to confirm the efficacy of caffeine citrate in the treatment of recurrent intermittent hypoxia and bradycardia in preterm newborns with primary apnea. The

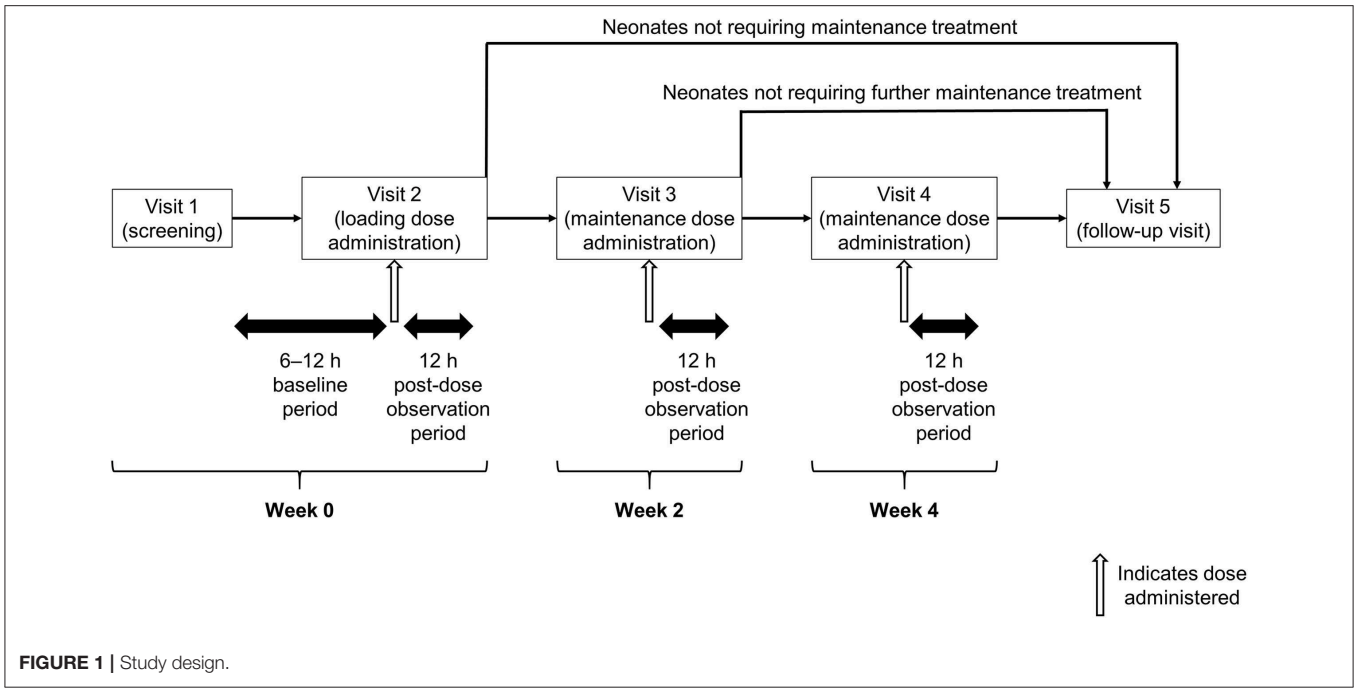

FIGURE 1 | Study design.

primary efficacy outcome was the change from baseline in the number of apnea events, accompanied by desaturation <80% SpO_2 and/or bradycardia <100 bpm, during the 12 h after the loading dose administration at Visit 2, as documented during continuous electronic pulse-oximeter recording. The baseline value was the number of apnea events that occurred during the 6–12 h between Visit 1 and administration of the loading dose at Visit 2.

Secondary efficacy outcomes included the change from baseline in apnea events at Visits 3 and 4, the proportion of neonates with ≥50% reduction from baseline in apnea events at each visit, and the change from baseline in bodyweight at Visits 3 and 4. Adverse events were recorded throughout the study, including at the follow-up visit (Visit 5).

Sample Size

This study was not formally powered, due to the lack of reference data. Regulatory requirements (as part of the approval of caffeine citrate in China) were for a study to be conducted with not less than 200 neonates. To cover a potential drop-out of 20%, the final planned sample size was 240 neonates, from approximately 20 neonatal intensive care units.

Statistical Methods

The number of apnea events at Visits 2, 3 and 4 were compared to baseline using the Wilcoxon signed rank-test. As the period over which the baseline data were collected (Visits 1 to 2) could vary, the baseline value was weighted based on actual monitoring time, and was then standardized to 12 h. Bodyweight at each visit was compared to baseline by means of a paired *t*-test. The percentage of neonates with ≥50% reduction from baseline in the number of apnea events was summarized descriptively.

The safety set included all neonates who received at least one administration of caffeine citrate. The full analysis set included all neonates in the safety set who had at least one available post-baseline efficacy evaluation, and the per protocol set included all neonates from the full analysis set without any major protocol deviations. The primary objective was analyzed both in the full analysis set and the per protocol set. The other efficacy variables were analyzed in the full analysis set only, with the safety data analyzed in the safety set.

RESULTS

Participants

The study was conducted between June 2014 and October 2015 in 19 neonatal intensive care units, all in China. Of 259 neonates screened, 248 were enrolled, with 247 receiving the caffeine citrate loading dose; these neonates comprised both the safety analysis set and the full analysis set, the baseline characteristics of whom are reported in **Table 1**. A total of 203 (81.9%) participants completed Visit 2. The reasons for withdrawal of the 45 neonates were adverse events (n = 15), treatment failure (n = 14), consent withdrawal (n = 5), hematocrit out of range (n = 3), abnormal test results (n = 2), requirement for assisted ventilation via an endotracheal tube or intermittent mandatory ventilation (n = 1) and "other" (n = 5). The Visit 3 (Week 2) analyses included 80 neonates, with 26 neonates included in the Visit 4 (Week 4) analyses.

TABLE 1 | Baseline characteristics (safety analysis set).

	Neonates (*N* = 247)
Gender, n (%)	
Male	147 (59.5%)
Female	100 (40.5%)
Race, n (%)	
Han nationality	238 (96.4%)
Other	9 (3.6%)
Gestational age, weeks	
Mean (SD)	30.9 (1.45)
Min, max	28, 35
Weight, g	
Mean (SD)	1489.1 (317.88)
Min, max	680, 2,200

Outcomes

For the primary endpoint, in the full analysis set, there was a significant reduction in the mean number of apnea events from baseline to Visit 2 of 3.9 events (**Table 2**). The results for the per protocol set were consistent with those for the full analysis set, with a mean change from baseline of −4.0 (range −25.3 to 4.6; $P < 0.001$). The subset of neonates who required maintenance doses also had significant reductions in the number of events at all visits ($P < 0.001$ for all). For example, the 80 neonates treated at Visit 3 had mean reductions from baseline of 3.9 events at Visit 2 and 4.8 events at Visit 3 (**Table 2**).

Most neonates at all visits had at least a 50% reduction in the number of apnea events (Visit 2, 200/247 [81.0%]; Visit 3, 77/80 [96.3%]; Visit 4, 24/26 [92.3%]). Furthermore, for the subgroup requiring maintenance therapy, there was a significant overall increase in bodyweight at both Visits 3 and 4 ($P < 0.001$ for all; **Table 3**).

Safety

Only one non-serious event was considered related to treatment (sinus tachycardia, which resolved spontaneously without treatment after study drug was discontinued), with no serious adverse events considered related to treatment (**Table 4**). Although 9 (3.6%) neonates died during the study, no deaths were considered related to caffeine citrate therapy.

TABLE 2 | Events of apnea per 12 h throughout the study, together with changes from baseline (full analysis set).

	Population included in Visit 2 analyses (*N* = 247)	Population included in Visit 3/Week 2 analyses (*N* = 80)	Population included in Visit 4/Week 4 analyses (*N* = 26)
Baseline*			
Mean (SD)	5.0 (3.49)	5.2 (2.96)	5.1 (2.78)
Range	1.0–25.3	1.3–19.2	2–10.9
Visit 2			
Mean (SD)	1.1 (1.76)	1.3 (2.04)	1.5 (1.70)
Range	0–12	0–12	0–6
Change from baseline at Visit 2			
Mean (SD)	−3.9 (3.73)	−3.9 (3.34)	−3.5 (2.14)
Range	−25.3 to 4.6	−19.2 to 3.96	−8 to 1
95% CI	−4.4 to −3.5	−4.6 to −3.1	−4.4 to −2.6
P-value	<0.001	<0.001	<0.001
Visit 3			
Mean (SD)		0.4 (1.16)	0.7 (1.85)
Range		0, 9	0, 9
Change from baseline at Visit 3			
Mean (SD)		−4.8 (3.22)	−4.3 (3.51)
Range		−19.2 to 4.0	−11.0 to 4.0
95% CI		−5.6 to −4.1	−5.7 to −2.9
P-value		<0.001	<0.001
Visit 4			
Mean (SD)			0.4 (1.03)
Range			0, 4
Change from baseline at Visit 4			
Mean (SD)			−4.6 (2.66)
Range			−10.5 to −0.5
95% CI			−5.7 to −3.5
P-value			<0.001

**Baseline values are standardized to a 12 h period.*

DISCUSSION

This is largest caffeine citrate trial in Chinese preterm neonates to date. The trial documented the efficacy and safety of caffeine citrate for apnea of prematurity. An initial loading dose of caffeine citrate significantly reduced the number of subsequent apnea events in a group of neonates who had experienced at least four apnea events since birth, with almost all of the participants having at least a 50% reduction in the number of events, confirming the rapid onset of the efficacy of caffeine citrate. Those neonates who received maintenance therapy had an overall reduction in apnea events at all visits and had significant improvements in bodyweight. Furthermore, caffeine citrate had a good overall safety profile, since although more than three-quarters of neonates had at least one adverse event, the majority were as expected for this population, with only one event considered related to treatment.

The results of our study are broadly consistent with previous studies conducted outside China. In one of these, 18 neonates were randomly assigned to a treatment or control group for 15 days (9). The nine neonates who received caffeine citrate had a significant decrease from baseline in apnea, with this benefit observed from the first day of

TABLE 3 | Bodyweight, together with changes from baseline (full analysis set).

Bodyweight, g	Population included in Visit 3/Week 2 analyses (*N* = 80)	Population included in Visit 4/Week 4 analyses (*N* = 26)
Baseline		
Mean (SD)	1,299 (245.3)	1,248 (239.7)
Range	700–2,000	770–1,690
Visit 3		
Mean (SD)	1,493 (275.0)	1,430 (241.5)
Range	810–2,150	960–1,890
Change from baseline at Visit 3		
Mean (SD)	194 (128.5)	183 (129.4)
Range	−210 to 570	−210 to 440
95% CI	166–223	130–235
P-value	<0.001	<0.001
Visit 4		
Mean (SD)		1,748 (262.1)
Range		1,160–2,320
Change from baseline at Visit 4		
Mean (SD)		500 (162.9)
Range		120–920
95% CI		435–566
P-value		<0.001

TABLE 4 | Overall experience of adverse events, including adverse events occurring in >5% of neonates, important adverse events occurring in >2% of neonates, and serious adverse events occurring in >0.5% of neonates (safety set).

n (%)	Neonates (*N* = 247)
Any adverse event	196 (79.4)
Anemia	82 (33.2)
Sepsis	26 (10.5)
Pneumonia	22 (8.9)
Infection	14 (5.7)
Necrotizing enterocolitis	14 (5.7)
Hypocalcemia	17 (6.9)
Jaundice	41 (16.6)
Atrial septal defect	20 (8.1)
Patent ductus arteriosus	19 (7.7)
Any treatment-related adverse event	1 (0.4)
Any serious adverse event	34 (13.8)
Sepsis	15 (6.1)
Necrotizing enterocolitis	14 (5.7)
Apnea	2 (0.8)
Adverse event leading to discontinuation	21 (8.5)
Adverse event leading to death	9 (3.6)

treatment; those in the control group had no improvement in apnea for the duration of the study. In a second study, 85 neonates were randomized to receive caffeine citrate or a placebo for up to 10 days, with caffeine citrate again associated with a rapid improvement in apnea and the difference vs. the placebo treatment approaching significance within 2 days (10).

These relatively small early studies were then followed by the Caffeine for Apnea of Prematurity (CAP) study, in which over 2,000 neonates were randomized to receive either caffeine citrate or a placebo (12). During the first 3 weeks after randomization, neonates receiving caffeine citrate gained less weight than those in the placebo group, with a mean decrease from the baseline. Indeed, failure to thrive and feeding intolerance are recognized as adverse reactions of caffeine citrate (although of unknown incidence) (14), with one study suggesting that long-term administration of caffeine in preterm neonates being associated with an increase in oxygen consumption and a consequent reduction in weight gain (15). The bodyweight data from the current study are therefore especially reassuring, given that the majority of the neonates gained weight between the baseline and Visit 3 (Week 2), with all neonates gaining weight between the baseline and Visit 4.

The primary endpoint of the current study, change from baseline in the number of apnea events following the initial loading dose, was assessed in the overall population, all of whom had experienced at least four apnea events over a 24 h period. Such infants are at risk of a range of long-term negative consequences including neurological development (1). One of the few studies examining the long-term benefits of caffeine citrate in neonates is the CAP trial, in which patients were followed up with at the age of 11 years (12). Those who received caffeine citrate as a neonate had an improved expiratory flow (16) and a reduced risk of motor impairment (13) at follow-up compared with those neonates who did not receive caffeine.

The overall safety profile of caffeine citrate seen in this study is consistent with that in a large post-authorization safety study, which evaluated the clinical use, outcomes, and the safety profile in 506 neonates (17). Adverse drug reactions were reported in 4.2% of the neonates; the only event to occur in more than 1% of neonates was tachycardia (in 2.4%), none of which was considered serious.

Given all the infants in this study were being managed according to current best (international) clinical practices (and indeed the study protocol was amended to ensure it met these conditions), the results should be generalizable. However, an obvious limitation of this study is the lack of a control arm, especially in terms of the interpretation of some of the secondary endpoints. The use of a placebo comparator would have been unethical in this population, given caffeine citrate is approved and is standard in the care of apnea in neonates. Furthermore, the only other first-line treatments available are theophylline and aminophylline. Although theophylline has similar short-term efficacy to caffeine citrate, it has therapeutic disadvantages, including higher rates of toxicity than caffeine citrate (5, 6). In addition, neither theophylline nor aminophylline are approved for the

management of apnea of prematurity in China. The use of theophylline or aminophylline as an active comparator would therefore be difficult to justify in this population—indeed, such a design could potentially also be argued as being unethical. The current single-arm design was therefore considered the most appropriate to address the overall study aim. Importantly, the study was specifically designed around the primary endpoint, which can be interpreted without a comparator group. Another aspect of the study that makes interpretation of the secondary endpoints challenging is the small proportion of neonates who required maintenance therapy for 2 or 4 weeks—this does however suggest that caffeine citrate provided a rapid improvement in apnea. Finally, although the study was multicentered, it was conducted in a single country. Although this limits the generalizability of the results, the rationale for conducting the study was driven by a post-approval regulatory request.

In conclusion, in this large, prospective, open-label study, premature infants with a history of apnea who received caffeine citrate were significantly less likely to experience future apnea events. The study helps to validate the recommendations to use caffeine citrate for such neonates.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on submission of a valid research proposal to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the independent ethics committees or research boards at each institution. Written informed consent to participate in this study was provided by the participants' parents or legal guardians.

AUTHOR CONTRIBUTIONS

AG, JL, DS, SN, and LF contributed to the conception and design of the study, and to the interpretation of the data. LD, XT, CC, and XG contributed to the acquisition and interpretation of the data. All authors revised the manuscript critically for intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00076/full#supplementary-material

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Conflict of Interest: LF, AG, JL, DS, and SN are employed by Chiesi, the sponsor of the study.

LD, XT, CC, and XG declare that they have no competing financial interests that might have influenced the work described in this manuscript.

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BRIEF RESEARCH REPORT
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Light or Deep Pressure: Medical Staff Members Differ Extensively in Their Tactile Stimulation During Preterm Apnea

Sven Martin[1], *Ulrich Herbert Thome*[2], *Martin Grunwald*[1] and *Stephanie Margarete Mueller*[1]*

[1] Haptic Research Lab, Paul Flechsig Institute for Brain Research, Leipzig University, Leipzig, Germany, [2] Department of Neonatology, University Hospital Leipzig, Leipzig, Germany

Background: Even though tactile stimulation is common practice to terminate preterm apnea, the style and intensity of these interventions is not specified during theoretical or practical training and has never been clinically evaluated.

Objective: The present study was designed to analyze the various modes of tactile stimulation used to terminate preterm apnea and measure the pressure intensity and frequency of these stimulations.

Methods: A model with the size and weight of an actual preterm infant was equipped with sensor technology to measure stimulation pressure and frequency of tactile stimulation. Additionally a camera system was used to record hand positions and stimulation modes. Seventy medical staff members took part in the experiment.

Results: We found extreme between subjects differences in stimulation pressure that could not be explained by professional experience but, to a degree, depended on apnea intensity. Pressures ranged from 11.11 to 226.87 mbar during low intensity apnea and from 9.89 to 428.15 mbar during high intensity apnea. The majority of participants used rhythmic stimulation movements with a mean frequency of ∼1 Hz. Different modes (rubbing, squeezing, tickling, and tapping) and finger positions were used.

Conclusion: Medical staff members intuitively adjust their tactile stimulation pressure depending on the premature infants' apnea intensity. However, mean pressure values varied greatly between subjects, with similar pressure ranges for low and high intensity apnea. The question remains which pressure intensities are necessary or sufficient for the task. It is reasonable to assume that some stimulation types may be more effective in rapidly terminating an apneic event.

Keywords: neonatology, very low birth weight, pressure sensor, stimulation frequency, apnea of prematurity, treatment

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Stuart Brian Hooper, Monash University, Australia

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Daniele Trevisanuto, University Hospital of Padua, Italy
Kazumichi Fujioka, Kobe University, Japan

***Correspondence:**
Stephanie Margarete Mueller
s.mueller@medizin.uni-leipzig.de

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INTRODUCTION

Despite preventive measures, repetitive apneas occur in nearly all very low birth weight infants (1–4). Generally, the monitoring system will set off an alarm if an infant's oxygen saturation is low or bradycardia occurs which will prompt medical staff to investigate the cause of the alarm. If a central apnea is detected, the most established nonpharmacological practice is to administer gentle

tactile stimulation to the infant's foot, hand, or torso. In most cases, these stimuli are sufficient to stabilize autonomous respiration. If gentle stimulation does not improve the parameters, more forceful tactile stimulations are applied, most commonly to the sole of the foot. Tactile stimulation has been shown to positively influence the occurrence and duration of preterm apnea (5–7).

While tactile stimulation is common practice, the style and intensity of tactile interventions have not been specified. Even though this intervention is used to treat highly critical situations with potentially life-long adverse effects if left untreated, the treatment approach is highly subjective. That means it is unclear what techniques and pressures are used by medical staff and if they differ in effectivity. We presume that each medical staff member has a different internal concept about what are gentle and what are strong tactile stimulations. To date no attempt has been made to objectively measure the different pressure intensities that are used to treat central apnea in premature infants. Similarly, no classification exists of the different modes of tactile foot stimulation. Do all staff members implicitly share an understanding of what 'tactile stimulation' means? Or are different approaches like squeezing, rubbing or stroking applied? And if so, how do they choose one or the other and do they differ in pressure intensity?

In the present study, we want to document the various modes of stimulation and measure their corresponding frequencies and pressure intensities. We expected to find a significant association of pressure and frequency with apnea intensity. Also we expected to find differences in applied pressure between the various modes of stimulation (e.g., squeezing, rubbing, stroking). In addition, we intended to analyze if mode and intensity of tactile stimulation are influenced by professional experience and age. Due to subjective nature of the task we expected to find pronounced between-subjects variance.

For medical as well as ethical reasons, using prototype electrical sensors on a premature infant's body was not considered. Therefore we developed a model, which resembles the size and weight of an actual preterm infant. The model was equipped with sensor technology designed to measure stimulation pressure and frequency of tactile stimulation. Additionally a camera system was used to record hand positions and stimulation modes.

MATERIALS AND METHODS

Model and Sensors

We used a small baby puppet as a basis for our model. The hollow polyvinyl chloride (PVC) scaffolding of the doll was filled with small sandbags to match the weight of a premature infant of 1,000 g. A water filled pouch (31.1 mm × 38.2 mm × 9.1 mm) was attached to the sole of the right foot (**Figure 1**) which was connected to a pressure sensor (24PCCFA6D, Honeywell Int. Inc., Morristown, New Jersey, US) that registered any pressure that was applied to the pouch (measuring range: ±1034.21 mbar). The sensor output was registered by a Sigma/Delta analog-to-digital-converter (MCP3423-E/UN, Microchip Technology Inc., Chandler, Arizona, US) with a 14 Bit resolution and a mean sampling rate of 60 samples per second.

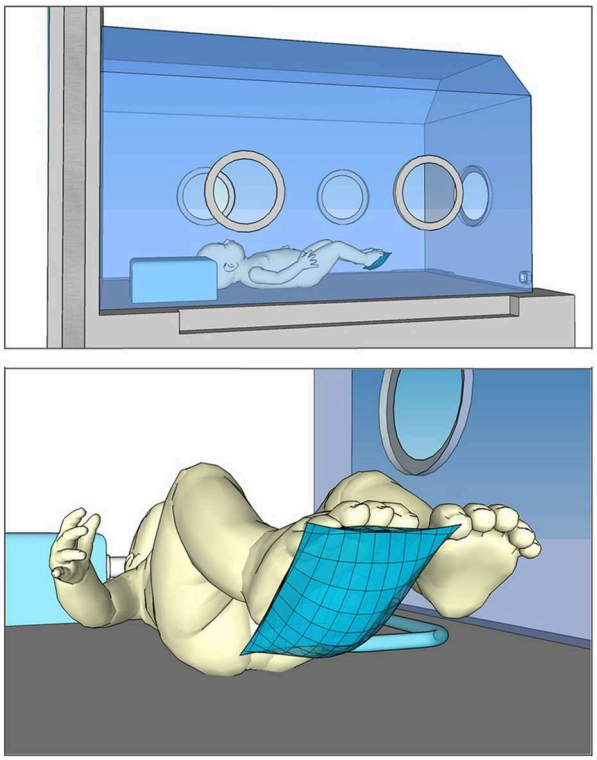

FIGURE 1 | Schematic representation of the experimental setting. Top: Model preterm infant inside the incubator. Bottom: Water filled pouch (pressure sensor) on the model's foot.

The infant model and measurement equipment were set up inside a state-of-the-art incubator. The manual stimulation process was videotaped via a webcam (Logitech C270; 640 × 480 pixel; 30 frames per second) which was attached to the incubator wall with a suction flange.

Experimental Setting and Instructions

The study was conducted on several consecutive days on a quiet corridor of a university NICU. Upon arrival participants were informed about the setup and the experimental procedure. They were allowed to reach inside the incubator and familiarize themselves with the model infant and the sensory equipment. Demographic characteristics (age, gender, professional experience, work place, and handedness) of the participant were gathered. If no further questions occurred, the participant was asked to perform an apnea intervention as he/she would in real life if an apnea alarm of low urgency occurred. Low apnea urgency was defined by verbal instruction as a minimal drop in oxygen saturation (The alarm of the monitoring system of the patient indicates a drop of oxygen saturation slightly below the lower alarm limit ("yellow" alarm). After ∼20 seconds of stimulation the participant was informed that the vital parameters of the infant model continued to deteriorate. Deep

apnea was defined as prolonged apnea with very low oxygen saturation and bradycardia ("You realize that your present intervention is not effective in stopping the apnea. The oxygen saturation drops further and heart rate slows down. How would you proceed?"). To simulate a nearly natural course of events apnea intensity was not randomized. In a preliminary round nursing staff have been asked about their usual procedure. The answers were condensed into this standardized instruction.

The participants were free to use any mode and duration of stimulation they chose. Most participants indicated how they would assess the apnea before they began an intervention. Besides foot stimulation participants also chose to stimulate the hand or torso and lift up the head or upper body of the model. Participants did not wear surgical gloves during the experiment to avoid measurement distortion due to friction between the latex gloves and the pressure sensor.

The duration of the trial was between 5 and 10 min per participant.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board of the Medical Faculty, University of Leipzig.

Parameters

Per person, two mean pressure values (mbar) were calculated from the raw data: one for low apnea intensity and one for high apnea intensity. Maximal pressure values were extracted for both apnea intensities. Furthermore, for those participants who performed rhythmic stimulation the stimulation frequency was computed.

To accomplish this, proprietary software was developed to synchronize the video signal and the data from the pressure sensor. Through this software we were able to denote the beginning and the end of the stimulation process and to exclude all pressure values ≤ 0 (overshooting or stimulation pauses) from the calculation of the means.

In addition, the video data were used to classify the positions of hand and fingers during foot stimulation (stimulation modes).

Participants

$N = 70$ full-time nurses of a university NICU participated in the present study. Of these $n = 42$ worked at the Intensive Care Unit (ICU) and $n = 28$ were employed at Intermediate Care (IMC). Preterm infants on the IMC are generally more stable and apneic events occur less often, however, nurses take care of more infants simultaneously.

Mean age of the participants was $M = 37.12$ years ($SD = 11.74$; range: 19–60). Gender was predominantly female with only $n = 3$ male participants. Their mean professional experience was $M = 14.03$ years ($SD = 12.93$; range: 1–42). All participants were right handed according to a test of handedness (8), took part voluntarily and gave written informed consent.

All tests were conducted between 12:30 pm and 3 pm during shift changeover.

Analyses

Due to limitations in normal distribution Wilcoxon signed rank and Mann Whitney *U*-tests were used for group comparisons. Spearman correlations (2-tailed) were used to assess the association between stimulation pressure, age and experience. Alpha was set at 5%. SPSS software version 24.0 was used (9). All datasets for this study are included in the manuscript/**Supplementary Material**.

RESULTS

Apnea Intensity

Mean pressure during low intensity apnea (LIA) was $M = 65.14$ mbar ($SD = 44.15$; Median = 50.83; Range: 11.11–226.87) with an average maximal value of M(max_LIA) = 143.23 mbar ($SD = 96.26$; Median = 110.06; smallest maximal value = 16.93, largest maximal value = 456.70).

Mean pressure during high intensity apnea (HIA) was $M = 126.09$mbar ($SD = 75.33$; Median = 108.41; Range: 9.89 – 428.15) with an average maximal value of M(max_HIA) = 253.42mbar (SD = 147.76; Median = 240.01; smallest maximal value = 40.66, largest maximal value = 768.76).

Group medians ($z = -6.781$, $p < 0.001$) and the average maximal values ($z = -6.463$, $p < 0.001$) differed significantly between LIA and HIA.

Rhythmic stimulation was used by $n = 62$ participants during LIA and $n = 58$ participants during HIA. The remaining $n = 9$ (LIA) and $n = 12$ (HIA) participants performed single or multiple isolated stimulations. The frequency of rhythmic stimulation was statistically equal ($z = -0.508$, $p = 0.611$) for LIA (M_{freq} =1.01 Hz; $SD = 0.85$; Median: 0.78; Range: 0.11–5.66) and HIA ($M_{\text{freq}} = 0.92$Hz; $SD = 0.61$; Median: 0.77; Range: 0.26–3.75).

Two main modes of stimulation were observed: Rubbing movements were performed by 81.4 and 80% of participants during LIA and HIA, respectively. During both LIA and HIA 14.3% squeezed the foot. The remaining 4.3% (LIA) and 5.7% (HIA) participants performed tickle or tapping stimulations (**Table 1**). Pressure was statistically equal for rubbing and squeezing stimulation (**Supplementary Table 1**). To rub or squeeze the foot participants used six different finger positions (**Figure 2**). Most participants ($n = 61$) used the same mode of stimulation during LIA and HIA. Of these, $n = 14$ switched to a different finger. Mean pressure values varied greatly between subjects and fingers, ranging from 11.11 to 226.87 mbar during LIA and from 9.89 to 428.15 mbar during HIA (**Figure 3**).

Professional Experience, Age and Workplace

Stimulation pressure of the participants who worked at the ICU did not differ from those who worked at the IMC (**Supplementary Table 2**).

Correlative analyses of age and stimulation pressure (mean and maximal value) did not reveal any associations (LIA: r_{mean} =0.019, $p = 0.873$; $r_{\text{max}} = 0.135$, $p = 0.266$; HIA: $r_{\text{mean}} = 0.049$, p =0.689; r_{max} =0.157, $p = 0.195$). Professional experience and stimulation pressure did not show any correlative associations either (LIA: $r_{\text{mean}} = -0.039$, $p = 0.749$; r_{max} =0.071, $p = 0.559$; HIA: r_{mean} =0.062, $p = 0.610$; r_{max} =0.159, $p = 0.188$).

We did find, however, highly significant correlation coefficients of the pressures applied during LIA and HIA.

TABLE 1 | Mean and maximal stimulation pressure in millibar of different stimulation modes and their occurrence rates.

	Squeezing					Rubbing						Tickle	Tapping
	Thumb	Thumb tip	Index finger	Two fingers	Whole hand	Thumb	Thumb tip	Index finger	Index finger tip	Two fingers	Whole hand		
Low Apnea Intensity (LIA)													
	N = 1	*N* = 3	*N* = 1	*N* = 2	*N* = 3	*N* = 29	*N* = 10	*N* = 9	*N* = 3	*N* = 5	*N* = 1	*N* = 2	*N* = 1
Median	226.87	48,45	98.54	99.60	59.54	48.15	53.00	58.52	27.56	101.20	38.83	26.70	14.44
M	226.87	52.69	98.54	99.60	66.63	60.26	60.62	65.35	40.97	101.22	38.83	26.70	14.44
SD	-	9.28	-	59.18	44.99	37.86	39.26	37.42	23.44	60.47	-	18.66	
Median max	315.64	115,63	158.44	248.74	163.12	94.52	99.84	106.73	64.83	264.85	120.80	67.21	36.30
M max	315.64	168.20	158.44	248.74	155.57	125.47	129.43	152.75	94.33	240.13	120.80	67.21	36.30
SD max	-	114.72	-	53.97	100.76	84.18	78.16	109.99	54.97	148.02	-	42.89	
High Apnea Intensity (HIA)													
	N = 2	*N* = 3	*N* = 0	*N* = 0	*N* = 5	*N* = 27	*N* = 12	*N* = 8	*N* = 2	*N* = 6	*N* = 1	*N* = 2	*N* = 2
Median	127.07	121.52	-	-	175.59	87.77	123.19	122.78	158.04	122.39	143.15	52.63	22.11
M	127.07	134.63	-	-	176.30	119.54	125.49	142.86	158.04	133.59	143.15	52.63	22.11
SD	141.13	53.17	-	-	73.20	87.92	45.28	83.57	73.82	54.01	-	19.93	17.28
Median max	180.15	238.15	-	-	339.25	155.57	279.58	203.67	350.12	288.67	354.08	144.56	68.01
M max	180.15	273.78	-	-	407.72	222.79	262.62	252.44	350.12	308.89	354.08	144.56	68.01
SD max	191.61	96.69	-	-	153.12	155.07	122.35	143.87	219.17	120.22	-	59.25	38.69

M, mean pressure across participants; SD, standard deviation; Mmax, mean of the maximal pressure values; SDmax, standard deviation of Mmax.

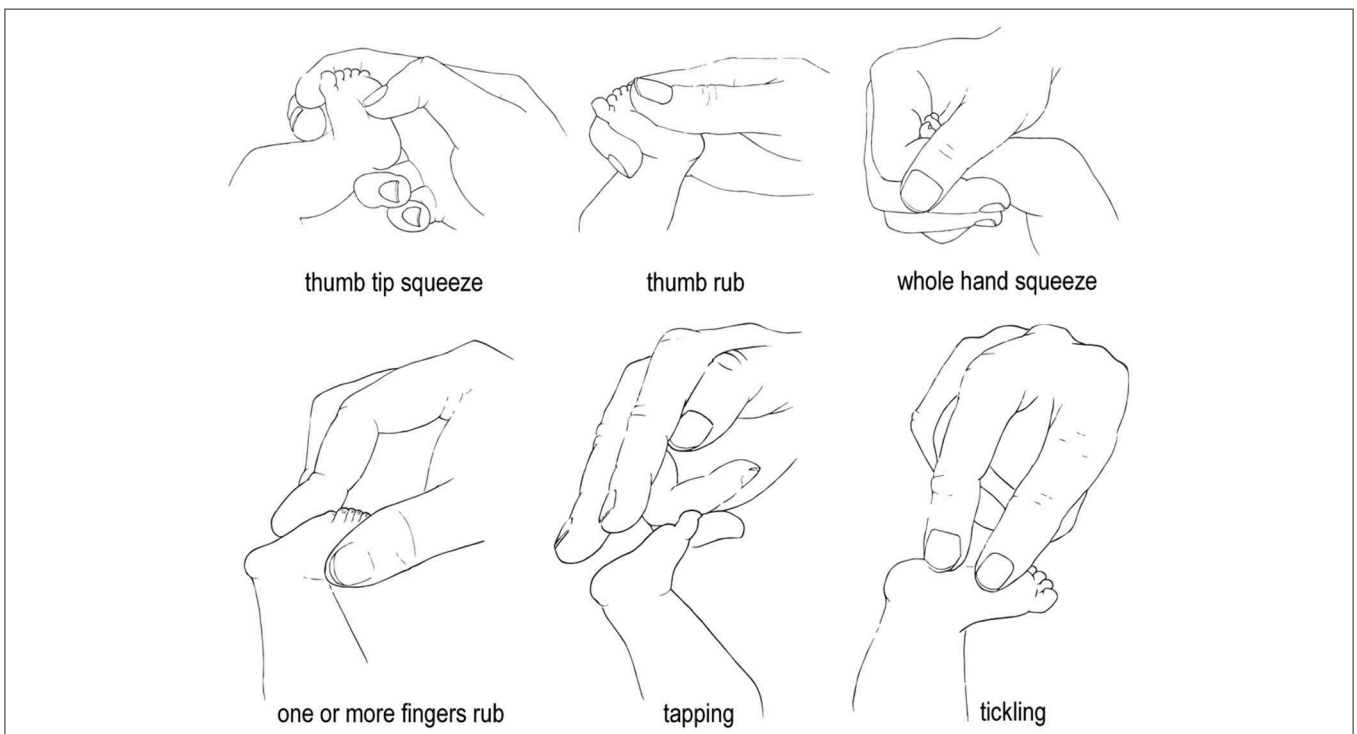

FIGURE 2 | Illustration of typical finger positions and stimulation modes. Drawings by Anna Zender.

The mean pressures used during LIA and HIA were strongly correlated (r_{mean} =0.689, $p < 0.001$). The maximal pressure values used during LIA and HIA were also strongly correlated (r_{max} =0.683, $p < 0.001$).

DISCUSSION

The present study was designed to analyze the various modes of tactile stimulation used to terminate preterm apnea and measure

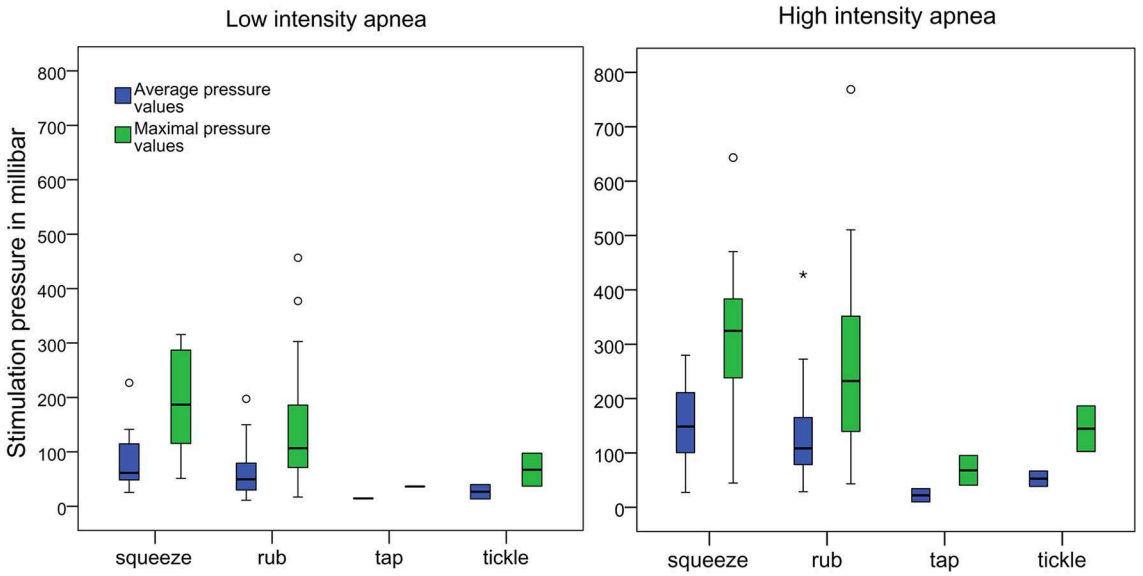

FIGURE 3 | Boxplots of the average and maximal pressure values of the four stimulation types during low intensity apnea (LIA) and high intensity apnea (HIA). Fat horizontal lines mark the medians. Circles and stars indicate outlier values.

the pressure intensity and frequency of these stimulations on a model puppet. Even though tactile stimulation is common practice to terminate apneic events, the style and intensity of these interventions is not specified during theoretical or practical training and has never been evaluated.

As hypothesized, we found significant differences in stimulation pressures depending on apnea intensity. Participants applied significantly less pressure when heart rate and oxygen level were borderline normal than when heart rate and oxygen level continued to decline. Accordingly, medical staff members intuitively adjust their tactile stimulation pressure depending on the premature infants' biomarkers. However, mean pressure values varied greatly between subjects, ranging from 11.11 to 226.87mbar during low intensity apnea and from 9.89 to 428.15mbar during high intensity apnea. That means that during both low and high apnea intensity participants showed a similarly wide range of stimulation pressures. We also found a highly significant correlation of pressures used during LIA and HIA. In other words, participants who used strong pressure during LIA were also among those who used strong pressure during HIA. Therefore, the question arises, if there is a minimally necessary pressure to influence an apneic event and if some of the stronger pressure values may be excessive. The absolutely largest maximal pressure value applied momentarily by a participant was 768.76 mbar. Given the very delicate nature of premature infants' skin some of the shear forces, especially if applied with a fingernail, may be unnecessarily painful, possibly even damaging.

To offer some reference to the applied pressures we conducted a comparative measurement with a conventional blood pressure gauge for preterm infants. As a result, the maximal pressure during blood pressure measurement was 95.79 mbar. In relation to this, only the mean tactile pressure during low intensity apnea (M_{LIA} = 65.14 mbar) was smaller than the maximal value of the blood pressure cuff. During high intensity apnea all but 4 participants used mean pressures that were stronger than the maximal values during blood pressure reading.

As expected, medical staff members used different modes (rubbing, squeezing, tickling, and tapping) and finger positions to perform foot stimulations. Rubbing and squeezing were most commonly used, but did not differ in stimulation pressure due to high levels of variance. Descriptively tickling and tapping reached the lowest mean pressure values. Overall six different finger positions were observed. Statistical comparisons of the mean pressures of different finger positions were not possible due to low numbers. The majority of participants used rhythmic stimulation movements with a mean frequency of ∼1 Hz. Stimulation frequency was the same during low and high intensity apnea.

The variance in mode and force of stimulation was not associated with professional experience (range: 1–42 years) or workplace (ICU or IMC). We conclude, that the between subjects variance in stimulation pressure cannot be explained by experience-based learning.

Because we used a model instead of a real infant and the biological parameters of the child were announced instead of indicated by an alarm the results of the present study should be used with caution. Even though the experimenter repeatedly urged the participants to do as they would in real life, the artificial situation may have influence the applied pressures.

Since all medical staff members showed the same confidence in their ability to disrupt an apneic event with their individual stimulation strategy, the question remains which pressure

intensities are necessary or sufficient for the task. It is reasonable to assume that some stimulation types may be more effective in rapidly terminating an apneic event.

Future studies should also try to assess whether different modes of stimulation and pressure intensities influence the duration and occurrence frequency of apnea.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the Medical Faculty, University of Leipzig. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SMa organized the database. SMu performed the statistical analysis. SMa wrote the first draft of the manuscript. All authors contributed to conception, design of the study, manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00102/full#supplementary-material

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ORIGINAL RESEARCH
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Study on the Relationship Between Respiratory Distress Syndrome and *SP-A1* (rs1059057) Gene Polymorphism in Mongolian Very Premature Infants

Xiaoli Wang[1], *Yuheng Zhang*[1], *Hua Mei*[1]*, *Caiyan An*[2]*, *Chunzhi Liu*[1], *Yayu Zhang*[1], *Yanbo Zhang*[1] *and Chun Xin*[1]

[1] Division of Neonatology, Department of Pediatric, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China, [2] Clinical Medical Research Center of the Affiliated Hospital, Inner Mongolia Medical University, Hohhot, China

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Edited by:
Yuan Shi,
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Li Wang,
Daping Hospital, China

***Correspondence:**
Hua Mei
meihuayani@sina.com
Caiyan An
acy_1999@163.com

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Aim: To study the relationship between rs1059057 polymorphism of pulmonary surfactant protein A1 (SP-A1) and respiratory distress syndrome (RDS) in Mongolian very premature infants.

Methods: Applying the strategy of case-control study, 120 Mongolian RDS very premature infants (58 males and 62 females) in the western part of Inner Mongolia were selected as the case group, and 120 subjects of non-RDS very premature infants (56 males and 64 females) with the same nationality, same sex and similar gestational age were used as the control group. The single nucleotide polymorphism (SNP) site rs1059057 of *SP-A1* was genotyped using polymerase chain reaction-single strand conformational polymorphism (PCR-SSCP).

Results: Two genotypes, *A/G* and *A/A*, were detected at the *SP-A1* rs1059057 locus in the western part of Inner Mongolia. In the case group, the frequencies of two genotypes were 53 and 47%, and the frequencies of *A* allele and *G* allele were 73 and 27%, respectively. In the control group, the frequencies of the two genotypes were 42 and 58%, and the frequencies of *A* allele and *G* allele were 79 and 21%, respectively. There was no significant difference in the genotype frequency of *SP-A1* (rs1059057) locus between the case group and the control group ($X^2 = 3.275$, $P > 0.05$), and no significant difference in allele frequency between the case group and the control group ($X^2 = 2.255$, $P > 0.05$).

Conclusion: The genotypes and allele frequencies of *SP-A1* (rs1059057) locus were not associated with the incidence of RDS in Mongolian very premature infants in western Inner Mongolia.

Keywords: respiratory distress syndrome (RDS), pulmonary surfactant protein A1 (SP-A1), gene polymorphism, Mongolian very premature infants, respiratory tract management

INTRODUCTION

Neonatal respiratory distress syndrome (NRDS), also known as hyaline membrane disease, is mainly due to the lack of pulmonary surfactant (PS), which leads to an increase in alveolar wall surface tension and decreased pulmonary compliance, and initiates newborn's sexual dyspnea shortly after birth, even clinical syndromes of respiratory failure (1). NRDS often occurs in premature infants, especially in premature infants within 34 weeks (2). The probability of NRDS in premature infants with gestational age within 28 weeks is up to 80% (3, 4). At present, international and domestic medical technologies are developing rapidly, and the levels of medical treatment in neonatal ward are also constantly improving. The survival problem of NRDS children has been basically solved, yet prognosis and treatment have remained difficult. Therefore, the respiratory tract management problems of children with NRDS should not be underestimated, we still need to continue to strive our efforts on them.

Pulmonary surfactant protein-A1 is a kind of alveolar cell surfactant protein synthesized and released by type II alveolar epithelium. The causes of NRDS are very complicated and there are many different opinions nowdays, but many studies have found that the lack and abnormal changes of SP-A1 are the main cause of NRDS (5–7). Studies have demonstrated that the incidence of NRDS may be related to *SP-A* gene polymorphism (8, 9). Through the cDNA sequence analysis of SP-A1, it is confirmed that SP-A1 has four alleles (6A, $6A^2$, $6A^3$, and $6A^4$), and different gene mutations can make the expression of SP-A1 abnormal, which leads to the occurrence of respiratory diseases (10). It is worth noting that there are some differences in the relationship between SP-A gene polymorphism and diseases among different regions, races, and ethnic groups (11). Therefore, our team detected the polymorphism of *SP-A1* gene locus in Mongolian very premature infants in western Inner Mongolia to explore its role in NRDS etiology. This paper mainly introduces the relationship between the gene polymorphism rs1059057 of *SP-A1* and the RDS of Mongolian very premature infants, in order to provide help for the rescue of Mongolian very premature infants in the western part of Inner Mongolia.

SUBJECTS AND METHODS

Subjects

Applying the strategy of case-control study, one hundred and twenty Mongolian RDS very premature infants (58 males and 62 females) who were hospitalized in the department of neonatal pediatrics in our hospital from January 2012 to January 2019 were selected as the case group. The selection criteria were as follows: ① the immediate family members have lived in Mongolians in the western part of Inner Mongolia for at least three generations. ② The sex ratio was roughly balanced, the birth weight was 0.138∼ 0.184 kg, and the birth weight was 28^{+3} weeks ≤ the gestational age < 32 weeks. ③ In accordance with the diagnostic criteria of RDS issued in Europe (4). One hundred and twenty Mongolian non-RDS very early infants (56 males and 64 females) who were hospitalized in the department of neonatal pediatrics in our hospital with the same period, race, sex, and gestational age were selected as the control group. The subjects were selected according to the following criteria: ① the immediate family members have lived in Mongolians in the western part of Inner Mongolia for at least three generations. ② The sex ratio was roughly balanced, the birth weight was 0.142∼0.190 kg, 29^{+1} week ≤ the gestational age < 32 weeks. ③ The common chest X-ray showed no pulmonary inflammation and RDS, and the blood routine and C-reactive protein examination showed no obvious infection.

The following subjects were excluded: ① congenital or genetic metabolic diseases; ② laboratory examination showed severe infection; ③ severe history of intrauterine or postnatal asphyxia; ④ gestational diabetes mellitus; ⑤ other diseases that may be accompanied by respiratory symptoms; ⑥ there are other diseases and related factors that may affect the experimental results.

Materials and Reagents

Blood Genome DNA extraction Kit and the main regents of PCR were from Sangon Bioengineering Co., Ltd (Shanghai, China). 6 × DNA Loading Dye and DNA Ladder Mix (100–10,000 bp) were from ThemoFisher (R0611 and SM0332). SanPrep column PCR product purification kit was also from Sangon Bioengineering Co., Ltd (Shanghai, China). Main reagent of DNA sequencing were from ThermoFisher (Applied Biosystems™).

Sample Collection and Processing

The venous blood of Mongolian RDS very premature infants and non-RDS very premature infants in western Inner Mongolia was collected and stored at −80°C. At the same time, the clinical data of gestational age, sex, and birth weight of very premature infants in the experimental group were collected.

Extraction and Detection of Genome DNA From Samples

The sample DNA was extracted strictly according to the instructions of genomic DNA extraction kit (Sangon Bioengineering Co., Ltd, Shanghai) and the extracted DNA was stored at −20°C. DNA quality detection: ① Five microliter of DNA solution was loaded to a 1% agarose gel and the gel was run in 1xTAE at 120 V. A single clear band indicates the extracted DNA to be intact and of sufficient concentration for a PCR reaction. ② The concentration and purity were detected by spectrophotometer, and 1 μL DNA solution was loaded to Nanodrop to determine the OD values. A value of OD260/280 between 1.7 and 2.0 demonstrates a reliable quality of the extracted DNA.

SP-A1 Gene Polymorphism

We selected rs1059057 of SP-A1 as our study SNP, according to the following reasons: ① SNP database Genbank (http://www.Ncbi.Gov/genBank) provides a number of SNP research sites located in the first functional gene (*SP-A1*) of *SP-A*, in which the site studied in this paper is numbered as rs1059057 in the genebank dbSNP database. ② Global minor allele frequency (GMAF) of rs1059057 is 0.08(>5%), and the

minimum allele >5% meets the basic conditions for SNP selecting. ③ Located in exon 6 of this gene coding region.

PCR Amplification

① Template: zero point five to one microliter of blood containing anticoagulant (EDTAK2) was directly added to 20 μL PCR reaction system. ② Paraffin-embedded tissue samples: a single 10 μm paraffin section was treated with 50–200 μL PCR reaction buffer containing 0.2 mg/ml protease K. The volume of buffer was proportional to the size of tissue section. The sample was bathed at 60°C for 1 h, and then inactivated at 98°C for 10 min. After cooling, the sample was centrifuged (16,000 × g, 2 min) and the supernatant was transferred to a new tube. One to two microliter of the supernatant was used as the template in a 20 μL PCR reaction. ③ PCR reaction conditions: pre-denaturation at 95°C for 3 min; denaturation at 94°C for 30 s; annealing at 55–60°C for 25–30 s; extension at 72°C for 30–50 s; 35 cycles followed by repair-extension at 72°C for 5–8 min. ④ PCR reaction: one to two microliter of template DNA at 20–50 ng/μL; forward primer 10 μM, 2 μL; reverse primer10 μM, 2 μL; dNTP (mix) 10 mM, 2 μL; 10×Taq Buffer (with $MgCl_2$), 5 μL Taq enzyme 5 U/μL, 0.5 μL; Add ddH_2O to 50 μL.

Genotyping of DNA Samples

The rs1059057 locus of *SP-A1* gene was genotyped by PCR-SSCP method. The results were compared with the normal sequences of Gen Bank gene pool and analyzed by sequence analysis software.

Statistical Analysis

The data were analyzed by SPSS 22.0 statistical software. The sex, mode of delivery, and regularity of lung maturation in the two groups were tested by X^2-test. Birth weight and gestational age were tested by *t*-test, and the ratio of gene polymorphism rs1059057 in *SP-A1* was tested by X^2-test. Statistical significance was considered at $P < 0.05$. A power calculation on the G*Power program was also performed, based on Cohen's method. When an effect size index of 0.2 (corresponding to "weak to moderate" gene effect) was used the present sample size revealed a >93% power for detection of significant association ($a < 0.05$).

RESULTS

No significant difference in sex, gestational age, birth weight, mode of birth, cesarean section, and regular lung maturation was observed between the case and the control groups ($P > 0.05$) (**Table 1**).

Two genotypes of *A/G and A/A* were detected at *SP-A1 rs1059057* locus in both the case and control group. In the case group, the frequencies of the two genotypes were 53 and 47%, and the frequencies of *A* allele and *G* allele were 73 and 27%, respectively. In the control group, the frequencies of the two genotypes were 42 and 58%, and the frequencies of *A* allele and *G* allele were 79 and 21%, respectively. No significant difference was observed in the genotype frequency of *SP-A1* (rs1059057) locus between the case and the control groups ($X^2 = 3.275$, $P > 0.05$). No significant difference was observed neither in the allele frequencies between the case and the control groups ($X^2 = 2.255$, $P > 0.05$) (**Table 2**).

DISCUSSION

Alveolar surfactant (PS) is a complex composed of lipids and special proteins synthesized and secreted by type II alveolar epithelial cells. It contains four protein components, SP-A, SP-B, SP-C, and SP-D, which play different roles based on functional and structural differences. They can not only reduce alveolar surface tension, but also participate in innate immunity (12). The lack of pulmonary surfactant can lead to the increase of alveolar surface tension and alveolar rupture, and affect the ventilation function of lung tissue, which has been considered to be the main cause of NRDS by previous studies, especially for very early births of younger gestational age (13). SP-A is a protein encoded by the *SFTPA1* gene on the long arm of chromosome 10, which is a member of the C-lectin subfamily (14,

TABLE 2 | Distribution of alleles and genotypes of *SP-A1* rs1059057 locus in two groups (cases, %).

Group	Number	Genotypic frequency		Allele frequency	
		AA	*AG*	*A*	*G*
Case	120	56 (47)	64 (53)	176 (73)	64 (27)
Control	120	70 (58)	50 (42)	190 (79)	50 (21)
x^2		3.275		2.255	
P		0.070		0.133	

Statistical significance was considered at P < 0.05.

TABLE 1 | Comparison of general data of the case-control groups.

General circumstances \ Group	Number	Case	Control	x^2/t	*P*
Gender (male/female)	120	58/62	56/64	0.067	0.800
Gestational age (x ± *s*,w)	120	30.40 ± 0.70	30.56 ± 0.66	−1.736	0.084
Birth weight (x ± *s*,g)	120	1584.75 ± 139.01	1620.83 ± 161.34	−1.856	0.065
Maternal pregnancy hypertension (yes/no)	120	53/67	42/78	0.000	1.000
Premature rupture of membranes (yes/no)	120	35/85	40/80	0.000	1.000
Intramuscular injection of dexamethasone (yes/no)	120	84/36	79/41	0.478	0.489
Cesarean section (yes/no)	120	64/56	57/63	0.817	0.366

Statistical significance was considered at P < 0.05.

15) and play an important role in regulating the homeostasis of pulmonary surfactants and preventing the invasion of respiratory pathogens by binding lipids and carbohydrates on the surface of microorganisms (16). SP-A is one of the most abundant surface active proteins secreted by type II alveolar epithelial cells, and its deficiency affects the normal function of pulmonary and the metabolism of alveolar surfactant (17). SP-A can participate in the inflammatory response of lung tissue by binding to pathogens (18). Meanwhile SP-A can also reflect the injury of alveolar epithelial cells (19). SP-A1 protein is one of the subtypes of SP-A protein, the deficiency or structural changes of which lead to abnormal alveolar function and affect the normal function of lung tissue. It was found that mice lacking only SP-A did not develop RDS after full-term birth (20), while mice with the *SP-A* gene knocked out were more likely to develop pulmonary infection (21). It can be inferred that RDS in very premature infants may occur under the dual effects of decreased lung function and pulmonary inflammation caused by lack of SP-A.

A large number of studies have found that *SP-A* gene polymorphism is related to the occurrence of RDS in premature infants. For example, Jo et al. found that $1A^0$ variants and homozygous $1A^0/1A^0$ genotypes of *SP-A2* gene had protective effects on RDS (22). The haplotype ($6A^2/1A^0$) of *SP-A1* may be closely related to the occurrence of RDS in an independent population, but this risk is limited only to very premature infants (23). *SP-A1* haplotype $6A^4$ is a susceptible factor for RDS in late Greek preterm infants (24). In a study on the United States population, it was found that some *SP-A* alleles/haplotypes were susceptible factors of RDS, such as ($1A^0$, $6A^2$, $1A^0/6A^2$), and some *SP-A* alleles/haplotypes were protective factors of RDS, such as ($1A^5$, $6A^4$, $1A^5/6A^4$) (25); However, the results obtained in the population study in South Korea were the opposite (22). A Dutch study of twin fetuses found that their haplotypes were not associated with the occurrence of RDS (26). Chang et al. found that the polymorphism of *SP-A* (+186A/G) gene was closely related to the occurrence of RDS in premature infants (27). In addition, our previous studies found that the genotype and allele frequencies of *SP-A1* (SNP) locus (rs1059047, and rs1136450) were not associated with the occurrence of RDS in Mongolian premature infants, and the haploid $6A^2$ of *SP-A1* allele was the susceptible gene of RDS in Mongolian premature infants, and haploid 6A was the protective gene (28). Thus, it can be seen that the association between *SP-A* gene polymorphism and the occurrence of RDS is affected by race or regional environment.

The main purpose of this study is to investigate the relationship between *SP-A1* rs1059057 locus gene polymorphism and Mongolian very premature infants' RDS. Our results showed that there was no significant association between the frequencies of genotypes and alleles of *SP-A1* rs1059057 locus and the incidence of RDS in Mongolian very preterm infants, which is consistent with the results of Dutch twin study (26) and our previous study on *SP-A1* (SNP) locus (rs1059047, rs1136450) (28). However, many previous studies also showed that *SP-A* gene polymorphism was related to the occurrence of RDS in premature infants (23–25, 27), which is inconsistent with our results. Two points are especially worthy of notice. The first is that the populations are different in those studies. The samples selected in our study are very premature Mongolian infants in the western part of Inner Mongolia, and the experimental results may be influenced by the stratification of the population, regional environment, ethnic groups, lifestyle, and other factors. Another point is that the technical approaches and sample size are different. The samples selected in this study were very premature Mongolian infants in western Inner Mongolia, the sample size was relatively small, and the time span of collecting samples was long; therefore, the genotyping method of PCR-SSCP used in the early stage of our research was used throughout the study for the consistency of experimental methods and conditions, which may also have a certain impact on the experimental results.

In a word, in this study we investigated the relationship between the rs1059057 gene polymorphism of *SP-A1* and the RDS of Mongolian very premature infants in western Inner Mongolia, and found that the gene polymorphism of *SP-A1* (rs1059057) was not related to the incidence of RDS in Mongolian very premature infants in western Inner Mongolia. Of course, it is necessary to increase the sample size and adopt more advanced and more sensitive detection methods to verify our current results in the future.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the affiliated Hospital of Inner Mongolia Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HM, CA, CL, YayZ, YanZ, and CX has made contributions to the research, design, revision and finalization of manuscripts. XW and YuZ contributed to the analysis and interpretation of the data and the drafting of the manuscript.

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Application of Neurally Adjusted Ventilatory Assist in Premature Neonates Less Than 1,500 Grams With Established or Evolving Bronchopulmonary Dysplasia

*Xiao Rong[1], Feng Liang[2], Yuan-Jing Li[2], Hong Liang[2], Xiao-Peng Zhao[2], Hong-Mei Zou[2], Wei-Neng Lu[1], Hui Shi[2], Jing-Hua Zhang[2], Rui-Lian Guan[2], Yi Sun[2] and Huayan Zhang[2,3]**

[1] Division of Neonatology, Guangzhou Women and Children's Medical Center Affiliated With Jinan University, Guanghzou, China, [2] Division of Neonatology, Guangzhou Women and Children's Medical Center, Guanghzou, China, [3] Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

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Edited by:
Yuan Shi,
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***Correspondence:**
Huayan Zhang
zhangh@email.chop.edu

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Background: Very low birth weight premature (VLBW) infants with bronchopulmonary dysplasia (BPD) often need prolonged respiratory support, which is associated with worse outcomes. The application of neurally adjusted ventilatory assist ventilation (NAVA) in infants with BPD has rarely been reported. This study investigated whether NAVA is safe and can reduce the duration respiratory support in VLBW premature infants with established or evolving BPD.

Methods: This retrospective matched-cohort study included patients admitted to our NICU between April 2017 to April 2019 who were born at <32 weeks' gestation with birthweight of <1,500 g. The study groups (NAVA group) were infants who received NAVA ventilation as a sequel mode of ventilation after at least 2 weeks of traditional respiratory support after birth. The control group were preterm infants who required traditional respiratory support beyond first 2 weeks of life and were closely matched to the NAVA patients by gestational age and birthweight. The primary outcome was to compare the total duration of respiratory support between the NAVA group and the control group. The secondary outcomes were comparisons of duration of invasive and non-invasive support, oxygen therapy, length of stay, severity of BPD, weight gain and sedation need between the groups.

Results: There were no significant differences between NAVA group and control group in the primary and most of the secondary outcomes (all $P > 0.05$). However, NAVA was well tolerated and there was a decrease in the need of sedation ($p = 0.012$) after switching to NAVA.

Conclusion: NAVA, when used as a sequel mode of ventilation, in premature neonates <1,500 g with evolving or established BPD showed a similar effect compared to conventional ventilation in respiratory outcomes. NAVA can be safely used in this patient population and potentially can decrease the need of sedation.

Keywords: premature infants, bronchopulmonary dysplasia, BPD, neurally adjusted ventilatory assist ventilation, NAVA, very low birth weight, VLBW, mechanical ventilation

INTRODUCTION

Bronchopulmonary dysplasia (BPD), a chronic neonatal lung disease, is among the most common and severe sequelae of preterm birth. Despite improvements in neonatal care over the past 30 years, BPD rates have not declined. Stoll et al. reported an overall incidence of BPD in infants born 22–28 weeks' gestation age (GA) and 401–1,500 g birthweight increased from 36% in 1993–1997 to 45% in 2008–2012 in the United States (1). In a recently published study, Lui et al. also reported increased incidence of BPD in very low birthweight infants (VLBW born at <1,500 g) and <32 weeks' GA over time in most of the 11 high-income countries participating in the International Network for Evaluating Outcomes (iNeo) of neonates. The overall rate of BPD in the iNeo network increased from 23.3% in 2007–2011 to 27.5% in 2012-2015 (2). BPD predisposes survivors to adverse neurodevelopment and cardiorespiratory health and is associated with substantial resource utilization and cost (3, 4). Unfortunately, there are few evidence-based therapies to prevent and treat the disease (1, 5, 6). Infants with BPD often require prolonged respiratory support, and some need extended duration of intubated mechanical ventilation. Current data suggest that both prolonged mechanical ventilation and respiratory support of any type is associated with poor outcomes in extremely low birthweight infants (7, 8). Therefore, decreasing the total duration of respiratory support, especially invasive mechanical ventilation is important in improving the outcomes of preterm infants.

Neurally adjusted ventilatory assist ventilation (NAVA) is a new form of ventilation developed in the recent years. In this form of ventilation, ventilatory support is initiated when an electrical signal from the diaphragm muscle is detected by a probe placed in the distal esophagus. The level of inspiratory pressure provided is synchronized and in proportion to the electrical activity of the diaphragm (EAdi) (9, 10). Compared to traditional ventilation with pressure or flow triggering mechanisms, this mode of ventilation may provide better synchronized breath and more precise amount of support that fits the patients' needs without sedation. NAVA has been considered to be one of the gentlest ventilation modes available and by improving patient-ventilator synchrony, it may potentially reduce ventilator induced lung injury, and decrease sedation use in preterm infants (11–13). However, data on the safety and efficacy of NAVA ventilation in the VLBW infants, especially in infants with evolving or established BPD are limited. In this study, we aimed to test the hypothesis that NAVA ventilation reduced the duration of respiratory support in VLBW infants with evolving or established BPD and examine the safety of NAVA use in this population.

MATERIALS AND METHODS

This retrospective matched-cohort study was performed in the Neonatal Intensive Care Unit (NICU) of Guangzhou Women and Children's Medical Center, China between April 2017 to April 2019. The study cohort included preterm infants born at <32 weeks' gestational age (GA) and birthweight < 1,500 g with evolving or established BPD, who were switched to NAVA ventilation from invasive or non-invasive ventilation beyond 2 weeks of life. A comparison cohort was selected by 1 to 1 matching to the NAVA patient using the following matching criteria: (1) preterm infants born at <32 weeks' GA and birthweight < 1,500 g who were admitted to our NICU during the study period; (2) matching to a patient in the NAVA group first by similar GA (within 10 days), and then by similar birthweight (within 250 g); (3) required respiratory support of CPAP or higher (BiPAP, NIPPV, or intubated mechanical ventilation) for more than 2 weeks after birth and remained on traditional respiratory support modes during the hospital stay. Infants who had congenital anomalies and who were transferred from another hospital to undergo surgery were excluded.

NAVA or NIV-NAVA was provided by the SERVO-n (Maquet Critical Care AB, Solna, Sweden) ventilator system with the NAVA option. When switching from conventional mechanical ventilation to NAVA, the NAVA level was changed to match the peak inspiratory pressures delivered during the previous conventional ventilation. During the NAVA or NIV-NAVA support, the NAVA level was adjusted, based on EAdi (EAdi peak between 5 and 15 μV), transcutaneous carbon dioxide ($tcPCO_2$) monitoring and blood gas analyses. PEEP was initially set at the same level as the previous ventilator PEEP and then adjusted based on chest X-ray findings to avoid hyperinflation. Settings similar to previous ventilator settings were used as the backup settings, with the "apnea time" set at 2–4 s initially and modified based on the severity of apnea. Back up ventilation will start when the ventilator could not detect the EAdi for more than the "apnea time" (set by the caregiver). When the ventilator detected a sufficient EAdi signal, the NAVA ventilation would resume. Weaning from NAVA support was done by decreasing the NAVA level and prolonging the apnea time in a step-wise manner as tolerated without clinical deterioration. When the NAVA level was <1, and the apnea time was more than 6 s, we would extubate and change to NIV-NAVA, nasal continuous positive airway pressure (nCPAP) or biphasic positive airway pressure (BiPAP) or wean to oxygen, according to the decision of the physician on duty. When changing from invasive NAVA mode to NIV-NAVA mode, the NAVA level would be increased to 1.5–2.0 and adjusted based on the EAdi (EAdi peak between 5 and 15 μV), tcPCO2 monitoring and/or blood gas analyses, with the same PEEP level, the "apnea time" would be decrease to 4 s, and FiO_2 adjusted by the SPO_2 target. To wean from NIV-NAVA, we would again decrease the NAVA level and prolong the apnea time in a step-wise manner as tolerated. When the NAVA level was <0.5, and the apnea time was more than 10 s, we would change to nCPAP or BiPAP or wean to oxygen, according to the decision of the physician on duty.

The primary outcome was to compare the total duration of respiratory support between the NAVA group and the control group. Secondary outcomes examined include severity of BPD, duration of invasive and non-invasive ventilation, duration of total oxygen, rate of home oxygen therapy (HOT), length of hospital stay, weight gain, medications use for the treatment of BPD, duration of sedation requirements, as well as major complication during the NICU stay. Major complications

assessed included the incidences of necrotizing enterocolitis (NEC), late onset sepsis (LOS), intraventricular hemorrhage (IVH)/periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and patent ductus arteriosus (PDA).

BPD and severity of BPD were defined based on the NICHD consensus definition: infants are diagnosed to have BPD if they received an accumulative oxygen therapy of at least 28 days after birth; and at 36 weeks' postmenstrual age (PMA), to have mild BPD if breathing room air, moderate BPD if on <30% oxygen, and severe BPD if on at least 30% oxygen or on positive pressure support (12). Respiratory severity scores (RSS) were calculated using mean airway pressure (MAP) x inspired oxygen concentration (FiO_2). RSS has been shown to reflect the severity of respiratory illness and correlated well with an oxygenation marker, the oxygen index (OI) in newborn infants (13). RSS was calculated on admission and again on the day NAVA support was started for the infants in the NAVA group and their matched comparison patient. For example, if an infant in the NAVA group was changed to NAVA on day of life 29, RSS was calculated for that infant based on the MAP and FiO_2 requirement in the morning that day before changing to NAVA. The RSS for his/her matching comparison patient was calculated based on the level of support on day of life 29.

"Sedation use day" in this study was defined as the total number of days during which a sedative or analgesic medication (i.e., midazolam, fentanyl, or morphine) was used. The sedation/analgesia policy in our NICU has been evolving over time. Before October 2018, Midazolam was the first-choice sedative when the preterm infants showed frequent desaturation and retractions due to agitation with supplemental oxygen needs over 40%. Fentanyl drip would be added if the infants still shows signs of agitation with midazolam up to 0.2 mg/kg.h. After October 2018, morphine has become the first-line chronic analgesia/sedation choice for infants on mechanical ventilation in our unit. Midazolam would be added when the infant was considered needing more sedation on morphine dose of 0.06 mg/kg.h. The doses of these medication would be gradually weaned when the infant was clinically improving and weaning on the ventilator support. Fentanyl is routinely administered before invasive procedures, such as thoracentesis, paracentesis, and chest tube placement.

The use of common medications frequently used in infants with evolving or established BPD were recorded. These medications included corticosteroid, diuretics and bronchodilators. In addition, the total accumulative dose of dexamethasone per kilogram body weight was also recorded. Indications for the use of indications were at the discretion of the treating physician and may include steroid use to facilitate extubation or weaning on ventilator support, diuretic use to decrease pulmonary edema and bronchodilator use for clinical wheezing.

In addition to comparing the NAVA patients with the matched comparison group. Patients in the NAVA group also served as self-controls. The weight gain velocity and the days on sedation/analgesia medication before and after starting on NAVA support were compared in the NAVA group. All data were abstracted from patients' medical records and the Institutional Review Board of Guangzhou Women and Children's Medical Center approved this study.

Statistical Analysis

Demographic data were summarized with standard descriptive statistics. For continuous measurement data, normal distribution variables were analyzed by *t*-test, and non-normal distribution variables were analyzed by Wilcolxon rank-sum test. Categorical variables between groups were analyzed using chi-square test. All statistical analyses were performed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, United States). In addition, for all statistical analyses executed, we considered a two-tailed *p*-value of <0.05 to be statistically significant.

RESULTS

During the two-year period, 15 preterm infants who were born at <32 weeks' GA and <1,500 g received NAVA ventilation. 15 infants who received traditional modes of respiratory support during the same period were selected by matching 1:1 to the NAVA patients according to the matching criteria. **Table 1** presents the basic characteristics of the NAVA group and the matched comparison group. There was no significant difference between the two groups.

The patients in the NAVA group were transferred to NAVA support at a median time of 34 days (quartile range 29, 39 days) after birth. Out of the 15 patients, 3 were started on NAVA prior to 28 days of life (on day of life 17, 25, and 27) and therefore considered to have evolving BPD at the time. Indications for

TABLE 1 | Basic characteristics of the study groups.

	Groups		*p*
	NAVA ***n* = 15**	**Control** ***n* = 15**	
Basic demographics			
Gestational age, week ± SD*	28.1 ± 1.4	28.0 ± 1.7	0.881
Birth weight g ± SD*	965.33 ± 217.48	998.67 ± 185.62	0.655
Gender, Male/Female	11/4	10/5	0.690
Cesarean section, *n* (%)	11 (73.3)	11 (73.3)	1.000
Antenatal steroids, *n* (%)	9 (81.8)	7 (63.6)	0.464
Apgar at 1 min, median (Q1, Q3)	8 (4,9)	8 (6,8)	0.680
Apgar at 5 min, median (Q1, Q3)	8 (7,9)	8 (8,9)	0.949
Severity of lung disease			
RSS on admission*	3.59 ± 1.37	3.63 ± 1.41	0.942
RSS when changed to NAVA mode*	2.52 ± 0.80	2.02 ± 1.93	0.369
Severity of BPD			
Moderate/severe	7/8	12/3	0.058

*RSS, respiratory severity score. Normal distribution variables were presented as mean ± SD, non-normal distribution variables were presented as median (quartile range). Normal distribution variables were analyzed by t-test, and non-normal distribution variables were analyzed by Wilcolxon rank-sum test. *Analyzed by t-test, others analyzed by Wilcolxon rank-sum test.*

transferring to NAVA included prolonged need of invasive or non-invasive ventilation beyond first 2 weeks of life and projected to not able to wean from ventilation within a short period of time. There were 12 patients changed from synchronized intermittent mandatory ventilation (SIMV) to NAVA invasive ventilation. Among these 12 patients, 10 were successfully extubated to either NIV-NAVA or nasal continuous positive airway pressure (nCPAP) or bi-level positive airway pressure (BiPAP) support. Two patients had clinical deterioration and need to convert to high frequency oscillatory ventilation (HFOV) or back to SIMV. However, both were on NAVA for more than 72 h (3 days and 8 days). Two patients directly extubated from SIMV mode to NIV-NAVA mode, then weaned to nCPAP. One patient who was on non-invasive ventilation for more than 28 days was changed from BiPAP mode to NIV-NAVA, and then successfully weaned to low flow oxygen.

There were no significant differences between the NAVA group and the control group in the primary outcome of total duration of respiratory support and most of the secondary outcomes including duration of invasive ventilation, duration of non-invasive ventilation, duration of oxygen therapy, length of hospital stay, severity of BPD, weight gain, or total days on sedation medications (all $p > 0.05$, **Table 2**). All patients in this study had moderate to severe BPD. In the NAVA group, patients were transferred to NAVA support on median GA of 33 weeks (quartile range 32, 35). Twelve of the fifteen patients in this group can be diagnosed with BPD at the time of starting on NAVA. However, only one patient reached 36 weeks PMA and could be diagnosed with severe BPD at the time. Although there was a trend towards more severe BPD in the NAVA group, it did not reach statistical significance.

However, there were significant decrease in the need of sedation after changing to NAVA ventilation in the NAVA group (**Table 2**). Of the 15 patients in the NAVA, only the two patients who needed to convert back to SIMV or HFOV continued to required sedation. One patient on chronic morphine therapy before switching to NAVA weaned to a tapering dose of enteral morphine and the rest of 12 patients did not required any sedation after switching to NAVA.

Overall, NAVA ventilation was well tolerated without significant events and the rate of the common complications in the premature infants, including necrotizing enterocolitis, LOS, intraventricular hemorrhage/periventricular leukomalacia, ROP, and PDA were comparable between the two groups (all $P > 0.05$, **Table 3**). Medication therapy for BPD treatment and the rate of HOT were also similar between the two groups (**Table 4**).

TABLE 2 | Comparison of primary and secondary outcomes between the two groups.

	Groups		*p*
	NAVA ***n* = 15**	**Control** ***n* = 15**	
Total duration of respiratory support, days ± SD	60.4 ± 19.2	59.5 ± 26.3	0.867
Duration of invasive respiratory ventilation, days ± SD	35.7 ± 18.3	29.1 ± 23.2	0.40
Duration of non-invasive ventilation,days ± SD	24.7 ± 12.9	30.4 ± 15.0	0.277
Duration of oxygen therapy, days ± SD	76.1 ± 18.8	69.2 ± 22.1	0.362
Length of hospital stay,days ± SD	84.1 ± 21.2	83.9 ± 19.7	0.979
Weight gain, gram/d	19.9 ± 5.5	19.3 ± 5.4	0.744
Sedation use day, median (Q1, Q3)	17.0 (0.0, 39.0)	6.0 (3.0, 32.0)	0.683
	NAVA group		*p*
	Before NAVA	**After NAVA**	
Weight gain, gram/d	17.2 ± 6.1	20.4 ± 8.9	0.258
Sedation use day, median (Q1, Q3)	17.0 (0.0, 38.0)	0.0 (0.0,0.0)	0.012*

**There were significant decrease in the need of sedation after changing to NAVA ventilation in the NAVA group.*

TABLE 3 | Comparison of complications of premature infants between the two groups.

Complications	**Groups**		*p*
	NAVA ***n* = 15 (%)**	**Control** ***n* = 15(%)**	
NEC	1 (6.7)	3 (20.0)	0.283
IVH/PVL	6 (40.0)	6 (40.0)	1.000
LOS	12 (80.0)	8 (53.3)	0.121
ROP	13 (86.7)	10 (66.7)	0.195
ROP required surgical treatment	1 (6.7)	4 (26.7)	0.142
PDA	9 (60.0)	9 (60.0)	1.000
PDA required medical treatment	7 (46.7)	7 (46.7)	1.000
PDA required ligation	2 (13.3)	4 (26.7)	0.361

NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; LOS, late onset sepsis; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus.

DISCUSSION

This study examined the utility of NAVA ventilation in premature infants with evolving and established BPD. Infants were switched to NAVA ventilation after being on conventional mechanical ventilation or high-level non-invasive ventilation for extended period of time (median time to NAVA 34 days). Although the NAVA group and the control group in this study were similar in the basic demographics, there was a trend toward more severe BPD in the NAVA group (8/15 vs. 3/15), which did not reach statistical significance. This could suggest that NAVA was used in patients with more severe lung disease. Despite this, transition to NAVA ventilation was well tolerated in all patients with no complications.

There have been limited data available regarding the use of NAVA in the neonates. Most of these studies examined the very short-term effects of NAVA. Some reported improved patient-ventilator interaction, or decreased PIP within 24 h of

TABLE 4 | Comparison of medical treatments for BPD between the two groups.

	Groups		
	NAVA $n = 15$	**Control** $n = 15$	***p***
Medical therapies of BPD			
Corticosteroid (%)	5 (33.3%)	7 (46.7%)	0.456
Total amount of Dexamethasone(mg/kg)	1.47±0.66	1.19 ± 0.40	0.381
Diuretics (%)	6 (40.0%)	8 (53.3%)	0.464
Bronchodilators (%)	6 (40.0%)	10 (66.7%)	0.143
HOT (%)	3 (20.0%)	4 (26.7%)	0.666

Dexamethasone dose was the total accumulative dose of the medication. HOT, home oxygen therapy.

NAVA use (10, 14). Oda et al. reported NAVA use in 14 extremely low birth weight infants. There was no difference in the incidence of BPD, HOT or the duration of intubation when the NAVA group was compared to a historical control of 21 ELBW patients before the implementation of NAVA. Although no difference was found in the total duration of sedation use, midazolam was discontinued in all patients after switching to NAVA (15). We found similar result in our study that there was no difference in the total duration of sedation use, but the NAVA group had significantly decreased sedation use after switching to NAVA.

Very few studies have reported NAVA use in infants with evolving or established BPD. In a crossover study, Shetty et al. enrolled 9 premature infants with evolving or established BPD and reported lower oxygen index, FiO_2 requirement, PIP and MAP after switching to NAVA from assist control ventilation for 1 h (16). Jung et al. reported decreased RSS and ventilator variables within the first 24 h of switching from SIMV to NAVA (17). However, neither of these studies reported outcomes beyond 24 h of use of NAVA. Lee et al. examined the use of NAVA in 9 infants with severe BPD who were on chronic mechanical ventilation via tracheostomy and compared to 5 similar infants on pneumatically triggered ventilation. They found decreased cyanotic episodes, as well as reduced need for sedatives and dexamethasone (18). Our study focused on infants with evolving and established BPD and reported outcomes at NICU discharge as compared to GA and birthweight matched controls with BPD. We found no difference in the duration of respiratory support, HOT or length of stay. However, our study demonstrated that NAVA use was safe in this patient population and associated with decreased sedation needs after being on NAVA. This was probably because NAVA allowed for the patient to trigger the ventilator easier and faster than on the conventional ventilator triggering mechanism. The better patient-ventilator synchrony therefore making them more comfortable on the ventilator and less agitated. With the concerns that prolonged and high dose sedation may have negative effects on the long-term neurodevelopmental outcomes of very low birthweight preterm infants, decreased need for sedation on NAVA support may have longer-term benefits in this population.

There are several limitations of this study. First, with the retrospective nature of the study, there might be a variety of confounders that could influence the outcome of the study. The small sample size makes the statistical power low. The negative findings of study could therefore result from type II error due to the small sample size. Increasing the number of patients in the comparison group by matching two patients to one NAVA patient might be able to increase the statistical power. Unfortunately, we were unable to find enough patients who were on respiratory support of CPAP or higher for more than 2 weeks after birth that were also closely matched in both GA and BW to the NAVA patients, to enable this 2 to 1 matching. Second, it was very hard to find an optimal control group. We have tried to select patients that were as closely matched to the NAVA group as possible. Although the basic demographics and RSS were similar between the two groups, there was a non-statistically higher number of patients with severe BPD in the NAVA group, which could have been a result of selection bias. This could also contribute to the finding of no difference in the primary outcome of the study. Third, the criteria for the application of NAVA had not been established. Variations in the use of NAVA ventilation and medications could also affects the outcomes. Luckily, the staffing of medical team was stable and there was no significant variation in the medical management between different patients during the study period. Despite these limitations, our study provided more data for the utility of NAVA in patients with BPD.

CONCLUSION

NAVA, when used as a sequel mode of ventilation, in premature neonates born at <1,500 g with established or evolving BPD showed a similar effect compared to conventional ventilation in respiratory outcomes. NAVA can be safely used in this patient population and potentially can decrease the need of sedation. Prospective studies with larger sample size are needed to delineate the effect of NAVA in patients with BPD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research ethics committee of Guangzhou Women and Children's Medical Center. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XR made substantial contributions to the conception and design of the study, acquisition of data, and drafted the

initial manuscript. FL participated in the design of the study, performed all the data analysis, and approved the draft of the manuscript. Y-JL, HL, X-PZ, H-MZ, W-NL, HS, J-HZ, R-LG, and YS participated in data acquisition and approved the draft of the manuscript. HZ developed the original study design and protocol, supervised the analyses, interpreted the results, and critically revised all drafts of the manuscript including the final manuscript.

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Volume Guarantee High-Frequency Oscillatory Ventilation in Preterm Infants With RDS: Tidal Volume and DCO_2 Levels for Optimal Ventilation Using Open-Lung Strategies

Funda Tuzun[1], Burak Deliloglu[1], Merve Meryem Cengiz[1], Burcin Iscan[2], Nuray Duman[1] and Hasan Ozkan[1]*

[1] Division of Neonatology, Department of Pediatrics, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2] Division of Neonatology, Department of Pediatrics, Tinaztepe University Faculty of Medicine, Izmir, Turkey

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***Correspondence:**
Funda Tuzun
fundatuzun@gmail.com

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High frequency oscillatory ventilation with volume-guarantee (HFOV-VG) is a promising lung protective ventilator mode for the treatment of respiratory failure in newborns. However, indicators of optimal ventilation during HFOV-VG mode are not identified yet. In this study, we aimed to evaluate optimal high-frequency tidal volume (VThf) and the dissociation coefficient of CO_2 (DCO_2) levels to achieve normocapnia during HFOV-VG after lung recruitment in very low birthweight infants with respiratory distress syndrome (RDS). Preterm babies under the 32nd postmenstrual week with severe RDS that received HFOV-VG using open-lung strategy between January 2014 and January 2019 were retrospectively evaluated. All included patients were treated with the Dräger Babylog VN500 ventilator in the HFOV-VG mode. In total, 53 infants with a mean gestational age of 26.8 ± 2.3 weeks were evaluated. HFOV mean optimal airway pressure (MAPhf) level after lung recruitment was found to be 10.2 ± 1.7 mbar. Overall, the mean applied VThf per kg was 1.64 ± 0.25 mL/kg in the study sample. To provide normocapnia, the mean VThf was 1.61 ± 0.25 mL/kg and the mean DCO_2corr was 29.84 ± 7.88 $[mL/kg]^2/s$. No significant correlation was found between pCO_2 levels with VThf (per kg) or DCO_2corr levels. VThf levels to maintain normocarbia were significantly lower with 12 Hz frequency compared to 10 Hz frequency (1.50 ± 0.24 vs. 1.65 ± 0.25 mL/ kg, $p < 0.001$, respectively). A weak but significant positive correlation was found between mean airway pressure (MAPhf) and VThf levels. To our knowledge, this is the largest study to evaluate the optimal HFOV-VG settings in premature infants with RDS, using the open-lung strategy. According to the results, a specific set of numbers could not be recommended to achieve normocarbia. Following the trend of each patient and small adjustments according to the closely monitored pCO_2 levels seems logical.

Keywords: HFOV, volume guarantee, lung recruitment, VThf, DCO_2, frequency, RDS, lung-protective strategies

INTRODUCTION

Despite the rising trend of non-invasive ventilation techniques, up to 50% of extremely preterm infants having respiratory distress syndrome (RDS) need to be intubated and mechanically ventilated. Prevention of repeated opening and closing of the alveoli, avoiding fluctuant and excessive tidal volumes are the fundamentals of the lung protective mechanical ventilation (1). Volume-targeted ventilation (VTV) strategies are increasingly used in the care of neonates and offer many advantages by avoiding disproportionate tidal volumes (2, 3). High-frequency oscillatory ventilation (HFOV) has been used over 30 years in newborn babies with severe respiratory failure (4, 5). HFOV with volume guarantee (HFOV-VG) is a promising new ventilatory mode for the treatment of respiratory failure in newborns. Theoretically, HFOV-VG is expected to result in less lung injury since it reduces fluctuations of high frequency tidal volume (VThf), reduces the number of out-of-target pCO_2 values and provides fewer hypoxia attacks compared with HFOV (6, 7).

During HFOV-VG, the clinician can set a target VThf, and the ventilator will automatically adjust the amplitude pressure to supply the targeted VThf. Tight control of VThf and automatic adjustments in amplitude using HFOV-VG may be particularly useful when the respiratory mechanics change rapidly (6, 8). Previous studies demonstrated that during HFOV-VG, the VThf can vary from 1 s to another, but it is kept very close to the target VThf in the long term (9).

CO_2 excretion during HFOV is defined by the diffusion coefficient of CO2 (DCO_2) as an indicator of alveolar ventilation. Since DCO_2 (ml^2/s) is formulated by "$DCO_2 = f \times VThf^2$", even small changes in VThf affect DCO_2 more than changes in frequency (10–12). DCO_2 has been considered an important parameter in the follow-up of CO_2 elimination, however, its value providing normocapnia varies from patient to patient. Recently, weight-corrected DCO_2 ($[mL/kg]^2/s$) has been proposed to reduce inter-individual variability (7).

To ensure optimal benefit from the HFOV, the alveoli should be opened and kept open using optimal continuous distension pressures (13, 14). Though lung volume recruitment and appropriate tidal volume settings are considered important strategies for the success of HFOV-VG, optimal VThf parameters are not identified yet for preterm infants during the acute phase of RDS. This study's objective is to evaluate optimal VThf and DCO_2 levels to achieve normocapnia during HFOV-VG using open-lung strategy in very premature infants with RDS.

MATERIALS AND METHODS

Study Design, Patients, and Interventions

The retrospective observational study was carried out at the third level neonatal intensive care unit (NICU) at Dokuz Eylul University Hospital, between January 2014 and January 2019. The Ethical Committee of Dokuz Eylul University Faculty of Medicine approved the study protocol. Infants suffering from RDS between 23 and 32 weeks of gestation, who started HFOV-VG with lung recruitment maneuver within 72 h of life, were eligible for the study. Infants who had (i) congenital anomalies affecting the cardiopulmonary system or (ii) endotracheal tube leaks of over 40% or (iii) air leak syndromes or (iv) pulmonary hypertension were excluded.

All interventions were performed according to the unit's ventilation protocol by considering the infants' characteristics. Surfactant treatment was given according to the European Consensus Guidelines of that period. If surfactant was considered, 200 mg/kg (poractant alpha) was given to the first dose and repeated doses were given as 100 mg/kg (15, 16). The endotracheal tube diameter was selected according to the current NRP guidelines and the maximum tolerable tube leakage was 40% according to the operating principles of the ventilator and our unit's ventilation protocol (17). Suction was avoided unless clinically indicated. If suction was needed a closed system is preferred. All of these patients received fentanyl analgesia; strong sedatives and muscle relaxants were not used.

Ventilation Strategies

We have been using HFOV-VG as elective or early-rescue ventilation mode for infants who were failing conventional ventilation or would benefit from HFOV according to the opinion of the attending clinician. In general, HFOV-VG ventilation has been started with the following reasons: higher VT need in conventional VG ventilation (> 6 ml/ kg), high peak positive pressure requirement (over 20 mbar), diffuse lung atelectasis requiring lung recruitment, or high FiO2 need (40%) despite proper PEEP and surfactant therapy.

All patients were treated with a ventilator (Dräger Babylog VN500) in HFOV-VG mode. An optimal volume strategy was applied in all infants. Depending on HFOV-VG starting time, MAPhf level was initiated with 8 or 2 mbar above the MAPhf in conventional mechanical ventilation. The MAPhf was increased with steps of 1 mbar every 2–3 min until a critical opening pressure, where oxygenation no longer improved, or the fraction of inspired oxygen (FiO_2) was $\leq$0.30, to give an arterial oxygen saturation of 90–94%. Next, the MAPhf level was decreased by 1–2 mbar stepwise every 2–3 min to find the closing distending pressure. Finally, the lung was reopened again with the previously defined critical opening pressure and a MAPhf level 2 mbar above closing pressure was set, corresponding to optimal continuous distending pressure (18). The lung recruitment maneuver was performed under VG mode to allow amplitude fluctuations to obtain stable VThf levels. Recruitment was stopped in case of bradycardia (heart rate < 100) or hypotension.

All of the infants received a frequency between 10 and 12 Hz and an oscillatory inspiratory/expiratory ratio of 1:1. The amplitude limit ($Ampl_{max}$) was set at 10–15% above the average amplitude required to reach the target VThf. Subsequently, the set VThf was adjusted by the clinical team up or down in increments of 0.1–0.2 mL/kg if the pCO_2 value was outside the target range. Capillary blood gases were assessed 30 min after the initiation of HFOV-VG and repeated at intervals of 4–6 h or more often as needed using a blood gas analyzer (ABLTM 700 Radiometer, Copenhagen, Denmark). The consecutive blood

gases that belong to the period in which HFOV was applied continuously without interruption were selected for the study. The normocapnia was defined as pCO_2 ranging from 40 to 55 mm Hg. Fractional inspired oxygen concentration (FiO_2) was adjusted to obtain a SaO2 between 90 and 94% by a pulse oximeter.

Data Acquisition and Analysis

The flow of gases in the airway and tidal volume was measured continuously using a hot wire anemometer positioned in the airway entrance while undertaking HFOV+VG. Critical parameters such as MAPhf (Paw), ΔPhf (swinging pressure around the mean Paw), VThf (ml), and DCO_2 (mL^2/s) were followed using VentView 2.n software (Draeger, Lubeck, Germany). The mean values of these parameters were assessed over 10 min before blood gas analysis was recorded. All calculations and correlations regarding VThf were performed according to the tidal volume normalized to body weight and given as mL/kg. Daily respiratory mechanics and blood gas analysis results and follow-up data were collected from the electronic and published patients' files.

Statistics

The normality of data was determined by the Shapiro-Wilk test. According to the distribution pattern, continuous data were presented as mean ± standard deviation (SD) or median (25–75 percentile). The statistical significance of mean differences between two independent groups was tested using the independent *t*-test. To test the significance of the difference between the means or medians of parameters in three or more independent groups, one-way ANOVA or Kruskal Wallis tests were performed, respectively. The relationship between categorical variables was tested with chi-square analysis. Pearson's correlation analysis was performed to determine the correlations between selected parameters. The effect of multiple independent variables on pCO_2 and optimal VThf levels was tested using the general linear model.

Post-hoc power analysis for differences of means was performed using an online statistical tool, "OpenEpi" (19). SPSS software was used for all statistical analyses (*IBM SPSS Statistics* for Windows, Version 24.0. Armonk, NY). Statistical significance was set at $p < 0.05$.

RESULTS

In total, 53 babies were included in the study between January 2014 and January 2019. Mean gestational age and birth weight of the infants were 26.3 ± 2.3 weeks and 882 ± 286 grams, respectively.

All of the infants received surfactant therapy in the delivery room or in the NICU according to the intubation time. Poractant alfa was instilled at 200 mg/kg for the first dose and then repeated at 100 mg/kg if needed according to RDS guidelines (15, 16). Delivery room intubation was performed for 38 infants. Median intubation time for the remaining patients was 10 h (min-max: 1–53 h). In 14 of these patients, a 12 Hz frequency was used according to the decision of the consultant neonatologist. The patient characteristics are shown in **Table 1**.

Overall, the mean applied VThf per kg was 1.64 ± 0.25 mL/kg in the study sample. Of the 274 blood gases evaluated, 178 (65.2%) were in the normocarbic range, while the remaining were within the hypocarbic (53 blood gases, 19.4%) or hypercarbic (42 blood gases, 15.4%) range. Only nine patients needed VThf ≥2 mL/kg to overcome hypercarbia during follow-up, and none of these babies required VThf > 2.4 mL/kg and DCO_2corr >50 $[mL/kg]^2/s$ to control hypercapnia. Four patients needed VThf settings smaller than 1.25 mL/kg for maintaining normocarbia. The patients that need very low VThf volumes were extremely preterm infants born at gestational age under 25 weeks.

The mean VThf level yielding normocapnic blood gases was 1.61 ± 0.25 mL/kg. Mean VThf levels corresponding to these three pCO_2 categories did not significantly differ between one or the other (**Table 2**). No significant correlation was found between VThf values and the corresponding pCO_2 values during the follow-up period (**Figure 1A**). When the ventilatory settings corresponding to normocapnic blood gases were examined, there was a very weak but significant positive correlation between VThf and MAP values (0.319, $p < 0.001$) (**Figure 1B**).

Subgroup analysis according to the frequency demonstrated that VThf levels to achieve normocarbia were significantly lower with 12 Hz frequency compared to 10 Hz frequency (1. 50 ± 0.24 vs. 1.65 ± 0.25 ml/ kg, $p < 0.001$) (**Table 2**).

Overall, the mean DCO_2 level to obtain normocarbia was 25.67 ± 16.55 ml^2/s and weight-corrected mean DCO_2corr level providing normocarbia was calculated as 29.84 ± 7.88 $[mL/kg]^2/s$ (**Table 2**). There was no significant difference in DCO_2corr levels between normocapnic, hypercapnic, or hypocapnic blood gases levels ($p = 0{,}415$) (**Table 2**). A significant correlation could not have been found between DCO_2corr levels and pCO_2 values.

To test the effect of multiple factors on optimal VThf values (ml/kg), birth weight, gestational age, frequency, and MAPhf levels were tested in a model using a general linear model. The results demonstrated that frequency and MAPhf levels were the main effectors of optimal VThf value ($p = 0.02$ and $p = 0.003$, respectively). Main ventilatory parameters were given as Supplementary Data (**Table S1**).

TABLE 1 | Patient characteristics.

Characteristic	*n* = 53
Gestational age (wk), mean ± SD	26.9 ± 2.4
Birth weight (g), mean ± SD	882 ± 286
Antenatal steroid, *n* (%)	30 (56.6)
Cesarean section *n* (%)	41 (77.4)
Male gender, *n* (%)	30 (56.6)
5' Apgar score, median (25–75 p)*	7 (5–8)
Intubation time (hour), median (25–75 p)	1 (1–1.5)
HFOV start time (hour), median (25–75 p)	8 (2–16)
Surfactant doses, median (25–75 p)	2 (1–3)
HFO duration (hour), (25–75 p)	49 (25–60)

**Median (25–75 percentile).*

TABLE 2 | Ventilatory parameters corresponding to three pCO2 categories*.

Parameter	Hypocarbia $n = 53$	Normocarbia $n = 178$	Hypercarbia $n = 42$	p
Vt hf (mL/kg)*				
f 10 Hz	1.70 ± 0.24	1.65 ± 0.25#	1.68 ± 0.22	0.50
f 12 Hz	1.64 ± 0.27	1.50 ± 0.24#	1.60 ± 0.20	0.09
Amplitude (mbar)**				
f 10 Hz	15 (13–20)	17 (14–20)	18.7 (15–25)	0.119
f 12 Hz	15 (12–20)	16 (12–18)	15 (10.5–16)	0.823
DCO_2 ml^2/s*				
f 10 Hz	26.1 ± 17.2	27.2 ± 17.3	29.7 ± 14.4	0.724
f 12 Hz	16.1 ± 6.6	21.06 ± 13.5	32.1 ± 17.6	0.085
DCO_{2corr} $[mL/kg]^2/s$*				
f 10 Hz	31.0 ± 8.2	29.4 ± 8.0	29.3 ± 6.3	0.599
f 12 Hz	32.9 ± 9.4	30.1 ± 7.4	35.4 ± 5.8	0.085
MAPhf (mbar)**				
f 10 Hz	10 (9–10)	10 (10–12)	10.5 (9.6–12)	<0.001
f 12 Hz	9 (8–10)	10 (8–11)	10.5 (9.6–12)	0.117
FiO2*				
f 10 Hz	31.5 ± 21.2	29.6 ± 11.0	32.4 ± 15.4	0.561
f 12 Hz	36.0 ± 17.5	30.2 ± 9.8	34.0 ± 8.0	0.113

*Mean ± SD.
**Median (25–75 percentile).
#Significant difference between two means $p < 0.001$.

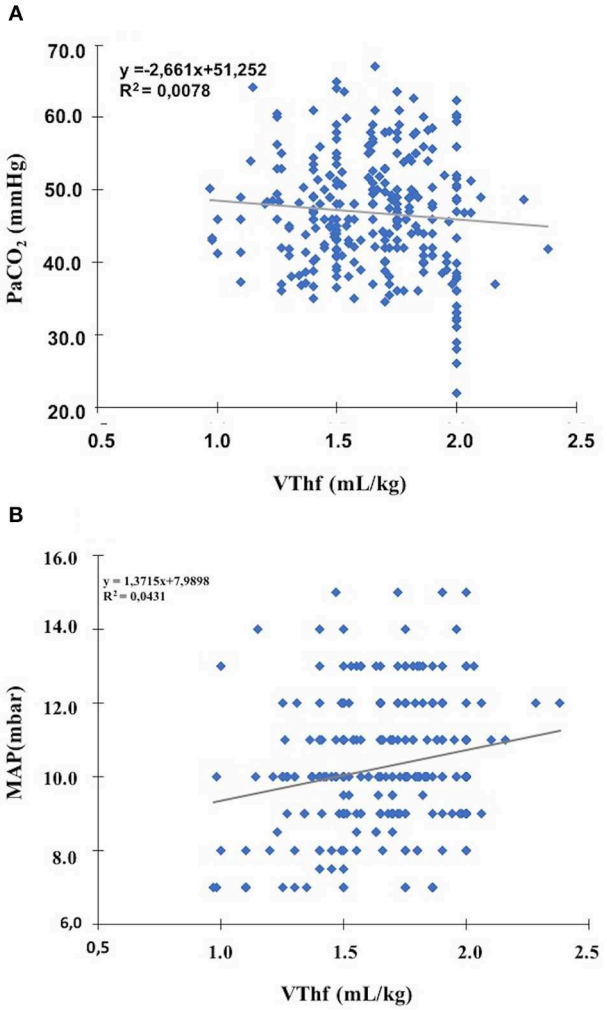

FIGURE 1 | Pearson correlation analysis between VThf, pCO_2, and MAPhf levels **(A)** no significant correlation between all VThf and pCO2 levels (Pearson coefficient = 0.01, $p = 0.899$) **(B)** a very weak, but significant correlation between optimal VThf and MAPhf levels (Pearson coefficient = 317, $p < 0.001$).

DISCUSSION

To our knowledge, this is the largest case series to evaluate HFOV-VG settings in premature infants with RDS. Results demonstrated that neither optimal VThf (mL/ kg) nor DCO_2corr levels ($[mL/kg]^2/s$) correlated with pCO_2 levels. It was also confirmed that higher frequencies need lower delivered tidal volumes for adequate ventilation during HFOV-VG.

HFOV- VG mode makes it possible to maintain DCO_2 and normocapnia while lowering VThf and increasing the frequency in an attempt to minimize lung injury (20, 21). In the present study, mean VThf levels corresponding normocapnic blood gases were around 1.50 cc mL /kg for 12 Hz, and 1.65 mL/ kg for 10 Hz. González-Pacheco et al. demonstrated that adequate VThf was 1.46 mL/kg for ELBW infants and 1.57 mL/kg for infants weighing 1,000–2,000 g using higher frequencies up to 17 Hz (21). In our study a VThf level over 2.4 mL/kg was not required. Consistent with these results, Belteki et al. demonstrated that VThf or DCO_2 have poor correlation with CO_2 levels but a volume of >2.5 mL/kg VThf is rarely needed (7). Parallel to our results, Zimova-Herknerova et al. showed that the median delivered normocapnic VThf during HFOV was 1.67 mL/kg in a heterogeneous group of newborns ventilated by HFOV at any time during their hospital stay (12). Few studies support higher VThf requirement during HFOV varying between 1.75–1.90 mL/kg using a constant frequency of 10 Hz (6, 22). Besides the frequency, gestational age, HFOV starting time, practicing open lung strategies, and severity of lung disease are possible determiners of VThf need. Our population was composed of a near- homogeneous group of patients suffering from RDS. We started HFOV as an early-rescue mode rather than rescue HFOV and median starting time (8 h) is indicating the initial phase of RDS rather than the other problems, such as hemodynamically significant PDA, pulmonary edema, VILI, chronic lung disease etc.

Although VThf is considered a key element for minute ventilation in HFOV, our study did not demonstrate a correlation between VThf and pCO_2 levels. Even the same patients had out-of-target pCO_2 levels with the same VThf levels. As a possible reason, allowing spontaneous breathing without the use of heavy sedatives or muscle relaxants may have affected the gas exchange in these infants in different ways. The narrow range of VThf values applied in this study may explain the similarity of mean VThf values corresponding to normocapnic

and hypo or hypercarbic blood gases. If we used higher VT values above 2 ml/kg, we might have seen the expected relationship between hypocarbia and high VT. Furthermore, we considered a relative narrow pCO_2 range between 40 and 55 mmHg as normocarbia. Despite this, 65% of the blood gases were normocarbic. If a larger range (5–8 kpa = 37.5–60 mmHg) had been considered as in the other studies (9) the rate of normocarbic blood gases would have been increased to 87.6%, a successful rate considering the high incidence of hypocapnia during HFOV.

Currently, a VThf requirement according to the patient's characteristics such as birth weight and disease severity is not as well-known as in conventional VG ventilation. However, a weak but significant correlation between MAPhf and optimal VThf levels in this study may indicate the need for higher VThf levels in infants with more severe lung disease or inadequate lung recruitment. Patients who responded well to recruitment probably needed lower MAPhf and VThf levels due to decreased physiologic dead space and shunt, similar to ARDS patients (23). However, there is no strong evidence to support this assumption.

In our study, the DCO_2 level was highly variable according to the birth weight of the infants. Then we considered the calculation of the DCO_2corr levels as previously recommended (7). Although DCO_2 is considered the best predictor of CO_2 elimination during HFOV, our study could not demonstrate a significant correlation between optimal VThf and DCO_2 levels. Targeting a weight-corrected DCO_2corr achieved more static levels; however, this adjustment does not change the results because there was not a significant correlation between DCO_2corr and VThf levels.

This study has several limitations. The most important limitation was its retrospective design. This patient group was selected since it was a relatively homogenous population composed of very preterm infants and started HFOV-VG because of severe RDS in the first 72 h of life. Although the selected study population is not heterogeneous, these results may not be generalized for all premature infants with RDS. Although the retrospective design and longer study period may be questionable, over the 5 years, our unit's RDS and HFOV-VG protocols have not been modified too much. The lack of continuous CO_2 monitoring during the infants' course is another important limitation. This restriction may lead to an incomplete representation of the real-time relationship between evaluated parameters. Ideally, instant monitoring of pCO_2 and ventilation parameters prospectively in a homogeneous patient group will allow a clear understanding of the relationship between them.

In summary, results could not allow making any recommendation on an optimal starting value for VThf. Optimal levels are dynamic and vary according to the instantaneous features of individuals. Therefore, it is unrealistic to recommend a general VThf value to all patients. The needs of each patient should be monitored within itself and the settings should be titrated according to close pCO_2 monitoring.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dokuz Eylul University Clinical Researches Ethical Commity. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FT, BD, and HO contributed to the conception and design of the study. ND, BI, MC, and BD organized the database. FT performed the statistical analysis and wrote the manuscript. BI wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00105/full#supplementary-material

Table S1 | Main ventilatory parameters.

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Use of Autologous Cord Blood Mononuclear Cells Infusion for the Prevention of Bronchopulmonary Dysplasia in Extremely Preterm Neonates: A Study Protocol for a Placebo-Controlled Randomized Multicenter Trial [NCT03053076]

*Zhuxiao Ren[1†], Xu Fang[2†], Qi Zhang[2†], Y. G. Mai[3], X. Y. Tang[4], Q. Q. Wang[5], C. H. Lai[6], W. H. Mo[7], Y. H. Dai[8], Q. Meng[9], Jing Wu[10], Z. Z. Ao[11], H. Q. Jiang[12], Yong Yang[13], L. H. Qu[14], C. B. Deng[15], Wei Wei[16], Yongsheng Li[16], QI Wang[2,16] and Jie Yang[2]**

[1] Department of Neonatology, School of Medicine, Jinan University, Guangzhou, China, [2] Department of Neonatology, Guangdong Women and Children Hospital, Guangzhou Medical University, Guangzhou, China, [3] Department of Neonatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [4] Department of Neonatology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [5] Department of Neonatology, Nanfang Hospital, Southern Medical University, Guangzhou, China, [6] Department of Neonatology, Zhongshan Boai Hospital, Zhongshan, China, [7] Department of Neonatology, Foshan Chancheng Central Hospital, Foshan, China, [8] Department of Neonatology, Foshan Women and Children Hospital, Foshan, China, [9] Department of Neonatology, Guangdong Second Provincial General Hospital, Guangzhou, China, [10] Department of Neonatology, Hexian Memorial Affiliated Hospital of Southern Medical University, Guangzhou, China, [11] Department of Neonatology, Heyuan Women and Children Hospital, Heyuan, China, [12] Department of Neonatology, Jiangmen Women and Children Hospital, Jiangmen, China, [13] Department of Neonatology, Dongguan Women and Children Hospital, Dongguan, China, [14] Department of Neonatology, Guangzhou Huadu Women and Children Hospital, Guangzhou, China, [15] Department of Neonatology, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, [16] Guang Dong Cord Blood and Stem Cell Bank, Guangzhou, China

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Edited by:
Yuan Shi,
The Children's Hospital of Chongqing Medical University, China

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Peng Li,
Guangzhou Institutes of Biomedicine and Health (CAS), China
Lin Zou,
Children's Hospital of Chongqing Medical University, China

***Correspondence:**
Jie Yang
jieyang0830@163.com

[†]These authors have contributed equally to this work

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Background: Despite the rapid advance of neonatal care, bronchopulmonary dysplasia (BPD) remains a significant burden for the preterm population, and there is a lack of effective intervention. Stem cell depletion because of preterm birth is regarded as one of the underlying pathological mechanisms for the arrest of alveolar and vascular development. Preclinical and small-sample clinical studies have proven the efficacy and safety of stem cells in treating and preventing lung injury. However, there are currently no randomized clinical trials (RCTs) investigating the use of autologous cord blood mononuclear cells (ACBMNC) for the prevention of BPD in premature infants. The purpose of this study is to investigate the effects of infusion of ACBMNC for the prevention of BPD in preterm neonates <28 weeks.

Methods: In this prospective, randomized controlled double-blind multi-center clinical trial, 200 preterm neonates <28 weeks gestation will be randomly assigned to receive intravenous ACBMNC infusion (5×10^7 cells/kg) or placebo (normal saline) within 24 h after birth in a 1:1 ratio using a central randomization system. The primary outcome will be survival without BPD at 36 weeks of postmenstrual age or at discharge, whichever comes

first. The secondary outcomes will include the mortality rate, other common preterm complication rates, respiratory support duration, length, and cost of hospitalization, and long-term outcomes after a 2-year follow-up.

Conclusion: This will be the first randomized, controlled, blinded trial to evaluate the efficacy of ACBMNC infusion as a prevention therapy for BPD. The results of this trial will provide valuable clinical evidence for recommendations on the management of BPD in extremely preterm infants.

Clinical Trial Registration: ClinicalTrials.gov, NCT03053076, registered 02/14/2017, retrospectively registered, https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0006WN4&selectaction=Edit&uid=U0002PLA&ts=2&cx=9y23d4 (**Additional File 2**).

Keywords: cord blood cells, bronchopulmonary dysplasia, prevention, extremely preterm infants, autologous

BACKGROUND

Preterm birth, a significant growing health concern around the world, affects 5–18% of newborn infants (1, 2). Bronchopulmonary dysplasia (BPD) is a severe and frustrating preterm complication causing adverse long-term outcomes (3, 4). The incidence of BPD in extremely preterm neonates was reported to be as high as 68% (5). The disruption of normal pulmonary vascular and alveolar growth after early birth subjects these infants to increased cardiopulmonary morbidity and mortality (6, 7). Currently, with the improvement of intensive care interventions, the mortality rate of extremely preterm neonates with BPD has decreased (7–9). However, many survivors still face a lifetime of disability, including long time dependence of oxygen therapy, asthma, and repeated hospital admission because of pneumonia even in developed countries (4, 6). Although new ventilation strategies and pharmacological treatments have been applied, there are no curative therapies available to target the underlying structural changes of the lungs leading to the symptoms (3).

The cord blood mononuclear cell (ACBMNC) layer is rich in valuable stem and progenitor cells (SPC) (10, 11). Although it is capable of self-renewal, it also has the potential to differentiate into various cellular phenotypes. In addition, its paracrine effect contributes to tissue repair and immune modulation (7, 11, 12). Animal studies have demonstrated the beneficial effects of the infusion of cord blood stem cells in the prevention and treatment of lung injury, including experimental BPD (13–15). Evidence from several clinical trials has proven the safety and feasibility of autologous cord blood infusion in neonates (9, 16–20). However, there is very limited data regarding its effects on preventing BPD, especially among extremely low-birth weight (ELBW) infants.

With these concepts in mind, the authors have tried to clarify the effects of ACBMNC cell infusion for the prevention of BPD since 2009. In the first study performed at our hospital, the safety and feasibility of ACBMNC infusion in preterm infants was demonstrated (9). Subsequently, we compared the effectiveness of ACBMNC infusion in those patients at our center (8). We found that ACBMNC infusion resulted in a significant decrease in the duration of mechanical ventilation (3.2 vs. 6.41 days, $p = 0.028$) and in the need for oxygen therapy (5.33 vs. 11.31 days, $p = 0.047$) (8). Given the small sample size and comparatively high gestational age of the enrolled preterm infants, no statistically significant differences in BPD incidence were observed in the previous small-sample trial. Therefore, our aim is to conduct a large-scale, multi-center, blinded randomized clinical trial (RCT) to evaluate the efficacy of ACBMNC infusion in BPD prevention in extremely preterm neonates.

METHODS AND ANALYSIS

Study Design and Settings

This study protocol describes a randomized, placebo-controlled, double-blinded, multi-center trial to be conducted at 14 medical centers (**Table 1**) in tertiary hospitals. The participating Neonatal Intensive Care Units (NICU) were selected by the expert committee based on the distance to Guang Dong Cord Blood and Stem Cell Bank and the level of intensive care that the NICUs could provide. The Guang Dong Cord Blood and Stem Cell Bank is a public provincial blood bank affiliated with the Guangdong Women and Children Hospital and collects cord blood routinely at these hospitals. To ensure that the cord blood would be processed and infused to the infants within 24 h after birth, the distance of these centers should fulfill this criterion. Furthermore, the NICUs in the selected centers are members of Guangdong Neonate Intensive Care Network. The staff working at these centers has been trained by the NICU of the Guangdong Women and Children Hospital, which means the selected centers use similar guidelines regarding treatment of patients. All the centers will hold quality control meetings frequently to ensure research consistency. A total of 200 neonates fulfilling the eligibility criteria will be enrolled. Subsequently, the participants will be randomly divided into two groups [ACBMNC infusion group and control [placebo] group] at a 1:1 ratio. The protocol for this study has been developed based on Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (**Additional File 1**). We have followed

TABLE 1 | Research centers.

01	Department of neonatology, Guangdong Women and Children Hospital
02	Department of neonatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University
03	Department of neonatology, The third Affiliated Hospital of Sun Yat-sen University
04	Department of neonatology, Nanfang Hospital, Southern Medical University
05	Department of neonatology, Zhongshan Boai Hospital
06	Department of neonatology, Foshan Chancheng Central Hospital
07	Department of neonatology, Foshan Women and Children Hospital
08	Department of neonatology, Guangdong Second Provincial General Hospital
09	Department of neonatology, Hexian Memorial Affiliated Hospital of Southern Medical University
10	Department of neonatology, Heyuan Women and Children Hospital
11	Department of neonatology, Jiangmen Women and Children Hospital
12	Department of neonatology, Dongguan Women and Children Hospital
13	Department of neonatology, Guangzhou Huadu Women and Children Hospital
14	Department of neonatology, The Fifth Affiliated Hospital of Guangzhou Medical University

the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the study design is illustrated in **Figure 1**. Consort flow diagram.

Trial Objectives

Primary Objective

The primary objective of this trial is to evaluate the efficacy of ACBMNC infusion in preventing BPD at 36 weeks of postmenstrual age or at discharge, whichever comes first, in extremely preterm infants (20).

Secondary Objectives

The secondary objectives of this trial are (1) to compare the infant mortality rate at 36 weeks of postmenstrual age; (2) to compare the rate of other common preterm complications included intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), respiratory distress syndrome (RDS), ventilation-associated pneumonia (VAP), hypoxic ischemic encephalopathy (HIE), late-onset sepsis (LOS), and anemia; (3) to compare the duration of mechanical ventilation and oxygen therapy in the two groups; (4) to determine re-intubation rate and time return to birth weight (BW); (5) to compare the duration of antibiotic usage; and (6) to determine the long-term outcomes after a 2-year follow up, including anthropometric characteristics, respiratory outcomes, and neurodevelopmental outcomes via standardized neurological examination.

Participants

Inclusion Criteria

Infants fulfilling all the following inclusion criteria will be enrolled in this trial: (1) birth at a study hospital; (2) a singleton birth; (3) <28 weeks gestational age, (4) signed informed consent from parents before labor; and (5) available umbilical cord blood (UCB).

Exclusion Criteria

Infants will be excluded from the study if: (1) they exhibit severe congenital abnormalities (detected via prenatal ultrasound); (2) mothers present with clinical chorioamnionitis, and (3) mothers are positive for hepatitis B (HBsAg and/or HBeAg) or hepatitis C virus (anti-HCV), syphilis, human immunodeficiency virus (HIV) (anti-HIV-1 and−2), or IgM against cytomegalovirus (CMV), rubella, toxoplasma, and herpes simplex virus.

Ethical Approval

This study was approved by the ethics committee of the Guangdong Women and Children Hospital, Guangzhou Medical University.

Sample Size

Based on our previous study and studies by others (9–16, 21), we found ACBMNC infusion was effective in reducing respiratory support duration in preterm infants. The rate of BPD among extremely preterm infants at our NICU was 60% (pA). What we expect to be an intended (or at least acceptable) effect of the ACBMNC infusion is a 25% (pB) reduction in the frequency of BPD. To detect this difference with a sensitivity of 80% (α) and an error probability of 5% (β), at least 94 patients per randomization group will be required based on the following formula:

$$n = (pA(1 - pA)\kappa + pB(1 - pB))(z1 - \alpha/2 + z1 - \beta pA - pB)2$$

To account for the possibility of loss to follow-up, our estimated sample size will be of at least 200 cases.

Randomization

The randomization sequence will be generated electronically using SPSS (version 21). Following enrolment, treatment will be assigned after verification of eligibility and consent status. Computer generated randomization will be performed by the statistician in our center at a 1:1 ratio. A randomization number will be assigned by computer for each enrolled infant. Infants will be randomized to the order in which they receive ACBMNC and placebo infusions. Those enrolled in the ACBMNC group will receive an infusion of ACBMNC within 24 h after birth. Those in the placebo group will receive an infusion of a placebo solution, consisting of normal saline with the same volume. Cell dose for all patients to be targeted at 5×10^7 cells per kilogram.

Blinding

All hospital ethics committees will review the study data during the trials. None will be involved in the study or will be aware of the treatment-group assignments for the infants. Only nurses and physicians conducting the infusions will be aware of the treatment assignment, and these individuals will have had no

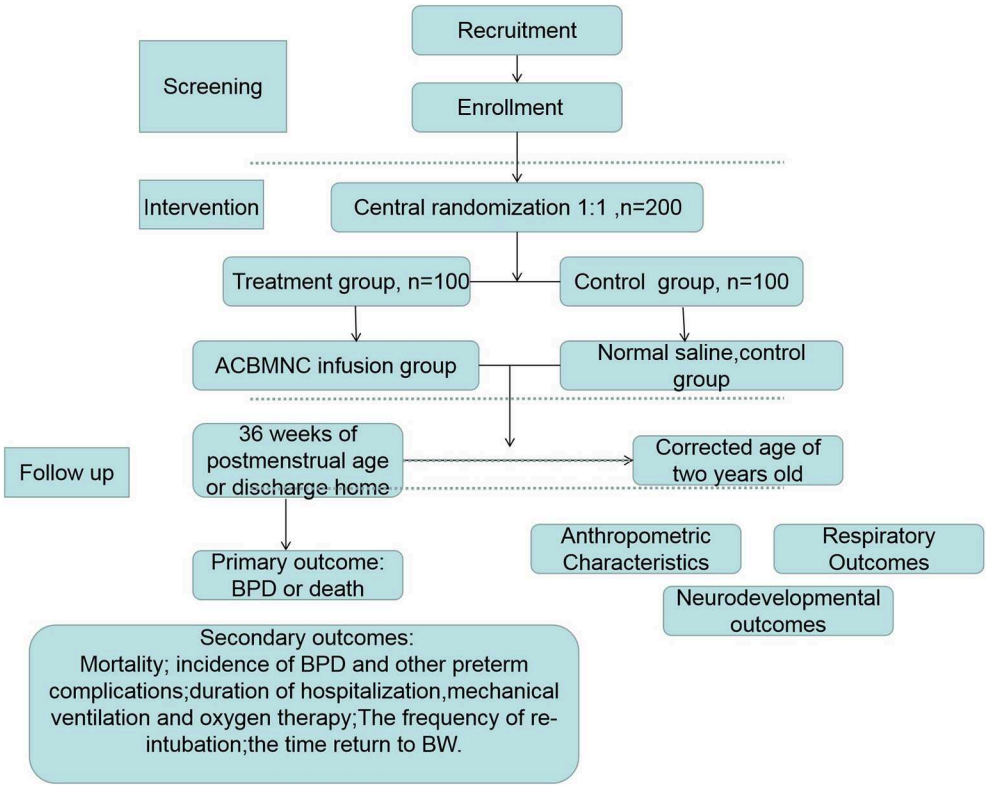

FIGURE 1 | Flow diagram.

contact with the staff that will collect and analyze the patient data. The parents will not be aware of the treatment assignment. This study will be double-blinded.

Intervention

Cord blood processing

The Guang Dong Cord Blood and Stem Cell Bank is a public provincial blood bank accredited for stem cell manipulation by National Health Commission of the People's Republic of China and American Association of Blood Bank (AABB). Procedures for cord blood collection and processing will be performed in accordance with cord blood bank guidelines (22). The umbilical cord will be clamped for collection using a blood-collection bag (WEGO, China) containing 28 mL of citrate-phosphate-dextrose anticoagulant immediately after birth and before the placenta is delivered. The umbilical vein will be sterilized and punctured with a 17-gauge needle. UCB will be collected by trained obstetricians or cord blood bank collection staff present at the hospital during weekdays for 8–12 h per day in each center. When collection is completed, the blood bag tubing will be closed and sealed. Cord blood labeled with the full name of the donor, group type, and volume of the blood product will be stored at 4°C and sent to the Cord Blood and Stem Cell Bank for immediate processing. Before processing, 2 mL samples will be taken from all collected CB units to test for the presence of viruses (HIV, HBV, HCV, CMV) by PCR and bacterial infections via bacterial smear. A sample of peripheral blood was collected from the mother and tested for the presence of maternal transmissible diseases. The results will be obtained immediately before the start of transfusion. After a sample is taken, it will be volume- and RBC-reduced after a 30 min incubation with 6% Hespan (Bethlehem, USA) following established CBB procedures using the SEPAX S-100 automated processing system (Biosafe, Geneva, Switzerland) if the unit contained >30 mL of UCB or manually, if the unit was <30 mL. The mononuclear layer will be isolated by density gradient centrifugation (1,000× g, 30 min, room temperature, Beckman, American), and then transferred to cryobags. Excessive nucleated cell-poor plasma will be expelled. Meanwhile, the MNC count, CD34 cell count, CFU-GM, and sterility detection (Sheldon Manufacturing Inc., Comelius, OR, USA) will be performed. Cell viability will be measured using a 7-aminoactinomycin D (7-AAD) detection kit by flow cytometry analysis (BD Bioscience, USA). After processing, the cord blood cells will be sent back to the hospitals where it was collected. All infusions will be administered at the NICU. Infusate and subject identities will be double-checked by research and clinical nursing staff. Infusions will also be monitored by research and clinical staff. Cells will be infused over 15 min, followed by a 2-mL saline flush to clear the intravascular line.

Trial Treatment Methods

Eligible infants will be observed at the NICU of the Guangdong Women and Children Hospital until discharge home. All patients in the study will be given intensive care therapy

in accordance with departmental guidelines, which include therapies such as positive pressure mechanical ventilation, non-invasive respiratory support, oxygen therapy, and exogenous surfactant replacement (Curosurf, Chiesi, Parma, Italy). Chest radiographs will be performed at admission and 8 h after CBT on the first day of life in all surviving patients. Blood gas will be monitored every 24 h until weaning from ventilation. All clinical diagnoses will be defined according to a standard reference (16). Soon after the preterm infant is delivered, written consent will be obtained from the parents, and ACBMNC infusion was applied to the baby in addition to routine pulmonary surfactant replacement, and mechanical ventilation support as indicated. Those assigned to the ACBMNC group will receive an infusion of ACBMNC with 24 h after birth. Infants in the control group will receive an infusion of a placebo solution consisting of normal saline with the same volume. Cell dose for all patients will be targeted at 5×10^7 cells per kilogram.

Safety Assessment

The trial will be strictly monitored by a safety monitoring board, which will be notified of specific severe adverse events (including death, LOS, NEC, severe IVH, cystic periventricular leukomalacia, and fever) within 48 h. Other adverse or unexpected events will be reviewed monthly. After each interim analysis, the data safety monitoring board will make a decision on whether to stop or continue the trial based on safety monitoring and sequential analysis of the primary outcome. Assessment of safety will be conducted at 12 and 24 h after infusion, as well as during hospitalization and return visits. Heart rate, systolic, diastolic, and mean arterial blood pressure, and arterial blood oxygen saturation levels will be monitored in the peripheral blood continually and will be documented. Moreover, laboratory investigations in the peripheral blood including blood routine tests and blood gas analysis will be monitored and kept stable during the whole treatment period. Infusion reactions and signs of circulatory overload will be checked.

Basic Clinical Data Collection

The following data will be collected: (1) clinical basic characteristics including sex, gestational age, birth weight, delivery mode, Apgar score at 1, 5, 10 min; (2) characteristics of cord blood processing including cord blood volume, cell number, cell concentration before and after processing, CFU-GM, CD34+ cell count, cell viability post processing; (3) characteristics of infusion cells including total cell number, time between collection (birth) and initiation of infusion, infused volume, and pathogen detection (including bacteria culture, fungus culture, HIV, HBV, HCV, CMW, and *Treponema pallidum*) results; and (4) other routine clinical interventions including dose and times of pulmonary surfactant (PS) replacement, postnatal steroid use, surgical closure of patent ductus arteriosus, and use of blood products.

We will use the following clinical definitions in this study:

1. Gestational age will be determined on the basis of a combination of the last menstrual period and early ultrasound findings
2. The diagnosis of common preterm complications will include the following (23):

BPD, defined as treatment with oxygen >21% for at least 28 days, and its severity will be assessed at 36 weeks of postmenstrual age or discharge home whichever comes first. Mild BPD, defined as breathing room air at assessment. Moderate BPD, defined as the need for <30% supplemental oxygen, and severe BPD defined as needing ≥30% supplemental oxygen or positive airway pressure. For these patients, BPD status will be analyzed by a committee of three independent experts blinded to the study group.

RDS will be defined if the infants show evidence of respiratory symptoms such as grunting and chest retraction, typical chest radiograph findings, and/or treatment with surfactant, and the need for assisted ventilation.

NEC will be defined using Bell's classification. Infants with stage II or above will be diagnosed with NEC.

LOS will be defined if the infants had a positive bacterial culture results after the first 72 h after birth.

ROP will be defined according to the International Classification for Retinopathy of Prematurity.

Anemia will be defined as hemoglobin no more than 140 g/L.

IVH and periventricular leukomalacia (PVL) will be defined by serial head ultrasound, performed according to the description by Volpe. The first head ultrasound will be performed within 3 days after birth and follow-up head ultrasound examinations will be performed every week until the day of discharge.

VAP will be defined as a pneumonia occurring after the patient has been intubated and has received mechanical ventilation for more than 48 h.

Outcome Measures

Primary outcome measure:

- The frequency of BPD or death in at 36 weeks of postmenstrual age or discharge home whichever comes first.

Secondary outcome measures:

- Mortality rate
- Incidence of BPD
- Incidence of other preterm complications including IVH, PVL, NEC, ROP, RDS, VAP, LOS, and anemia [all clinical diagnoses will be defined according to a standard references (16)].
- Duration of hospitalization.
- Duration of mechanical ventilation and oxygen therapy
- Frequency of re-intubation.
- The time (days) return to BW.

Follow Up

All the infants will be followed until the corrected age of 2 years old, the following parameters will be recorded.

- Anthropometric characteristics: weight, length, and head circumference.
- Respiratory outcomes including the occurrence of wheezing, asthma, nocturnal cough, supplemental oxygen requirement, and rehospitalization because of pneumonia.

TABLE 2 | Contents and points of data capture: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule of enrolment, interventions, and assessments.

Visit	Screening	Intervention	Follow up	
	V1	V2	V3	V4
Time point	born	Within 24 h after birth	36 weeks of postmenstrual age	Corrected age of 2 years old
Informed consent form	√			
Screening the subject	√			
Demographic information	√			
Inclusion/exclusion criteria	√			
Get random number	√			
Cord blood process		√		
Vital signs	√	√	√	
Chest radiographs		√		
Pulmonary surfactant replacement		√		
Mechanical ventilation	√	√		
Arterial blood oxygen saturation	√	√		
Laboratory tests	√	√	√	
Blood routine test	√	√		
Blood gas	√	√		
Safety outcomes		√	√	√
Record adverse events		√	√	√
Postnatal steroid use		√	√	√
Surgical closure of patent ductus arteriosus		√	√	
Blood products use		√	√	
Bronchopulmonary dysplasia			√	
Other preterm complications			√	
Duration of hospitalization			√	√
Anthropometric Characteristics			√	√
Respiratory Outcomes				√
Neurodevelopmental outcomes				√

- Degree of neurodevelopmental impairment via standardized neurological examination [using the revised Brunet-Lézine [RBL] global developmental quotient score (16)], and other major neurodevelopmental outcomes including cerebral palsy, seizures, auditory impairment, and visual impairment (**Table 2**).

Statistical Analysis

Statistical analyses between the two groups will be performed using an unpaired two-tailed Student's *t*-test or Chi-squared Test as appropriate. A logistic regression model will be used for the entire study population (i.e., without removing deaths) to adjust for the effect of treatment on primary outcome according to baseline characteristics and events known to affect the occurrence of BPD (i.e., gestational age, birth weight and other characters that are different in two groups after initial analysis), and to investigate the effect of treatment on the following outcomes: extubation rates, severe adverse events, and death before discharge. The Breslow-Day test and Corchran-Mental-Haenszel (CMH) test will be used to adjust the data derived from different participating centers. The results will be reported as odds ratio (OR) with 95% confidence intervals (CI). All statistical tests will be two-tailed and a $p < 0.05$ will be considered statistically significant. All statistical analysis will be performed using SPSS 21.0 (IBM).

DISCUSSION

BPD is still a major complication of prematurity. Currently, therapy for BPD includes non-invasive ventilation strategies, inhaled nitric oxide, antioxidants, vitamin A, caffeine, and corticosteroids, however, these strategies are mainly palliative and do not address the underlying structural changes involved in BPD including the reduced numbers of alveoli, blood vessels, and prominent fibrosis of the lungs (24–29). Stem cells are showed to have beneficial effects on both treatment and prevention of BPD in several preclinical and clinical settings (16–19, 30–34). Cord blood MNCs are rich in stem cells. As a convenient and safe source of stem cells, it could provide regrowth to underdeveloped lung tissue of preterm infants by providing more stem/progenitor cells. In addition, its paracrine effects help to improve lung function, vascularization of the airways, and reduce fibrosis, and therefore have considerable potential for reducing lung injury in preterm infants (35–40). However, few studies have evaluated the effects of ACBMNC infusion for prevention of BPD in extremely preterm infants.

The outcome of our study would be a major step forward solving this problem. To our knowledge, this would be the first clinical trial to assess ACBMNC infusion soon after birth in extremely preterm neonates in terms of the rate of BPD and other prematurity-related complications. Considering the novelty of the therapy and the randomized double-blinded characters of this study, it may take longer time to complete this trial. These may be potential shortcomings of the study.

CONCLUSION

In conclusion, this randomized, placebo controlled, double blinded study aims to investigate the effects of ACBMNC for preventing BPD in extremely preterm infants.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by [Guangdong Women and Children Hospital Ethics committee]. The legal guardian of participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Endotracheal Surfactant Combined With Budesonide for Neonatal ARDS

*Burak Deliloglu, Funda Tuzun, Merve Meryem Cengiz, Hasan Ozkan and Nuray Duman**

Division of Neonatology, Department of Pediatrics, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey

Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by acute diffuse inflammatory lung injury and severe hypoxemia. In 2017, the Montreux Consensus defined diagnostic criteria for ARDS in the neonatal period. The management of ARDS includes strict adherence to lung-protective ventilation strategies and therapeutic agents to improve gas exchange. We report two similar cases of premature infants with gestational ages of 23 and 24 weeks diagnosed with neonatal ARDS according to the Montreux definition. These patients developed acute worsening of oxygenation on the 30th and 28th day of life, respectively, while they were ventilated on volume-guarantee assist/control mode. Chest X-rays revealed bilateral diffuse opacity, there were no cardiogenic origins for pulmonary edema, and their oxygenation indexes were >8. Both cases fulfilled the neonatal ARDS criteria and the patients' clinical conditions were associated with late onset neonatal sepsis. After lung recruitment maneuver, the infants began HFO volume-guarantee ventilation and received surfactant treatment. Since they showed a poor short-term response, intratracheal surfactant of 100 mg/kg plus budesonide of 0.25 mg/kg were administered and their oxygenation indexes were reduced stepwise. Both patients survived and were discharged home with spontaneous breathing of room air. Neonatal ARDS is generally an underdiagnosed condition associated with sepsis, pneumonia, and meconium aspiration. Impaired surfactant activity and reduced lung compliance play important roles in its pathophysiology. To our knowledge, this is the first case report indicating the possible therapeutic role of budesonide plus surfactant in ARDS treatment. Since ARDS is an entity not recognized in newborns, we want to emphasize neonatal ARDS diagnosis and underline that the combination of budesonide and surfactant may be a novel therapeutic option in the treatment of ARDS.

Keywords: neonatal ARDS, Montreux criteria, surfactant plus budesonid, ELGAN Extremely low gestational age newborn, surfactant

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Quen Mok,
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Liam Mahoney,
Southmead Hospital, United Kingdom
Alan King Woon So,
The Chinese University of Hong Kong, China

****Correspondence:***
Nuray Duman
nuray.duman@deu.edu.tr

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by acute diffuse inflammatory lung injury and severe hypoxemia. Neonatal ARDS is a novel diagnosis for newborns. De Luca et al. defined the Montreux Consensus diagnostic criteria for ARDS in the neonatal period for the first time (1). Although specific treatments do not exist other than the treatment of the underlying disease, the management of ARDS includes strict adherence to lung-protective ventilation strategies and therapeutic agents to improve gas exchange. Exogenous surfactant treatment has been considered to be beneficial in pediatric cases because of the importance of the

impaired surfactant activation during the course of ARDS (2). The increased inflammatory status of the lungs is a central reference point in the pathophysiology of ARDS. Considering its potent local pulmonary anti-inflammatory effect, budesonide may be an effective treatment option for ARDS (3).

In this report, we present two cases of neonatal ARDS in newborns of extremely low gestational age treated successfully with endotracheal surfactant plus budesonide. Written informed consent was obtained from the parents of both patients for the publication of these case reports.

CASE REPORTS

Case 1

A 497-g triplet preterm female infant was born vaginally at the 23rd gestational week. The patient was intubated in the delivery room and received surfactant. Her Apgar scores at 1 and 5 min were 3 and 5, respectively. During the acute phase of respiratory distress syndrome, the infant was given two doses of surfactant and required high-frequency oscillatory ventilation plus volume guarantee (HFOV-VG) as a rescue therapy. Between the 3rd and the 30th day of life (DOL), the infant remained on ventilator therapy despite two unsuccessful extubation attempts, which failed due to patent ductus arteriosus and late-onset neonatal sepsis. Although the patient was clinically stable for at least a week and ventilated on conventional assist/control mode with volume guarantee at FiO_2 of 0.3, on the 30th DOL the patient's oxygen requirement doubled and her FiO_2 levels reached 0.6 within 12 h. A chest X-ray revealed bilateral diffuse lung opacities (**Figure 1A**), while blood gas analyses revealed respiratory acidosis with an oxygenation index of 12. To clarify this acute worsening, a full sepsis workup was completed including routine blood tests (complete blood count, peripheral blood smear, C-reactive protein), cultures from body fluids, tracheal aspirate culture, and respiratory viral PCR tests for influenza, parainfluenza, respiratory syncytial virus, metapneumovirus, coronavirus, rhinovirus, enterovirus, parechovirus, adenovirus, and bocavirus. Laboratory tests revealed an elevated C-reactive protein level (68 mg/L) and an elevated immature/total leukocyte ratio (0.41). The tracheal sample culture was sterile and viral PCR test results were negative. Echocardiography was performed, which revealed patent foramen ovale without any cardiogenic deterioration. The patient was diagnosed with neonatal ARDS on the basis of the acute worsening of her respiratory condition, diffuse opacities in the lungs as shown by radiography, the absence of pulmonary edema of cardiac origin, and an oxygenation index above four. After neonatal ARDS diagnosis, the patient underwent a lung recruitment maneuver under HFOV-VG to provide optimal lung volumes. To improve oxygenation, endotracheal surfactant was administered, which briefly decreased the oxygen requirement within hours; however, the FiO_2 level again reached 0.6. In the presence of short-lasting clinical response to surfactant treatment, alternative treatment options were considered due to rapid surfactant inactivation. Considering ARDS, a therapy combining surfactant of 100 mg/kg (beractant, Survanta Bovine, Ross/Abbott Laboratories, Columbus, OH, USA) and budesonide of 0.25 mg/kg (Pulmicort nebulizing suspension, Astra Zeneca, London, UK) was administered via endotracheal route twice in an 8 h interval (4). The oxygenation index dropped to three after 12 h, the FiO_2 level decreased to 0.35, and chest X-rays revealed better aeration (**Figure 1B**). In this case, with the support of laboratory findings, the ARDS etiology was determined to be clinical late-onset neonatal sepsis, although all cultures remained sterile. After the treatment, the patient's ventilator settings improved, and the patient could be weaned from the ventilator to non-invasive support on the 48th DOL. The patient was discharged to home on the 95th DOL without oxygen supplementation. The other two infants of this set of triplets died in the first week of life due to severe respiratory insufficiency.

Case 2

A 694-g twin preterm male infant was born via cesarean section at the 24th gestational week. The patient was intubated in the delivery room and received surfactant. His Apgar scores at 1 and 5 min were 4 and 6, respectively. During the first 2 weeks of life, the patient required HFOV-VG as a rescue therapy. Despite late systemic steroid treatment for weaning from the ventilator, he did not tolerate extubation. On the 28th DOL, the patient developed acute worsening of oxygenation with a FiO_2 need of 0.75 under assist/control volume-guarantee ventilation. Blood gas analysis revealed respiratory acidosis and the patient's oxygenation index was 10. Chest X-rays revealed bilateral irregular diffuse opacity (**Figure 2A**), and there was no cardiogenic origin for pulmonary edema, as confirmed by echocardiography. The patient met the criteria for neonatal ARDS, including acute onset hypoxemic respiratory failure, diffuse bilateral lung opacification, absence of pulmonary edema due to cardiogenic disease, and an oxygenation index exceeding four. Tracheal aspirate samples obtained for bacterial culture and viral PCR tests were negative. His diagnosis of ARDS was also associated with a coexisting blood culture that proved late-onset neonatal sepsis, with *Staphylococcus epidermidis* as the pathogen. After a lung recruitment maneuver, the patient was ventilated on HFOV-VG mode and received a dose of 100 mg/kg surfactant (Poractant alfa, Curosurf, Chiesi Pharmaceuticals, Parma, Italy) plus 0.25 mg/kg budesonide (Pulmicort nebulizing suspension, Astra Zeneca, London, UK) endotracheally. As a result, his oxygenation index reduced stepwise to 2.6, the FiO_2 requirement decreased to 0.4, and chest X-rays revealed better aeration (**Figure 2B**). Extubation was successful on the 43rd DOL and the patient was discharged to home without respiratory support on the 76th DOL.

DISCUSSION

The diagnosis of neonatal ARDS is based on the Montreux criteria, which implicate the timeframe, oxygenation index, origin of pulmonary edema, and lung imaging. To fulfill the criteria, a patient's clinical status has to be acute onset (i.e., within a week), with an oxygenation index >4 and lung imaging showing diffuse bilateral opacification with no cardiogenic origins for pulmonary edema, as confirmed by echocardiography (1). ARDS became slightly more recognized by neonatologists

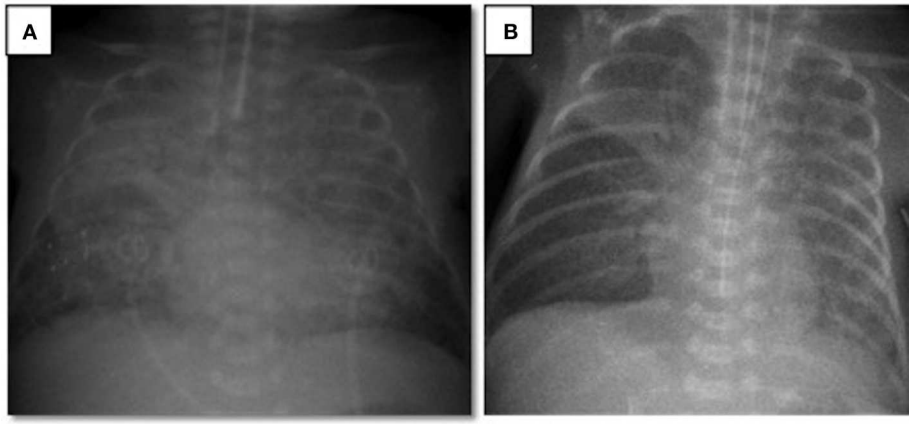

FIGURE 1 | Chest radiograms of Case 1: **(A)** At the time of ARDS diagnosis, an X-ray revealed bilateral diffuse lung opacities; **(B)** after two doses of surfactant plus budesonide treatment, a chest X-ray revealed better aeration.

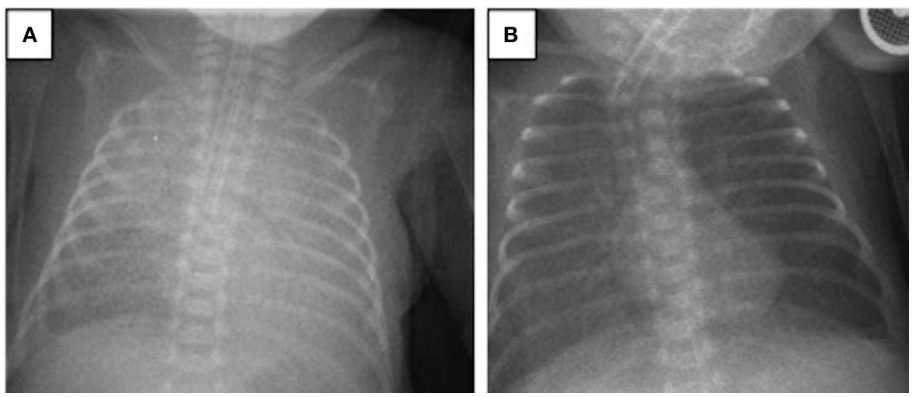

FIGURE 2 | Chest radiograms of Case 2: **(A)** At the time of ARDS diagnosis, an X-ray revealed bilateral irregular diffuse opacity; **(B)** improvement in lung aeration was seen after one dose of surfactant plus budesonide treatment.

after the publication of the Montreux criteria, but it still remains an underdiagnosed condition in neonatal intensive care units (5). Both of our patients, as newborns of extremely low gestational age, developed neonatal ARDS during their NICU stay.

The incidence of ARDS is 2.9–9.5 per 100,000 and its mortality rate is 18–35% in the pediatric population (6). However, the incidence and mortality rates of ARDS during the neonatal period remain unknown. Mid-term data from the ESPNIC/ESPR neonatal ARDS worldwide network concerning the epidemiology of neonatal ARDS revealed that 162 neonates recruited prospectively had a mortality rate of 17.3% at the 36th postmenstrual week (7).

Inflammation plays a key role in the pathophysiology of ARDS, as it triggers endothelial cell activation, capillary leakage, and protein-rich fluids in the alveolar space, as well as increasing the secretion of proinflammatory cytokines that can prompt surfactant inactivation. Surfactant deficiency causes reduced compliance, normal, or slightly increased resistance in diffuse lung tissue, and hypoxemic respiratory failure (2). Commonly seen neonatal respiratory disorders such as meconium aspiration, pneumonia, and hemorrhage affecting the alveolar–epithelial layer are classified as direct triggers for ARDS. Conditions corrupting the alveolar–capillary layer are classified as indirect triggers, including sepsis, asphyxia, and *in utero* inflammation. The data of the ESPNIC/ESPR neonatal ARDS worldwide network indicate that sepsis is the most common trigger (39.1%), followed by pneumonia (29.1%); meconium, blood, or milk aspiration (27.2%); asphyxia (12.6%); and pulmonary hemorrhage (11.9%) (7). The patients that we present here exhibited late-onset neonatal sepsis; sepsis was proven by blood culture in Case 2 and by clinical and laboratory findings in Case 1.

Treatment of ARDS centers on adequate ventilation, improved oxygenation, adequate perfusion, and the reduction of inflammation (8). To improve lung function and gas exchange, an open lung strategy combined with exogenous surfactant was found to be efficient in a neonatal ARDS model (9). Alongside ventilation strategies, therapeutic agents such as surfactants, inhaled nitric oxide, sildenafil, prostacyclin, and corticosteroids can be used to improve oxygenation and ventilation (8). Studies on exogenous surfactant treatment among pediatric ARDS patients showed improved oxygenation but no difference in ventilation support or mortality. Although the Pediatric

Acute Lung Injury Consensus Conference Group (PALICC) does not recommend the routine use of surfactant in ARDS treatment, it was highlighted that specific patient populations may benefit from specific dosing and delivery regimens (10). Neonates may frequently develop surfactant inactivation and secondary dysfunction caused by direct or indirect triggers, especially in cases of pulmonary parenchymal diseases, and during this specific period exogenous surfactant treatment may be considered (11).

The anti-inflammatory effect of budesonide is clearly defined, and its combination with exogenous surfactants may advance its distribution and effect. In an animal study investigating the biophysical profile of a suspension combining surfactant and budesonide, the mixed suspension was observed to be biophysically and chemically stable (12). In an animal model of meconium aspiration syndrome, the combined therapy improved functional lung measurements, mean airway pressure, and oxygenation index and had a longer-lasting effect than either of the single administrations (13).

Budesonide combined with surfactant was also used in a clinical trial among preterm infants during the acute phase of respiratory distress syndrome in order to prevent the development of bronchopulmonary dysplasia (BPD) (4). In that study, the combination of 100 mg/kg beractant and 0.25 mg/kg budesonide was used endotracheally and, as a result, decreased pulmonary inflammatory status was achieved. The group receiving surfactant and budesonide had lower rates of death and BPD compared to the control group.

The definition of neonatal ARDS covers a group of respiratory conditions that mainly have similar pathophysiologies resulting in severe hypoxemic respiratory failure. Marked reduction of the alveoli, decreased alveolar surface area, and altered cardiopulmonary physiology in preterm infants with BPD leads to acute episodes of pulmonary decompensation characterized by hypoxemia (14). Unlike the recently defined neonatal ARDS criteria, BPD exacerbation does not have a strict definition. It is generally characterized by worsening of oxygenation, recurrent hypoxic episodes, and increased need for ventilatory support. In moderate or severe cases, pulmonary hypertension arising as a result of the abnormalities of the pulmonary vasculature and parenchymal lung disease may worsen the clinical picture (15). Distinct from the clinical exacerbations in cases of BPD, the definition of neonatal ARDS also requires acute onset (i.e., within a week), oxygenation index of >4, and lung imaging showing diffuse bilateral opacification with no cardiogenic origins for pulmonary edema (1). BPD has not been defined as an exclusion criterion for the diagnosis of neonatal ARDS. Before the definition of the Montreux criteria, some of the clinical pictures defined as BPD exacerbation would probably have fulfilled the criteria of neonatal ARDS. The specific contribution of BPD to the development of neonatal ARDS is not known. Disrupted pulmonary growth and immune function in preterm infants with BPD could potentially act as a basis for predisposal to neonatal ARDS. Until recently, neonatal ARDS was not defined well for newborns. Therefore, this may have led to the under-diagnosis of ARDS in this population with underlying BPD (16). Following the Montreux definition, cases diagnosed as neonatal ARDS on the basis of BPD will probably increase, and new cases may provide more accurate data in terms of management strategies. In both of our cases, we encountered acute worsening of pulmonary status, like in most preterm infants with BPD, but the severity of hypoxemia defined objectively with the oxygenation index and diffuse pulmonary parenchymal changes led us to consider a neonatal ARDS diagnosis on the basis of BPD. Whether a case is BPD exacerbation or neonatal ARDS, no specific therapy exists, and treatment of the underlying condition is essential. The most certain distinctions between the treatment of these conditions seem to be related to ventilation strategies and exogenous surfactant therapy. In pediatric patients, a ventilation strategy allowing lower tidal volumes and higher PEEP levels has been considered appropriate in ARDS management, similar to neonatal RDS management. In contrast to a low tidal volume and high PEEP strategy, larger tidal volumes delivered at slower ventilation rates with longer inspiratory times were recommended for BPD patients to improve the distribution of ventilation and minimize gas trapping (14, 17). Since the definition of ARDS is very new, specific ventilation strategies are not yet established for newborns. Because of the diffuse lung opacity pattern, we recruited the patients first and then switched to HFO mode to provide higher MAP levels and lower tidal volumes. Another difference in the treatments of ARDS and BPD exacerbation appears to be exogenous surfactant therapy. Unless there is evidence of secondary surfactant deficiency, surfactant treatment has not been recommended in cases of BPD exacerbation. Despite the fact that surfactant abnormalities in ARDS are not the essential pathogenic variables, surfactant insufficiency may result from primary or secondary inactivation of pulmonary surfactant in the alveolar cavity. Collapse and pulmonary edema worsen in the alveoli due to lack of surfactant, leading to the characteristic pathophysiology of ARDS. Some studies have demonstrated that exogenous surfactant may improve outcomes in infants and children (2). In our cases, because of the partial response to supportive management and ventilator management directed at ARDS, we considered exogenous surfactant treatment. In Case 1, the effect of a single dose of surfactant lasted only a few hours. Therefore, we decided to use budesonide combined with surfactant treatment to (i) minimize the inactivation of surfactant, (ii) utilize the local anti-inflammatory effects of budesonide, and (iii) improve the distribution of budesonide with the surfactant as a vehicle.

Neonatal ARDS is considered a novel diagnosis in the neonatology field. Our current scientific knowledge is largely based on ARDS studies in pediatric and adult populations. Establishing neonatal multicenter studies could have significant benefits for better understanding ARDS in the neonatal population in terms of etiological factors, clinical characteristics, and therapeutic options targeting better outcomes.

CONCLUSION

Knowing the potential anti-inflammatory effects of budesonide on lung injury and that its instillation with surfactant promotes surfactant distribution and may protect against surfactant inactivation, we examined combined treatment with budesonide and surfactant in two cases, which we believe are the first cases

of neonatal ARDS treated with endotracheal surfactant with budesonide to be reported.

Since ARDS is seldom recognized in newborns, we encourage clinicians to consider the diagnosis of neonatal ARDS and we emphasize that budesonide combined with surfactant may be a novel therapeutic option in treating neonatal ARDS.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

Written informed consent was obtained from the parents of the participants for the publication of this case report.

AUTHOR CONTRIBUTIONS

BD and FT contributed to the study's conception and design. BD and MC participated in obtaining the clinical data. BD and FT wrote the manuscript. ND and HO critically revised it. All authors have approved this final version of the manuscript and have agreed to be accountable for all aspects of the work.

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Minimally Invasive Surfactant Administration for the Treatment of Neonatal Respiratory Distress Syndrome: A Multicenter Randomized Study in China

*Tongyan Han[1], Huiqiang Liu[1], Hui Zhang[1], Ming Guo[2], Xuefeng Zhang[2], Yang Duan[3], Fuqiang Sun[3], Xinjian Liu[4], Xiang Zhang[4], Mingtao Zhang[4], Fang Liu[5], Lisha Bao[5], Min Xiao[6], Weili Liu[6], Rui Jiang[6], Jun Zheng[7], Xiuying Tian[7], Qi Gao[7], Wanxian Zhang[7], Wei Guo[8], Ling Li[8] and Xiaomei Tong[1]**

[1] Department of Pediatrics, Peking University Third Hospital, Beijing, China, [2] Department of Neonatology, Fifth Medical Center, General Hospital of the Chinese People's Liberation Army, Beijing, China, [3] Department of Neonatology, Second Hospital of Tianjin Medical University, Tianjin, China, [4] Department of Neonatology, Hebei PetroChina Central Hospital, Langfang, China, [5] Department of Neonatology, Bethune International Peace Hospital, Shijiazhuang, China, [6] Department of Neonatology, Cangzhou Central Hospital of Hebei Province, Cangzhou, China, [7] Department of Neonatology, Tianjin Central Hospital of Obstetrics and Gynecology, Tianjing, China, [8] Department of Neonatology, Xingtai People's Hospital, Xingtai, China

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Edited by:
Yuan Shi,
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Henry Lee,
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***Correspondence:**
Xiaomei Tong
tongxm2007@126.com

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Background/Aims: Nasal continuous positive airway pressure (nCPAP) was recommended as the initial respiratory support for spontaneous breathing in infants with very low birth weight and neonatal respiratory distress syndrome (NRDS). Less invasive surfactant administration (LISA) and minimally invasive surfactant therapy (MIST) have been reported to reduce the incidence of bronchopulmonary dysplasia (BPD). This study aimed to explore the applicability of minimally invasive surfactant administration (MISA) in China.

Materials and Methods : MISA was a randomized controlled study conducted at eight level III neonatal intensive care units (NICUs) in China. Spontaneously breathing infants born at 25+0 to 31+6 weeks' gestation who progressively developed respiratory distress during the first 6 h after birth were randomly assigned to receive MISA or endotracheal intubation surfactant administration (EISA). The primary outcome was the difference in the morbidity of BPD between two groups of infants with MISA and EISA at 36 weeks corrected gestational age.

Results : Demographic and clinical characteristics of the 151 infants in the MISA group were similar to the 147 infants in the EISA group. The comparison showed no clear benefits in the MISA group in the incidence of BPD, while infants from the EISA group had higher rates of patent ductus arteriosus (PDA) (60.5 vs. 41.1%, $p = 0.001$). The duration of surfactant infusion and the total time of surfactant administration in the MISA group were significantly longer than in the EISA group. A slightly increased heart rate was noted 1 h post surfactant administration in the EISA group. In subgroup analysis, the comparison of 51 smaller (<30 weeks) preterm infants, named MISAs ($n = 31$) and

EISAs ($n = 20$), showed a significant reduction of BPD (29.0 vs. 70.0%, $p = 0.004$) and PDA (29.0 vs. 65.0%, $p = 0.011$). In the subgroup analysis of blood gas, arterial oxygen saturation (SaO_2) value at 1 and 12 h and partial pressure of arterial oxygen (PaO_2) at 12 h were all higher in the EISA group compared to the MISA group.

Conclusion : MISA had no clear benefit on the incidence of BPD, but it was related to a reduction in PDA. It is an appropriate therapy for spontaneous breathing in infants with extremely low birth weight and NRDS.

Keywords: minimally invasive surfactant administration, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, patent ductus arteriosus, extremely low birth weight infants, preterm infants

INTRODUCTION

Pulmonary surfactant is key to normal alveolar expansion. It is secreted by the type II pneumocytes to decrease surface tension, leading to increased compliance and decreased atelectasis (1). Neonatal respiratory distress syndrome (NRDS) is a disorder of surfactant deficiency, especially preterm infants <32 weeks old with very low birth weight whose type II pneumocytes are too immature to produce sufficient surfactant to support normal alveolar expansion (2). Treatment includes respiratory support and exogenous surfactant. Fujiwara et al. introduced surfactant treatment into neonatology in 1980 (3), which significantly reduced the need for invasive positive pressure ventilation of infants with NRDS. Traditionally, the surfactant is administered to intubated RDS infants by intratracheal bolus on positive pressure ventilation as early as possible (4). Victorin LH, a Swedish neonatologist, was the first to use an INSURE (INSURE = INtubation SURfactant Extubation) approach in the Arab countries (5). INSURE reduces the duration of positive pressure ventilation and the risk of ventilator-induced lung injury (VILI), but still needs intubation, which means a slight damage to the endotracheal epithelium mucosae of the immature airway.

In spite of the optimal approach for the initial respiratory support of infants with extremely low birth weight (ELBW) and very low birth weight (VLBW) being uncertain, stabilization by nasal continuous positive airway pressure (nCPAP) rather than immediate intubation in delivery room is advocated for them who are breathing spontaneously (6). Even brief exposures to tracheal intubation and positive pressure ventilation can increase the risk of lung injury. Application of non-invasive respiratory support, and especially nCPAP, has become a popular strategy.

Though many ELBW/VLBW infants with surfactant deficiency disorder completely recover after numerous treatments in NICU, a subset of patients tends to develop bronchopulmonary dysplasia (BPD) (7). Northway and colleagues were the first who described this condition in 1967 (8). Nowadays, BPD primarily affects ELBW/VLBW infants who are <32 weeks' gestational age and in the canalicular and saccular stages of lung development (9). Because endotracheal intubation and brief positive pressure ventilation can be harmful to the endotracheal epithelium mucosae and immature lung, methods that would allow for less invasive surfactant administration (LISA) have been investigated. LISA that has been applied in European countries (10) and the minimally invasive surfactant therapy (MIST) are among these methods (11, 12). These were derived from two methods: the Hobart method and the Cologne method. The Hobart method, which was first described by Dargaville and coworkers, instilled surfactant by semi-rigid vascular catheter with direct laryngoscopy (12). The Cologne method put the tip of a gastric catheter through the vocal cords with the aid of the Magill's forceps (10). Infants are continued on nCPAP or intermittent nCPAP throughout the procedure.

The objective of this study was to assess whether minimally invasive surfactant administration (MISA) is applicable in preterm infants with a gestational age less than 32 weeks in China. We hypothesized that MISA decreases incidence of BPD at 36 weeks corrected gestational age compared with invasive endotracheal intubation surfactant administration (EISA).

MATERIALS AND METHODS

Study Design and Patients

This MISA study was a multicenter, randomized controlled study completed at eight level III neonatal intensive care units (NICUs) in Beijing, Tianjin, and Hebei province, China, between July 1, 2017, and December 31, 2018. Each institution's Ethics Review Board approved the study. MISA is registered with ClinicalTrials.gov, NCT04077333.

A written informed consent for participation was obtained from a parent during the prenatal high-risk consultation before delivery or as quickly as possible after admission to the NICU (up to 120 min post-admission). The gestational age was estimated based on the Ballard score assessment postnatally (13). Inclusion criteria were as follows: (1) infants with gestational age between less than 31 weeks and 6 days were eligible; (2) infants with respiratory distress using NCPAP as ventilation support; (3) infants who had signs of respiratory distress (respiratory rate >60/min, with retractions, nasal flaring, grunting, or cyanosis; fraction of inspired oxygen [FiO_2] >0.4 for transcutaneous oxygen saturation [SpO_2] >85%) that had progressively developed, and finally needed surfactant administration within 6 h of life. Exclusion criteria were as follows: (1) infants who were intubated in the delivery room or before the surfactant administration; (2) infants with major congenital malformations affecting respiratory function; (3) infants who died or were transferred to other hospitals for surgery or with uncompleted data; (4) infants who were enrolled in

other interventional studies; (5) for the MISA group, repeated surfactant doses by intubation and positive pressure ventilation support during the first 72 h were excluded.

Randomization

Eligible infants were randomly assigned in a 1:1 ratio to receive surfactant via MISA during nCPAP (intervention group) or via EISA during positive pressure ventilation (control group). Sequentially numbered, opaque, and sealed envelopes were used to complete the group assignment. Multiple-birth infants were allocated to the same group.

Blinding

The assigned treatment was not blinded, as the mode of respiratory management was apparent to clinicians and nurses in the NICU. All enrolled infants were given routine clinical interventions according to established guidelines or protocols. Furthermore, the primary outcome and the secondary outcomes were based on objective sets of criteria applied to both groups.

Study Intervention

For infants in the MISA group, the intervention process was performed according to the flowchart shown in **Figure 1**. Once the decision regarding the surfactant administration was made, the process was initiated. A 5F end hole gastric tube catheter was used. A 5-ml syringe was prefilled at 70–100 mg/kg of body weight of the calf pulmonary surfactant preparation. This syringe was connected with the gastric tube. The tube was grasped by a 10-cm ophthalmic forceps near the tip. When the infant was breathing via nCPAP, a laryngoscope was gently introduced to provide a glottal view. The tip of the tube was positioned up to 1.0 cm below the vocal cords. The tube was tightly fixed in this position by the thumb and forefinger of the clinician. The laryngoscope and the ophthalmic forceps were removed, and the infant's mouth was closed. The surfactant was instilled by a nurse over 60 to 300 s by mini-boluses. In the case of transient bradycardia, gentle massage of the infant's back skin was performed by another nurse, until recovery. The tube was immediately removed. Sedation and analgesia were not used. During surfactant administration, nCPAP therapy was continued. During the first 72 h after birth, the nCPAP level was kept within a range of 6 and 8 cmH_2O. The nCPAP level was titrated to 5 to 6 cmH_2O to achieve the lowest FiO_2 level after 72 h.

For infants in the EISA group, once respiratory distress progressively developed and they were diagnosed as nCPAP failure, they were intubated and received positive pressure ventilation support. The surfactant was administered through an endotracheal tube. Sedation and analgesia were not used. Clinicians in NICUs were advised to use INSURE method. Positive pressure ventilation support was performed following predefined standards. Investigators were encouraged to wean the infant from positive pressure ventilation as soon as possible. Extubation criteria were established as $FiO_2 < 0.3$ and mean airway pressure (MAP) of < 8 cm H_2O.

Infants in both groups received calf pulmonary surfactant preparation (Calf pulmonary surfactant, Beijing Double-Crane Pharmaceuticals Co. Ltd.), at doses of 70–100 mg surfactant/kg of body weight. When the FiO_2 level exceeded 0.4, with progressively developed respiratory distress, repeated doses of surfactant were allowed in both groups. For the MISA group, infants with a second dose of surfactant by MISA were included. However, if the infants needed $FiO_2 > 0.40$ lasting more than 2 h during nCPAP after the first dose of surfactant and had intubated ventilation support during the first 72 h after birth, the data of the patients would be excluded from the final analysis. All infants who were spontaneously breathing and those for whom the extubation was planned received caffeine. All other clinical interventions were applied according to established standards/protocols.

Primary and Secondary Outcomes

The primary outcome was the difference in the morbidity of BPD between MISA and EISA groups of infants at 36 weeks corrected gestational age. Infants who were supported by mechanical ventilation or nCPAP or those with a fraction of inspired oxygen (FiO_2) exceeding 0.30 were diagnosed as having BPD, which was defined by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (14). If the infants were discharged before 36 weeks, they were classified according to their oxygen status at discharge.

An additional pre-specified secondary outcome was the incidence of significant complications. The infants with presence of clinical signs (respiratory rate >60/min with retractions, nasal flaring, grunting, or cyanosis) who progressively developed respiratory distress and needed supplemental oxygen ($[FiO_2] > 0.4$ for $[SpO_2] > 85\%$) received an RDS diagnosis following chest X-ray confirmation. In some cases, supplemental oxygen was necessary for progressively developed respiratory distress ($[FiO_2] > 0.4$), as well as surfactant administration before chest X-ray (6). If the chest X-ray could not confirm RDS, the infant was diagnosed as no RDS. The neonatal pneumonia was diagnosed on a combination of clinical signs, physical examination findings, and X-ray evidences from each NICU. The subtype of neonatal pneumonia included congenital pneumonia, early-onset pneumonia, and late-onset pneumonia (including ventilator-associated pneumonia, VAP) (15). Neonatal sepsis included clinical sepsis and blood culture-confirmed sepsis. Clinical sepsis was defined as clinical signs without proof of causative agent. Blood culture-confirmed sepsis was defined as clinical sepsis with proof of causative agent in the blood culture. Patent ductus arteriosus (PDA) was based on clinical signs and echocardiographic confirmation. Echocardiography was performed during screening to identify malformations, to diagnose hemodynamically significant PDA (hsPDA), and during the treatment in oral ibuprofen to monitor the closure of PDA and to estimate measurements, such as internal diameter of the duct size, pulmonary artery systolic pressure, the left ventricular ejection fraction, and so on. Surgical ligation was considered when two courses of oral ibuprofen failed to close the hsPDA (16). White matter injury and intraventricular hemorrhage (IVH) were seen on cranial ultrasound and IVH was graded as grades 1–2 and grades 3–4 (17). The diagnosis and staging of retinopathy of prematurity (ROP) were based on retinal examination, both

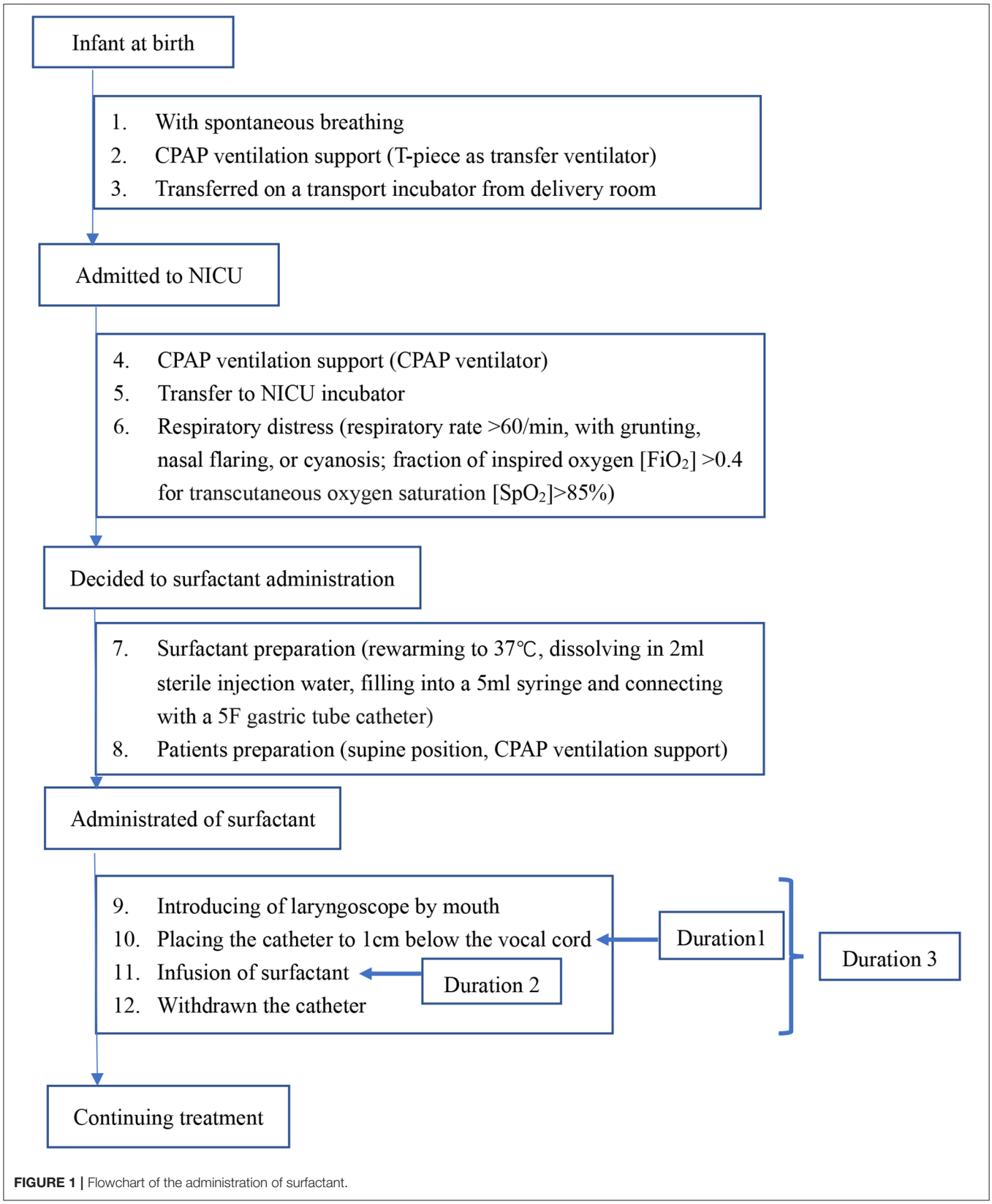

FIGURE 1 | Flowchart of the administration of surfactant.

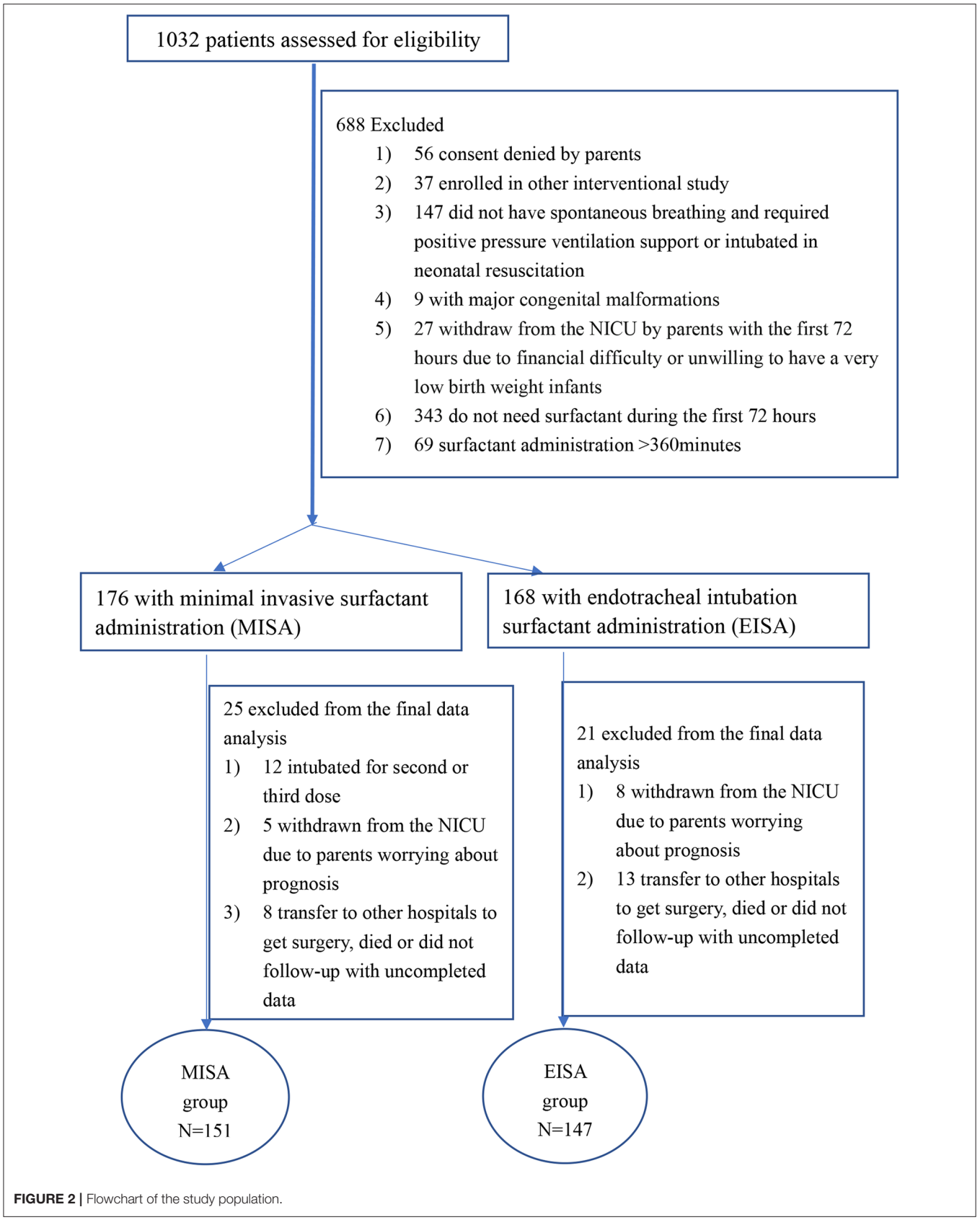

FIGURE 2 | Flowchart of the study population.

in the NICU and post-discharge. Severe ROP was defined as stages 3–5 (18). The diagnosis of necrotizing enterocolitis (NEC) was based on more than one clinical sign (e.g., bilious vomiting or hematemesis, abdominal distention, gross, or occult blood in the stool) and more than one X-ray finding (e.g., pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum) (19). Since all eight centers were level III NICU, NEC, and PDA in need of surgery were transferred to other hospitals, resulting in uncompleted data and exclusion from the final analysis. Duration of positive pressure ventilation, days on supplemental oxygen, length of NICU stay, and body weight on discharge were compared.

Short-term safety variable analyses included the following events: transient bradycardia (heart rate <100/min), SpO_2 <85%, choking and coughing, laryngeal spasms, or failure of surfactant administration. Investigators were advised to report any events and duration, including the nadir and the way of remission. Data on serious adverse events were collected.

Statistical Analysis

Based on an estimated incidence of BPD of 25.0% among infants <32 weeks of gestation (20), we calculated an alpha of 0.05 and a power of 90%; 130 infants were enrolled in each group (with a 1:1 design) to detect an absolute difference of 10 percentage points in the incidence of BPD at 36 weeks of corrected age. Therefore, we planned to recruit at least 140 infants in each group, to account for dropouts; 298 patients were enrolled until December 2018.

Analyses were performed on a pre-protocol basis according to a prespecified statistical analysis plan. The incidence of RDS, BPD, PDA, IVH, NEC, and ROP was compared between the two groups. In planned subgroup analyses (51 infants total), smaller infants with gestational age at 25+0 to 29+6 weeks were compared, and assigned to the MISA group and the EISA group, respectively.

Data are expressed as a proportion or mean ± standard deviation (mean ± SD). Proportions were compared by chi-square test or Fisher's exact test analysis. Continuous variables were compared by Student's *t*-test. A two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Subjects Characteristics

During the study period, 1,032 eligible participants were screened at the eight NICUs. However, 688 were excluded due to ≥1 exclusion criterion, or because they did not need surfactant or the surfactant was administrated after 6 h (**Figure 2**). The study was extended from 12 to 18 months because of low recruitment in some centers. Recruitment rates ranged from 12.8 to 56.5%. Parental consent was obtained within 2 h after admission to NICU if it was not obtained antenatally. A total of 344 infants were enrolled, 176 infants in the MISA group, and 168 infants in the EISA group. In the MISA group, data of 12 patients were excluded from the final data analysis because they were intubated for the second or third dose or intubated ventilation support during the first 72 h after birth. Furthermore, 34 patients in two groups were excluded from the final data analysis due to incomplete data, because they were withdrawn from the NICU care, transferred to other hospitals for surgery, or died before 28 days. Finally, data from 151 infants were analyzed in the MISA group and data from 147 infants were analyzed in the EISA group. The last follow-up was on March 30, 2019.

TABLE 1 | Demographic and clinical characteristics.

Groups	MISA ($n = 151$)	EISA ($n = 147$)	χ^2/t	p
Male*	80 (53.0)	85 (57.8)		0.400
IVF*	19 (12.6)	20 (13.6)		0.794
Antenatal corticosteroids*				0.356
No use	41 (27.1)	33 (22.4)		
Incomplete course	30 (19.9)	24 (16.3)		
Full course	80 (53.0)	90 (61.2)		
Multiple births*	33 (21.9)	38 (25.9)		0.418
Maternal complications*				
Gestational hypertensive diseases	37 (24.5)	36 (24.5)		0.998
Gestational diabetes	21 (13.9)	33 (22.4)		0.056
Premature rupture of membranes	49 (32.5)	43 (29.3)		0.550
Cesarean section*	101 (66.9)	112 (76.2)		0.075
Gestational age, weeks**	30.6 ± 1.6	30.8 ± 1.3	1.298	0.195
Birth weight, g**	1427.6 ± 290.2	1418.7 ± 273.0	0.271	0.786
Birth length, cm**	40.27 ± 3.0	40.1 ± 3.3	0.342	0.733
Birth weight < 1000 g*	11 (7.3)	7 (4.8)		0.361
Apgar score**				
1 min	8.6 ± 1.6	8.5 ± 1.8	0.062	0.950
5 min	9.3 ± 1.3	9.2 ± 1.5	0.437	0.662
10 min	9.5 ± 0.7	9.5 ± 0.8	0.640	0.645
Cord blood pH**	7.20 ± 0.06	7.22 ± 0.06	0.550	0.079

*Data are expressed as the mean ± SD or number (%). Comparisons were performed with *Pearson χ^2 or **Student's t test. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; IVF, in vitro fertilization.*

All preterm infants were treated in the hospitals in which they were born. Mean gestational age and birth weight of the study population was 30.68 ± 1.47 weeks and 1423.22 ± 281.39 g, respectively. Male:female ratio was 165:133. The basal demographic characteristics of subjects are compared in **Table 1**. The infants receiving MISA were well matched with the infants in the EISA group with similar baseline demographic and clinical characteristics.

Primary Outcomes and Complications

Following discharge from the NICU, the proportions of infants with each of the specified primary outcomes were compared between the two groups (**Table 2**). These outcomes included RDS, requiring two doses of surfactant, pulmonary hemorrhage, BPD, PDA, IVH (grades 1–2 and grades 3–4), white matter injury, pneumonia, clinical sepsis (early or late onset), stage 1 or 2

TABLE 2 | Comparison of primary outcomes and complications between two groups.

	MISA ($n = 151$)	EISA ($n = 147$)	p
RDS	139 (92.1)	141 (95.9)	0.161
Requiring two doses of surfactant	18 (11.9)	10 (6.8)	0.130
Pulmonary hemorrhage	2 (1.3)	2 (1.4)	0.679
BPD	29 (19.2)	38 (25.9)	0.170
IVH			0.351
Grades 3–4	10 (6.6)	10 (6.8)	
Grades 1–2	37 (24.5)	26 (17.7)	
White matter injury	7 (4.6)	4 (2.7)	0.381
PDA	62 (41.1)	89 (60.5)	0.001
Pneumonia	63 (41.7)	62 (42.2)	0.937
Neonatal sepsis	24 (15.9)	27 (18.4)	0.481
NEC (stage 1 or 2)	4 (2.6)	2 (1.4)	0.429
ROP	8 (5.3)	11 (7.5)	0.440

Data are expressed as number (%). Comparisons were performed with Pearson χ^2. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhages; PDA, patent ductus arteriosus, ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.

NEC, and less than stage 3 retinopathy of prematurity. Although the comparison showed no clear benefits of MISA therapy on the incidence of BPD, there was a tendency for a reduction of incidence of BPD (29/151 vs. 138/147, 19.2 vs. 25.9%, $p = 0.170$). As to the incidence of PDA, infants in the EISA group had higher rates compared to infants in the MISA group (60.5 vs. 41.1%, $p = 0.001$).

Surfactant Administration

Short-term safety variables were evaluated. In the MISA group, tube position was successfully performed in all infants, for 116 (73.62%) infants at the first attempt, and 35 (23.2%) at the second attempt. Transient bradycardia was reported in 17 infants (11.2%) from the MISA group and 12 infants (8.2%) from the EISA group, without differences between the two groups ($p = 0.367$). There was no reported case of occurrence of bloody sputum, apnea, reflux of surfactant, or the need to terminate dosing during surfactant administration.

The surfactant administration was compared between the two groups, including the surfactant infusion time after birth, dose of surfactant, and the qualification of the clinician to practice the surfactant administration (**Table 3**). The surfactant administration process is shown in **Figure 1**. The duration of surfactant infusion (Duration 2) in the MISA group (102.16 ± 158.24 s) was significantly longer than that in EISA (43.92 ± 43.29 s) ($p < 0.0001$). The total time of administration of surfactant (Duration 3) was significantly different between the two groups (122.24 ± 163.74 vs. 65.16 ± 73.84, $t = 3.896$, $p < 0.0001$). Although the clinicians' working experience between the two groups was not significant, the clinicians who practiced minimally invasive therapy had ∼1 more year of experience compared to those who practiced intubation therapy.

TABLE 3 | Comparison of surfactant administration between two groups.

	MISA ($n = 151$)	EISA ($n = 147$)	t	p
Surfactant administration time after birth, h	2.5 ± 1.7	2.47 ± 1.7	0.716	0.475
Dose of surfactant, mg/kg	100.0 ± 14.3	101.5 ± 24.9	0.645	0.519
Duration 1, s	20.5 ± 45.4	15.4 ± 15.5	1.289	0.198
Duration 2, s	102.2 ± 158.2	43.9 ± 43.3	4.358	0.000
Duration 3, s	122.2 ± 163.7	65.2 ± 73.8	3.896	0.000
Working experiences in pediatrics, years	8.5 ± 5.4	7.7 ± 5.2	1.377	0.169
Working experiences in neonatology, years	7.3 ± 4.5	6.5 ± 4.6	1.553	0.122
Working experiences in NICU, years	6.5 ± 4.4	5.8 ± 4.5	1.267	0.206

Data are expressed as mean ± SD. Comparisons were performed with Student's t test. Comparisons were performed with Pearson χ^2. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; Duration 1, placing catheter time, seconds; Duration 2, surfactant infusion duration through the catheter, seconds; Duration 3, total time of administration of surfactant, from introducing of laryngoscope by mouth, placing catheter, surfactant infusion to withdrawn of the catheter, seconds.

TABLE 4 | Blood gas comparison between two groups at three-time points.

		MISA ($n = 151$)	EISA ($n = 147$)	t	p
Pre-surfactant					
	PH	7.30 ± 0.18	7.29 ± 0.09	0.401	0.682
	PO_2, mmHg	80.15 ± 28.28	77.80 ± 25.87	0.743	0.458
	PCO_2, mmHg	47.56 ± 14.21	46.26 ± 12.37	0.830	0.407
	SaO_2, %	93.60 ± 6.75	93.68 ± 5.17	0.115	0.908
	BE, mmol/L	−5.04 ± 2.82	−4.50 ± 2.76	1.651	0.100
Post-surfactant					
1 h	PH	7.35 ± 0.09	7.34 ± 0.09	0.524	0.600
	PO_2, mmHg	75.72 ± 28.56	73.68 ± 20.89	0.685	0.494
	PCO_2, mmHg	37.20 ± 10.85	38.89 ± 12.30	1.212	0.227
	SaO_2, %	93.97 ± 6.18	94.38 ± 6.75	0.510	0.611
	BE, mmol/L	−4.53 ± 2.59	−4.15 ± 2.97	1.184	0.237
12 h	PH	7.34 ± 0.09	7.35 ± 0.10	1.103	0.271
	PO_2, mmHg	76.29 ± 23.15	76.54 ± 22.91	0.094	0.925
	PCO_2, mmHg	38.16 ± 9.38	38.39 ± 9.15	0.222	0.825
	SaO_2, %	93.85 ± 5.24	94.79 ± 5.61	1.497	0.135
	BE, mmol/L	−3.81 ± 2.67	−3.37 ± 2.67	1.411	0.159

Data are expressed as mean ± SD. Comparisons were performed with Student's t test. PO_2, partial pressure of oxygen; PCO_2, the partial pressure of carbon dioxide; SaO_2, arterial saturation of peripheral oxygen; BE, base excess.

Blood gas Analysis

The blood gas analysis of two groups of infants was done at three time points, before surfactant and 1 h and 12 h post surfactant administration (**Table 4**). The arterial pH, the partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), and the arterial oxygen saturation (SaO_2) value were not significantly different between the two groups at three time points.

TABLE 5 | Comparison of heart rate and blood pressure between two groups.

		MISA ($n = 151$)	EISA ($n = 147$)	t	p
Pre-surfactant					
	HR (bpm)	137.6 ± 11.1	136.3 ± 14.9	0.829	0.408
	SBP (mmHg)	61.0 ± 8.1	59.8 ± 9.6	1.247	0.213
	DBP (mmHg)	32.4 ± 6.1	32.3 ± 7.6	0.158	0.875
Post-surfactant					
1 h	HR_1 (bpm)	136.7 ± 13.4	139.6 ± 10.5	2.086	0.038
	SBP_1 (mmHg)	60.9 ± 8.5	59.5 ± 8.0	1.488	0.138
	DBP_1 (mmHg)	32.8 ± 7.3	33.2 ± 6.3	0.545	0.586
6 h	HR_6 (bpm)	137.3 ± 10.8	139.1 ± 10.5	1.419	0.157
	SBP_6 (mmHg)	61.7 ± 7.2	61.4 ± 7.1	0.428	0.669
	DBP_6 (mmHg)	32.7 ± 5.4	33.0 ± 5.0	0.491	0.624
12 h	HR_{12} (bpm)	136.4 ± 11.4	136.7 ± 11.3	0.292	0.770
	SBP_{12} (mmHg)	62.1 ± 7.6	61.1 ± 6.8	1.134	0.258
	DBP_{12} (mmHg)	33.0 ± 6.3	32.9 ± 4.8	0.294	0.769
24 h	HR_{24} (bpm)	137.0 ± 11.1	137.1 ± 10.0	0.098	0.922
	SBP_{24} (mmHg)	62.9 ± 8.3	62.8 ± 7.9	0.113	0.910
	DBP_{24} (mmHg)	34.1 ± 5.4	34.0 ± 5.2	0.085	0.932

Data are expressed as mean ± SD. Comparisons were performed with Student's t test. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; HR heart rate (bpm); SBP, systolic blood pressure (mmHg); DB, diastolic blood pressure (mmHg).

Heart Rate and Blood Pressure

Heart rate, systolic blood pressure, and diastolic blood pressure were compared between the two groups before surfactant administration and 1, 6, 12, and 24 h after surfactant administration (**Table 5**). A slightly increased heart rate was noted 1 h post surfactant administration in the EISA group ([139.63 ± 10.54] bpm) compared to the MISA group ([136.72 ± 13.36] bpm, $t = 2.086$, $p = 0.038$); the observed difference was statistically significant.

Respiratory Support and Discharging Data

There were no differences in the duration of nCPAP respiratory support and supplemental oxygen (**Table 6**) between the two groups. Infants in both groups stayed at NICU for nearly 40 days, with around 36 weeks corrected gestational age and gained similar body weight.

Subgroup Analysis

In the subgroup analysis, demographic, clinical characteristics, and neonatal complications of 51 smaller preterm infants (defined as 25+0 weeks to 29+6 weeks) between the two groups, named minimally invasive administration smaller (MISAs) group and endotracheal intubation administration smaller (EISAs) group, were compared (**Table 7**). The comparison showed a significant reduction in morbidity of BPD (9/31, 29.0 vs. 14/20, 70.0%, $p = 0.004$) and PDA (9/31, 29.0, vs. 13/21, 65.0%, $p = 0.011$).

The blood gas analysis of small preterm infants was compared at two time points, 1 and 12 h post surfactant administration (**Table 8**). Arterial oxygen saturation (SaO_2) value was higher in the EISAs group (96.06 ± 4.10) compared with the MISAs group (91.68 ± 8.31) at 1 h ($t = 2.075$, $p = 0.044$). In the EISAs group, at 12 h after surfactant administration, the partial pressure of arterial oxygen (PaO_2, [82.33 ± 23.24] vs. [67.46 ± 19.54], $t = 2.461$, $p = 0.017$) and SaO_2 ([96.39 ± 3.23] vs. [92.67 ± 6.32], $t = 2.422$, $p = 0.019$) were higher than in the MISAs group.

TABLE 6 | Comparison of respiratory support and discharge data between two groups.

	MISA ($n = 151$)	EISA ($n = 147$)	t	p
nCPAP duration, days	10.3 ± 12.2	10.7 ± 11.2	0.286	0.755
Supplemental oxygen duration, days	15.7 ± 16.4	16.1 ± 15.7	0.237	0.813
Hospitalization days, days	39.8 ± 17.1	39.5 ± 15.4	0.201	0.841
Corrected gestational age, weeks	36.1 ± 2.1	36.3 ± 1.8	1.098	0.273
Body weight, g	2075.2 ± 217.1	2071.5 ± 191.3	0.157	0.875

Data are expressed as mean ± SD. Comparisons were performed with Student's t test. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; nCPAP, nasal continuous positive airway pressure.

TABLE 7 | A subgroup comparison of smaller preterm infants between two groups.

Groups	MISAs ($n = 31$)	EISAs ($n = 20$)	t	p
Gestational age, weeks**	28.1 ± 1.2	28.4 ± 0.5	0.471	0.195
Birth weight, g**	1140.8 ± 187.6	1167.5 ± 203.7	0.271	0.786
RDS*	27 (87.1)	20 (100.0)		0.094
BPD*	9 (29.0)	14 (70.0)		0.004
IVH*				0.176
Grades 3–4	3 (9.7)	0 (0)		
Grades 1–2	10 (32.3)	4 (20.0)		
White matter injury*	2 (6.5)	1 (5.0)		0.830
PDA*	9 (29.0)	13 (65.0)		0.011
Pneumonia*	13 (41.9)	7 (35.0)		0.771
Clinical sepsis (early or late onset) *	7 (22.6)	5 (25.0)		0.842
ROP*	4 (12.9)	5 (25.0)		0.269

*Data are expressed as the mean ± SD or number (%). Comparisons were performed with *Pearson χ^2 or **Student's t test. MISA, minimally invasive surfactant administration; EISA, endotracheal intubation surfactant administration; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhages; PDA, patent ductus arteriosus, ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis.*

DISCUSSION

In this study, we evaluated whether MISA was applicable in infants at 25 weeks to 31 + 6 weeks gestational age in China, and whether this method of surfactant administration decreases incidence of BPD at 36 weeks corrected gestational age compared with intubation surfactant administration therapy. Although the comparison showed no clear benefits of MISA therapy on the reduction of BPD in infants less than 32 weeks gestational age, a reduced incidence of BPD was observed

TABLE 8 | A subgroup post-surfactant blood gas comparison of smaller preterm infants between two groups.

		MISAs ($n = 31$)	EISAs ($n = 20$)	t	P
1 h	PH	7.35 ± 0.10	7.33 ± 0.75	0.806	0.424
	PO_2, mmHg	69.31 ± 20.89	78.97 ± 24.97	0.344	0.156
	PCO_2, mmHg	38.67 ± 12.12	34.27 ± 9.59	1.310	0.197
	SaO_2, %	91.68 ± 8.31	96.06 ± 4.10	2.075	0.044
	BE, mmol/L	−3.85 ± 2.79	−4.86 ± 1.80	1.371	0.177
12 h	PH	7.33 ± 0.09	7.30 ± 0.12	1.200	0.236
	PO_2, mmHg	67.46 ± 19.54	82.33 ± 23.24	2.461	0.017
	PCO_2, mmHg	36.82 ± 9.58	39.95 ± 8.74	1.181	0.243
	SaO_2, %	92.67 ± 6.32	96.39 ± 3.23	2.422	0.019
	BE, mmol/L	−3.88 ± 3.20	−4.37 ± 2.13	0.608	0.546

Data are expressed as mean ± SD. Comparisons were performed with Student's t test. PO_2, partial pressure of oxygen; PCO_2, the partial pressure of carbon dioxide; SaO_2, arterial saturation of peripheral oxygen; BE, base excess.

in smaller infants, i.e., less than 30 weeks gestational age. A significant reduction rate of survival without PDA in the MISA group was demonstrated. The duration of required MISA was as long as 5 min, which was longer than the intubation therapy. Fluctuations in heart rate of intubated infants were observed more than MISA infants. Subgroup comparison of smaller infants (<30 weeks) in the minimally invasive group showed a significant reduction in morbidity of BPD and PDA. Also, according to blood gas analysis, SaO_2 and PaO_2 values of smaller infants were relatively lower compared with intubation controls.

Over the last decade, there have been many changes in the ventilation support and the modality of exogenous surfactant administration to RDS infants (21). Due to the potential injury of intubation and positive pressure ventilation to the immature lung, attempts have been made to use non-invasive methods in the management of these patients. The nCPAP has been recommended as the initial respiratory support for spontaneous breathing infants (6). However, in the COIN study, more than 50% of ELBWs failed on nCPAP (22), although stabilization in the delivery room with nCPAP was successful. LISA and MIST reflect the efforts of neonatologists for pursuing the most protective technique to the most immature lung of the ELBW infants (10–12, 23). The core of these less invasive techniques involves the use of a thin catheter (24).

In the current study, we named our method MISA for the following three reasons. First, there is a potential for injury to the mucosa of upper airway because of the introduction of direct laryngoscope, so we used the word "minimally."A 5F end hole gastric tube catheter and ophthalmic forceps were used through the mouth into the pharynx directly under laryngoscopy. Second, since Magill forceps were unavailable in our NICUs, the small ophthalmic forceps were used as an alternative to grasp the gastric tube catheter, which was made of soft polyethylene. This technique may be easier for those who are not experienced in Magill forceps. Third, we kept the infant's mouth closed and continued nCPAP during surfactant administration. Our method had more or less differences with the LISA and the MIST, so we named it MISA.

In the current study, MISA was successfully performed in all eight NICUs, although in some cases, a second attempt was needed. However, in this study, the clinicians that practiced minimally invasive therapy had approximately one more year of experience compared to the ones who practiced intubation therapy, which means that clinicians need one additional year of training in the neonatal endotracheal intubation.

In this study, the surfactant was instilled by hand as long as 300 s by mini-boluses. Cases requiring intubation and positive pressure ventilation support during the first 72 h in the MISA group were excluded because even a brief exposure to positive pressure ventilation has been shown to be related to the occurrence of BPD and to induce ventilator-associated lung injury (25). Although potential adverse events were previously reported, only bradycardia was detected in this study. In cases with bradycardia, surfactant infusion was suspended until heart rates recovered to normal while nCPAP was continued (26). Also, there was a slightly increased heart rate in intubation therapy after 1 h of surfactant administration (27). Consequently, we believe that MISA is applicable to the level III NICUs in China, provided there is a staff experienced in neonatal endotracheal intubation.

BPD affects more than 30% of infants with body weight <1,250 g at birth. Despite the use of surfactant and NICU advances permitting more premature infants to survive, the incidence of BPD is slowly growing (7). The less invasive method of surfactant injection has attracted more attention in the neonatal respiratory diseases sector. In a meta-analysis, Lau et al. compared subjects in the thin catheter group with the INSURE group. They found that fewer infants developed BPD (18/166 [10.8%] vs. 27/162 [16.7%]). Forest plot showed a 34.4% reduction in the risk of BPD (RR = 0.656; 95% CI = 0.375–1.149; $p = 0.141$) without statistical significance (28). Several previous studies enrolled subjects with younger gestational age and birth weight compared to our MISA study. In the Take Care study, Kanmaz et al. recruited 100 RDS infants in the LISA group with 28.3 ± 2 gestational age and mean birth weight 1093 ± 270 g (29). The subjects in the study of Mohammadizadeh et al. had a gestational age of 30 ± 2 weeks and a birth weight of 1289 ± 219 g (30). Another study in China conducted by Bao et al. enrolled infants in LISA with a gestational age of 29.1 ± 1.5 weeks and a birth weight of 1034 ± 221 g (27). In these three mentioned studies, researchers proved that the BPD rate was significantly lower in the thin catheter group (29).

There was no apparent benefit of MISA therapy on the incidence of BPD in this study. An alternative explanation for the unfavorable outcome for this study population was the relatively larger gestational age and birth weight, which was a limitation of the study. We speculate that reason for this finding may be the strategy of initial respiratory support and the optimal time of surfactant supplement. As we know, the CPAP stabilizes the alveoli, lessens retraction during inspiration,

improves compliance, and respiratory mechanics. This leads to a better gas exchange. In NRDS infants, surfactant supplement at the optimal time decreases surface tension, leading to increased compliance and improved functional residual capacity. In smaller NRDS infants, the action between CPAP support and surfactant supplement may have better effectiveness. Then, in the subgroup analysis, there is a significant reduction rate of survival without BPD in infants <30 weeks gestational age in the MISAs group. Although it seems to suggest a particular patient subgroup where the technique could be more useful, the cases with intubation and positive pressure ventilation support during the first 72 h were excluded in the data analysis in the current study. Thus, we could only prove that the incidence of BPD was not different between the two groups. It cannot be decided if it were minimally invasive therapy per se, never being intubated, or never being under invasive ventilation support that reduced BPD in infants smaller than 30 weeks gestational age.

A significant reduction rate of survival without PDA was demonstrated in minimally invasive therapy, which is the most promising result of the study. Pulmonary circulation embryology is intrinsically related to cardiovascular and pulmonary development. The transition from intrauterine to extrauterine life is a critical phase in physiological adaptation, which impacts many organ systems, especially the heart and the lungs (31). While alterations in the respiratory system can significantly affect cardiovascular function, the opposite is also exact. Infants with RDS had decreased lung compliance and increased airway resistance, which led to increased work of breathing, alveolar hypoventilation, and CO_2 retention. In more severe cases, this can also compromise oxygenation and cardiac function. The deleterious effects of the PDA with significant left to right shunting and increased pulmonary blood flow on lung function are also well established (32). A hemodynamically relevant PDA has been associated with pulmonary edema and respiratory compromise has been associated with a resultant higher incidence of BPD. Excessive pulmonary blood flow via the pulmonary vascular bed results in an interrupted lung structure similar to the characteristic BPD changes in immature infants with extremely low birth weight (33). Therefore, a more stable hemodynamics with less PDA could explain the significant reduction in morbidity of BPD in the MISAs group in the subgroup analysis.

Intubation resulted in higher levels of arterial oxygen saturation (SaO_2) values at 1 h and higher levels of SaO_2 and PaO_2 values at 12 h after surfactant administration in the subgroup comparison of smaller infants. Although the mechanisms of BPD development were complicated, hyperoxia damage was thought to be one of the main factors (34). Although necessary to sustain the preterm infant's life, relatively high oxygenation, and positive pressure ventilation damage the lung by dysregulation of the growth of the pulmonary vasculature and the lung parenchyma. It has been established that intubation and exposure to high concentrations of oxygen, even for a brief period, may cause harm, predisposing infants to lung injury and subsequent BPD (25). In a meta-analysis, Askie et al. collected the data from five clinical trials completed between 2005 and 2014 (35). A total of 4,965 infants born before 28 weeks' gestation were randomized to two SpO_2 target range groups, the lower (85–89%) and the higher (91–95%). The results suggested that the lower group was related to a higher risk of death and NEC, and a lower risk of ROP and BPD. Therefore, lower levels of arterial oxygen saturation (SaO_2) values at 1 h and lower levels of SaO_2 and PaO_2 values at 12 h could explain the significant reduction in morbidity of BPD in the MISAs group in the subgroup analysis.

There are some limitations to this study. First, as mentioned above, the subjects had relatively larger gestational age and birth weight. Second, group allocation was not blinded, so it is possible that the clinical treatment of the individual infant was influenced by the treating clinicians knowing the group assignment. Third, although extubation criteria were established, there were eight NICUs in the study, which means that the extension of positive pressure ventilation in some cases of the intubation group could not be ruled out, thus resulting in longer days of positive pressure ventilation and an ultimately higher rate of BPD. Future study in this field is required to consider the abovementioned factors, i.e., surfactant administration by minimally invasive or INSURE, intubated or never intubated, and invasive or non-invasive ventilation support.

CONCLUSION

MISA was not superior in relation to the primary outcome of the study, but it was related to benefits in reducing the incidence of PDA, which suggests less hemodynamic interference in infants with extremely/very low birth weight during the critical transition phase of physiological adaptation shortly after birth. MISA is an applicable therapy for extremely/very low birth weight preterm infants with respiratory distress syndrome. However, before its endorsement in all regions, clinicians should undergo necessary training to gain more experience.

WHAT IS KNOWN

Minimally invasive surfactant administration to the spontaneous breathing preterm infants with nasal continuous positive airway pressure support could reduce the risk of bronchopulmonary dysplasia.

WHAT IS NEW

Minimally invasive surfactant administration is associated with a decreased incidence of patent ductus arteriosus in infants with extremely/very low birth weight.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University Third Hospital

Medical Science Research Ethics Committee (M2017160). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TH, HL, HZ, XuZ, FS, XiZ, MZ, LB, WL, RJ, XTi, QG, WZ, and LL made contributions to the conception or design of the work or data acquisition, analysis, and interpretation. TH, HL, HZ, and XTo performed formal analysis and data curation, drafted the work, or critically revised for important intellectual content. TH, MG, YD, XL, FL, MX, JZ, WG, and XTo provided approval for publication of the content. All authors agree to be responsible for all aspects of the work to ensure proper investigation and resolution of issues related to the accuracy or integrity of any part of the work.

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REVIEW
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A Review on Non-invasive Respiratory Support for Management of Respiratory Distress in Extremely Preterm Infants

Yuan Shi[1], *Hemananda Muniraman*[2], *Manoj Biniwale*[3] *and Rangasamy Ramanathan*[4]*

[1] Ministry of Education Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics, Children's Hospital of Chongqing Medical University, Chongqing, China, [2] Department of Pediatrics, Creighton School of Medicine, Omaha, NE, United States, [3] Neonatology Association Limited, Obstetrix Medical Group of Phoenix, Mednax, Arizona, AZ, United States, [4] Division of Neonatology, LAC+USC Medical Center, Keck School of Medicine of the University of Southern California, Los Angeles, CA, United States

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***Correspondence:**
Rangasamy Ramanathan
ramanath@usc.edu

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Majority of extremely preterm infants require positive pressure ventilatory support at the time of delivery or during the transitional period. Most of these infants present with respiratory distress (RD) and continue to require significant respiratory support in the neonatal intensive care unit (NICU). Bronchopulmonary dysplasia (BPD) remains as one of the major morbidities among survivors of the extremely preterm infants. BPD is associated with long-term adverse pulmonary and neurological outcomes. Invasive mechanical ventilation (IMV) and supplemental oxygen are two major risk factors for the development of BPD. Non-invasive ventilation (NIV) has been shown to decrease the need for IMV and reduce the risk of BPD when compared to IMV. This article reviews respiratory management with current NIV support strategies in extremely preterm infants both in delivery room as well as in the NICU and discusses the evidence to support commonly used NIV modes including nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), bi-level positive pressure (BI-PAP), high flow nasal cannula (HFNC), and newer NIV strategies currently being studied including, nasal high frequency ventilation (NHFV) and non-invasive neutrally adjusted ventilatory assist (NIV-NAVA). Randomized, clinical trials have shown that early NIPPV is superior to NCPAP to decrease the need for intubation and IMV in preterm infants with RD. It is also important to understand that selection of the device used to deliver NIPPV has a significant impact on its success. Ventilator generated NIPPV results in significantly lower rates of extubation failures when compared to Bi-PAP. Future studies should address synchronized NIPPV including NIV-NAVA and early rescue use of NHFV in the respiratory management of extremely preterm infants.

Keywords: bronchopulmonary dysplasia (BPD), nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC), nasal high frequency ventilation (NHFV), noninvasive ventilation (NIV), noninvasive ventilation-neurally adjusted ventilatory assist (NIVNAVA)

INTRODUCTION

Providing optimal ventilation strategies remains the key to success of managing extremely preterm infants. Majority of the extremely preterm infants have respiratory distress (RD) needing significant respiratory support immediately after birth or after admission to the neonatal intensive care unit (NICU) due to poor inspiratory effort, weak intercostal muscles, and poor diaphragmatic function. These infants are at very high risk of developing bronchopulmonary dysplasia (BPD) and adverse neurodevelopmental outcomes, which are directly related to the duration of invasive mechanical ventilation (IMV) and supplemental oxygen. The strong association between ventilator dependency and neurologic injury, such as severe intraventricular hemorrhage (IVH) and periventricular leucomalacia, emphasizes the severity of their illness (1). A recent study showed more than 60 days of positive pressure support regardless of invasive or non-invasive ventilation (NIV) mode was associated with a higher risk for neurodevelopmental problems (2). Avoiding intubation and using NIV modes in preterm infants minimizes the risk for lung injury and optimizes neonatal outcomes. Use of nasal continuous positive airway pressure (NCPAP) in the delivery room and nasal intermittent positive pressure ventilation (NIPPV) in the NICU has been shown to decrease the need for IMV in extremely preterm infants without increasing major morbidities (3).

In extremely preterm infants, BPD is associated with long term impaired pulmonary function and adverse neurological outcomes (4–6). While the etiology of BPD is multifactorial, lung injury particularly with IMV and resulting inflammation play a major role in the pathogenesis (7). NIV has been shown to reduce the risk of BPD when compared to IMV (8). Ventilatory practices have evolved over the last few decades with preference for NIV in the management of respiratory distress syndrome (RDS) in extremely preterm infants (4). Also, the definition of BPD is constantly evolving. Existing definitions mostly relied on level and duration of supplemental oxygen and did not take into account the major changes in NIV modes that are currently used in preterm infants. Recently, in a study using 18 pre-specified definitions of BPD that used disease severity based on level of respiratory support and supplemental oxygen at 36 weeks' postmenstrual age (PMA), only mode of respiratory support best predicted early childhood morbidity, regardless of supplemental oxygen use. Our focus should be to assess and follow the extremely preterm infants based on level of non-invasive as well as invasive positive pressure support at the time of discharge and after discharge (9).

MODES OF NON-INVASIVE VENTILATION

Six modes of NIV are currently used in extremely preterm infants. Four of the six modes commonly used in most of the NICUs include NCPAP, bilevel positive airway pressure (Bi-PAP) or sigh breaths above a baseline CPAP pressure (Si-PAP), NIPPV and high flow nasal cannula (HFNC) (**Figure 1**). Remaining 2 modes, namely, nasal high frequency ventilation (NHFV) using nasal high frequency oscillatory ventilation (NHFOV) or nasal high frequency jet ventilation (NHFJV) and non-invasive neurally adjusted ventilatory assist (NIV-NAVA) are

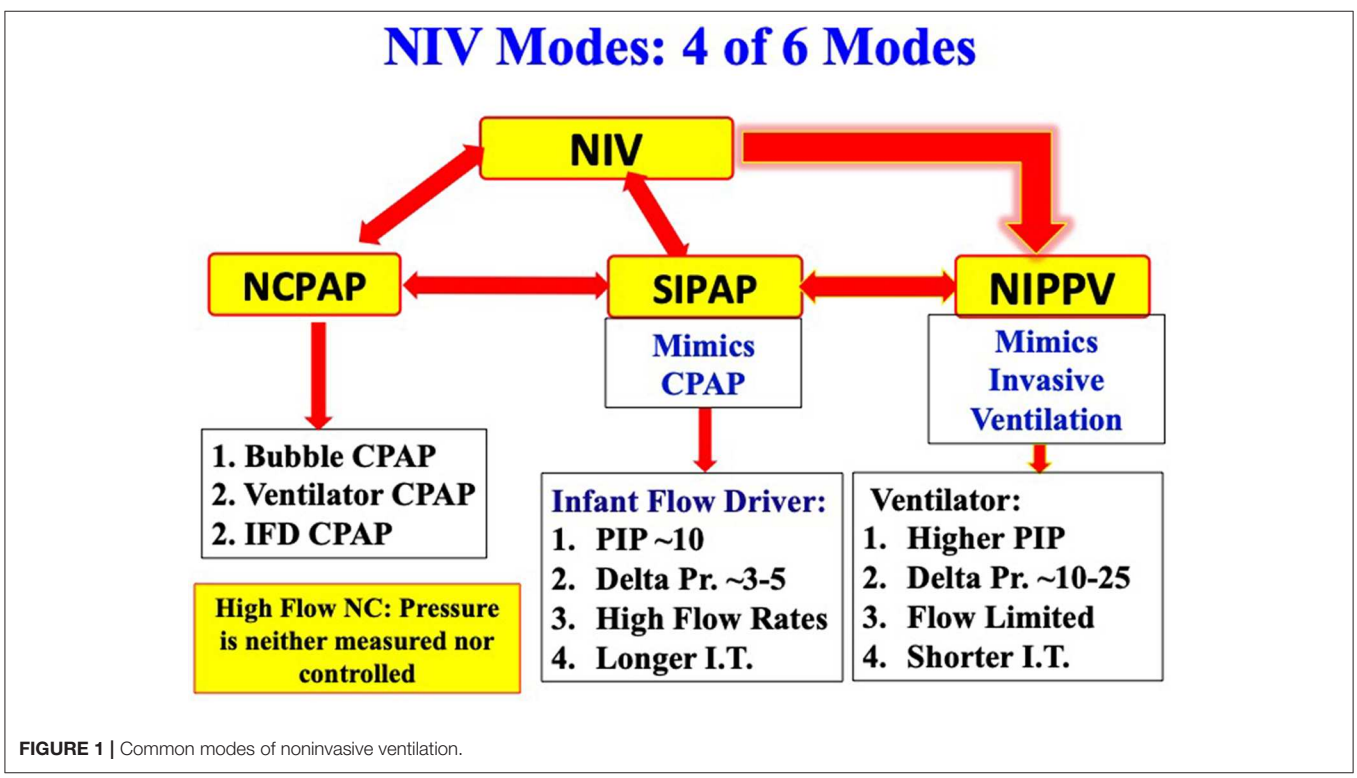


FIGURE 1 | Common modes of noninvasive ventilation.

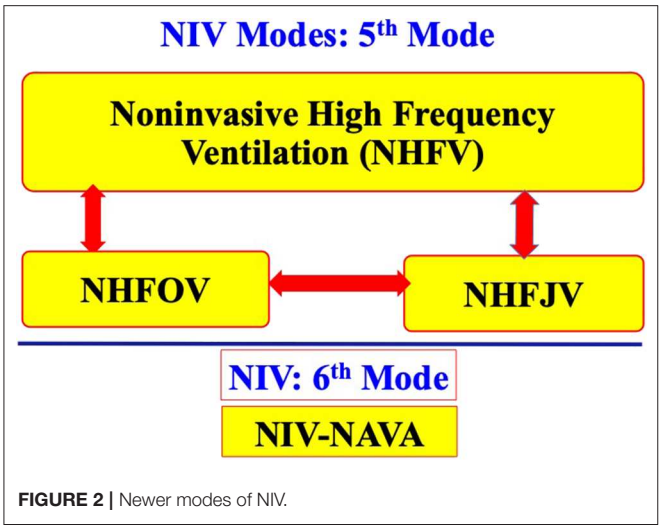


FIGURE 2 | Newer modes of NIV.

not well-studied in extremely preterm infants and need further evaluations before routine use of these modes (**Figure 2**). Positive pressure delivery during NIV involves pressure generators, nasal interfaces (**Figure 3**) and ability to provide one or two levels of pressures at different ventilator rates. NIV in the NICU can be provided by these modalities either as a primary mode of respiratory support or following extubation after a period of IMV. NHFV modes are also being used increasingly as a rescue mode to treat hypercarbia and to decrease the need for intubation in extremely preterm infants failing other modes of NIV support. NIV can also be used in combination with early, rescue surfactant treatment. Surfactant can be delivered using invasive techniques such as INSURE (INtubation, SURfactant, and Extubation), minimally invasive techniques including SurE (surfactant without endotracheal intubation) using a feeding tube or a specially designed catheter, laryngeal mask airway, or non-invasive technique, like, nebulization (10–13).

MECHANISMS OF NIV

Physiological mechanisms leading to improvement in the lung mechanics are somewhat similar with all these modes of NIV. NCPAP reduces upper airway resistance, helps to establish functional residual capacity (FRC), decreases chest wall distortion, augments spontaneous breathing efforts, preserves endogenous surfactant, decreases the need for surfactant administration, and decreases the need for, and duration of IMV (14). However, in patients with hypopnea or apnea, NCPAP often fails, needing intubation and IMV. Providing a backup rate using NIPPV with adequate peak inspiratory pressure (PIP) decreases apneic spells, improves ventilation and decreases the need for intubation. NIPPV is a time cycled, pressure limited mode of ventilation. Conventional ventilator is used to generate two levels of pressures, namely, PIP and positive end expiratory pressure (PEEP). Additionally, a backup rate is provided typically using longer inspiratory time. Benefits of NIPPV mode include all of the benefits of NCPAP listed above, and pharyngeal dilation with further decrease in upper airway resistance, augmentation of spontaneous inspiratory effort via Head's paradoxical reflex, improving compliance and reopening of partially collapsed airways, increase in FRC, increase in tidal volume (Vt) and minute volume, better alveolar recruitment due to higher mean airway pressure (MAP), reduction in chest wall distortion, and improved respiratory unloading with decrease in work of breathing (15). Head's paradoxical reflex is seen typically during a rapid inflation of the lungs causing a deep inspiration or gasp. It is mediated by the irritant receptors of the major airways receptive to lung inflation. The reflex is seen most commonly on the first day and may help to establish and maintain FRC. Head's paradoxical reflex has also shown to possibly increase neural inspiratory time in patients receiving NIV-NAVA (16). NIPPV also stimulates the Hering-Breuer inflation reflex with inflation of lungs resulting in cessation of respiratory activity preventing hyperinflation. This reflex is mediated through the stretch receptors in the smooth muscles of the major airways and is time-dependent with a longer inspiratory time resulting in a longer period of respiratory inhibition before the next breath. Both NCPAP and NIPPV modes may trigger this reflex, causing slower spontaneous respiratory rate. In the preterm infants, this reflex produces rapid, shallow tidal breathing. In older infants this reflex prevents excessive tidal volumes and can only be stimulated if the inflating volume is increased beyond a critical threshold.

Proposed mechanisms for the use of HFNC include washout of nasopharyngeal dead space, decrease in inspiratory resistance, and provision of positive pressure. However, pressure generated during HFNC is neither measured nor controlled by the clinician and is very unpredictable (17). NHFV modes promote better lung recruitment and removal of carbon dioxide.

DEVICES FOR DELIVERING NIV

NCPAP may be provided using a water column as a resistor to generate CPAP (Bubble CPAP), or using a flow generator as in infant flow driver (IFD) device, or using a conventional ventilator with continuous or variable flow rates. Studies comparing different modes of providing NCPAP have shown no significant difference in extubation failure rates (18, 19). Most commonly used bi-level modes include Bi-PAP, Si-PAP, and Duo-PAP. IFDs are variable flow devices, and generate two levels of pressures, a high pressure and a low pressure or CPAP by varying the flow rates. Bi-PAP/Si-PAP mimics NCPAP due to low delta pressure in these modes. The delta pressure during bi-level mode is between 5 and 10 cmH_2O, which often is not enough to treat hypercapnia or support poor spontaneous respiratory efforts.

Most of the conventional ventilators can provide NIPPV with PIP, PEEP, and rate to provide adequate support. Furthermore, flow can be adjusted to provide adequate pressure or compensate for leaks. Newer ventilators have NIV modes with excellent leak compensation. Only one type of ventilator provides NIV-NAVA mode. Both high frequency oscillatory ventilator as well as high frequency jet ventilators can be used to provide NHFV. HFNC

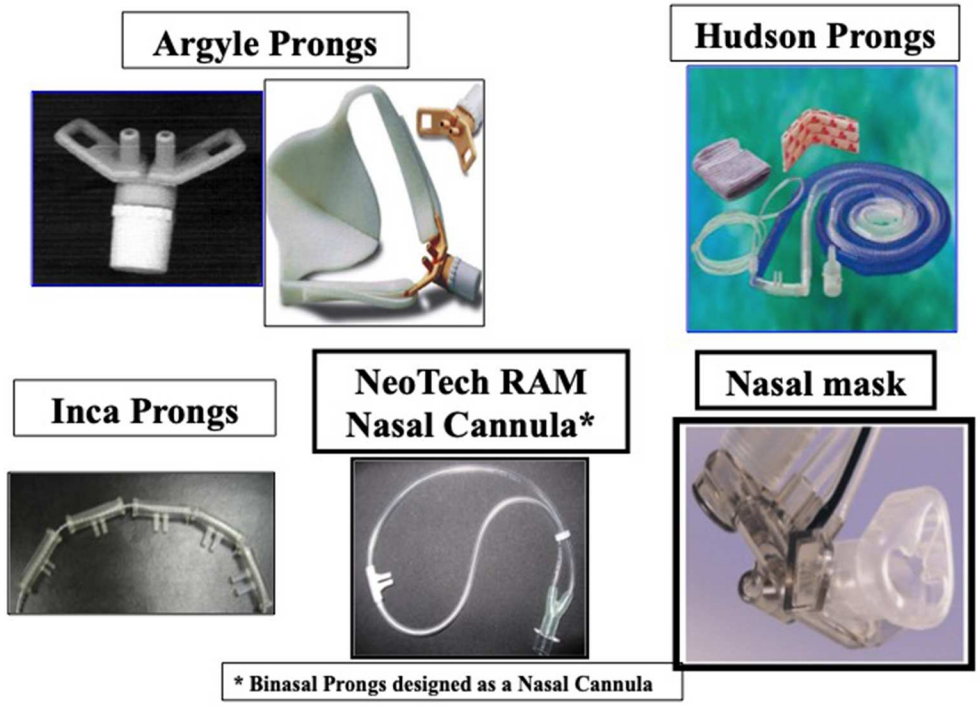


FIGURE 3 | Nasal interfaces to provide NIV.

is provided by dedicated devices where only flow is adjusted to optimize gas exchange.

NASAL INTERFACES IN DELIVERY ROOM AND NICU

Common interfaces used in the delivery room (DR) to provide NIV support are round and anatomical mask, single or bi-nasal nasopharyngeal prongs, bi-nasal prongs, nasal mask, or RAM nasal cannula (NC) (Neotech RAM Nasal Cannula®, Neotech Products, Valencia, California, USA) with pressure generating devices including self-inflating or flow-inflating bag, and T piece resuscitator (20). Bag and mask resuscitation is often not effective in the DR even when performed by the experienced personnel in extremely preterm infants. Three major issues with bag and mask ventilation are: mask leak, upper airway obstruction from the tongue falling backwards toward the oropharynx and increase in dead space with the gas in the oropharynx not contributing to gas exchange (21–24). Corrective ventilation steps during resuscitation are taught using MRSOPA mnemonic: Mask adjustment, Repositioning airway, Suctioning, Opening the mouth, Increasing inspiratory pressure, and Alternative airway. These steps are not always successful, especially among very preterm infants. The greater the number of MRSOPA steps used in the DR, the more likely intubation occurred (25). In another study, MRSOPA maneuvers improved tidal volume delivery in some cases, but, worsened exhaled tidal volumes in others. In fact, these authors found MRSOPA steps actually induced mask leak and airway obstruction in some cases (26). In a randomized, controlled trial, use of NC vs. face mask for primary neonatal resuscitation in the DR in more mature neonates (mean GA 36 weeks), NC use resulted in significantly less need for intubation (0.6 vs. 6.3%; $p < 0.001$) and chest compressions (1.65 vs. 8.28%; $p = 0.001$) in the NC group (27).

Successful use of RAM NC for the resuscitation of very low birth weight infants and decreased the need for intubation even among the lower gestational age infants (mean GA 27 weeks) has been reported (28). A recent study in <29 weeks' gestation infants used sustained lung inflation (SLI) followed by NCPAP ranging from 6 to 8 cmH_2O, using RAM NC resulted in a significant reduction in intubation rates in the DR (29). Success with the use of RAM NC as an interface is likely due to delivery of tidal volume through the nasopharynx, eliminating dead space by avoiding oropharyngeal space, ease of application with T-Piece resuscitator, and minimizing upper airway obstruction (**Figure 4**) (30). In addition, sustained inflation or NIPPV may be applied in preterm infants needing additional support without manipulating the tiny infants during resuscitation. Among the pressure delivery devices, T piece resuscitator delivers targeted inflation pressure more consistently compared to self-inflating or flow inflating

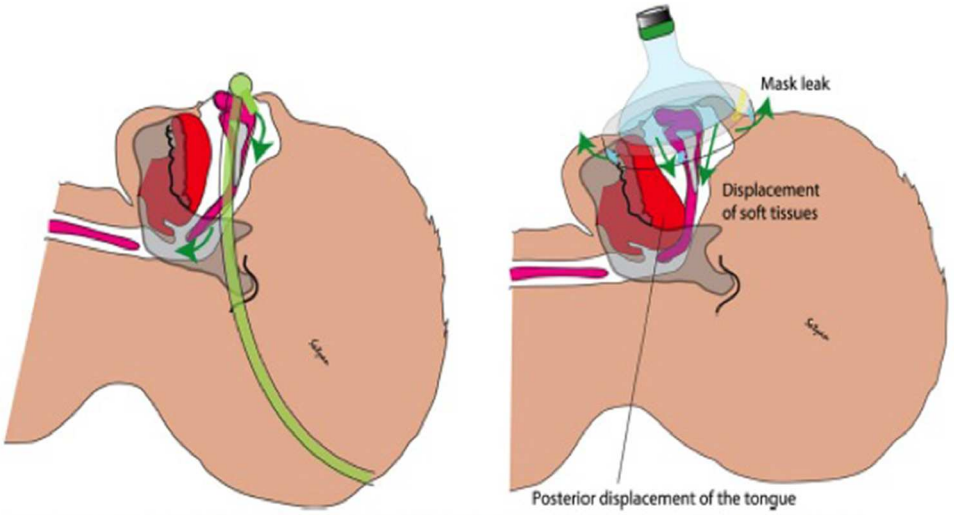


FIGURE 4 | Application of RAM NC in the NICU.

bag although this has not been shown to improve clinical outcomes (31).

Various interfaces used in the NICU include varieties of short nasal prongs, RAM NC and nasal masks. There is considerable variation in measured resistance between these interfaces. When applying smallest size interfaces for extremely preterm infants all nasal interfaces result in decrease in pressures due to high resistance. Pressure drop may vary based on the set flow, internal diameter and length of the prongs. Use of interfaces with high resistance may result in a greater drop in delivered airway pressure in comparison to set pressure (32). Application and advantages of RAM NC to provide NIV in the NICU are shown in **Figure 5**. Clinicians need to be aware of adjusting pressure and flow settings while using the ventilator to provide NIV. A meta-analysis of studies with nasal mask comparing to binasal prongs showed significantly decreased the risk of CPAP failure (4 RCTs [$N = 459$]; relative risk [RR]: 0.63; 95% confidence interval [CI]: 0.45–0.88; $P = 0.007$; $I^2 = 0\%$, NNT: 9), and the incidence of moderate to severe nasal trauma (3 RCTs [$N = 275$], RR: 0.41; 95%CI, 0.24–0.72; $P = 0.002$; $I^2 = 74\%$, NNT: 6) (33). Larger studies are needed to validate safety and efficacy of using nasal masks in extremely preterm infants.

Pressure Transmission During NIPPV

Pressure transmission to the hypopharynx or to the lung during NIPPV is difficult to measure. It depends on the size of the prongs, length of tubing, leaks around the nostrils, and set inspiratory time and whether the infant's mouth is open or closed. Using a computerized test lung simulator, pressure transmission using different size RAM NCs has been reported. In this well-designed study with a 30% leak, authors demonstrated around 70, 80, and 90% of set PIP delivered to the hypopharynx with preemie, newborn, and infant size RAM NCs respectively (34). More studies are needed comparing similar diameter prongs and similar leak settings. If a higher CPAP or PEEP is needed, then, the leak at the nasal interface may be decreased by using cannulaide® (Beever Medical Solutions, OR, USA).

Temperature and Humidity During NIV

Heating and humidification of inspired gas is a routine practice when providing respiratory support in infants. Unconditioned dry and cold gas can result in impaired ciliary function, reduced clearance of secretions, damage to the airway mucosa which may impair lung function by reducing compliance and FRC. Different NIV interfaces deliver inspiratory gases of variable temperature and humidity. Some HFNC and variable flow CPAP devices at higher gas flow may not achieve the recommended temperature and humidity (35). Higher NHFOV settings with low frequencies, high amplitudes, and high inspiratory to expiratory ratios may also place infants at an increased risk of upper airway injury due to decreased humidification (36). There are no studies on humidity or temperature of gas

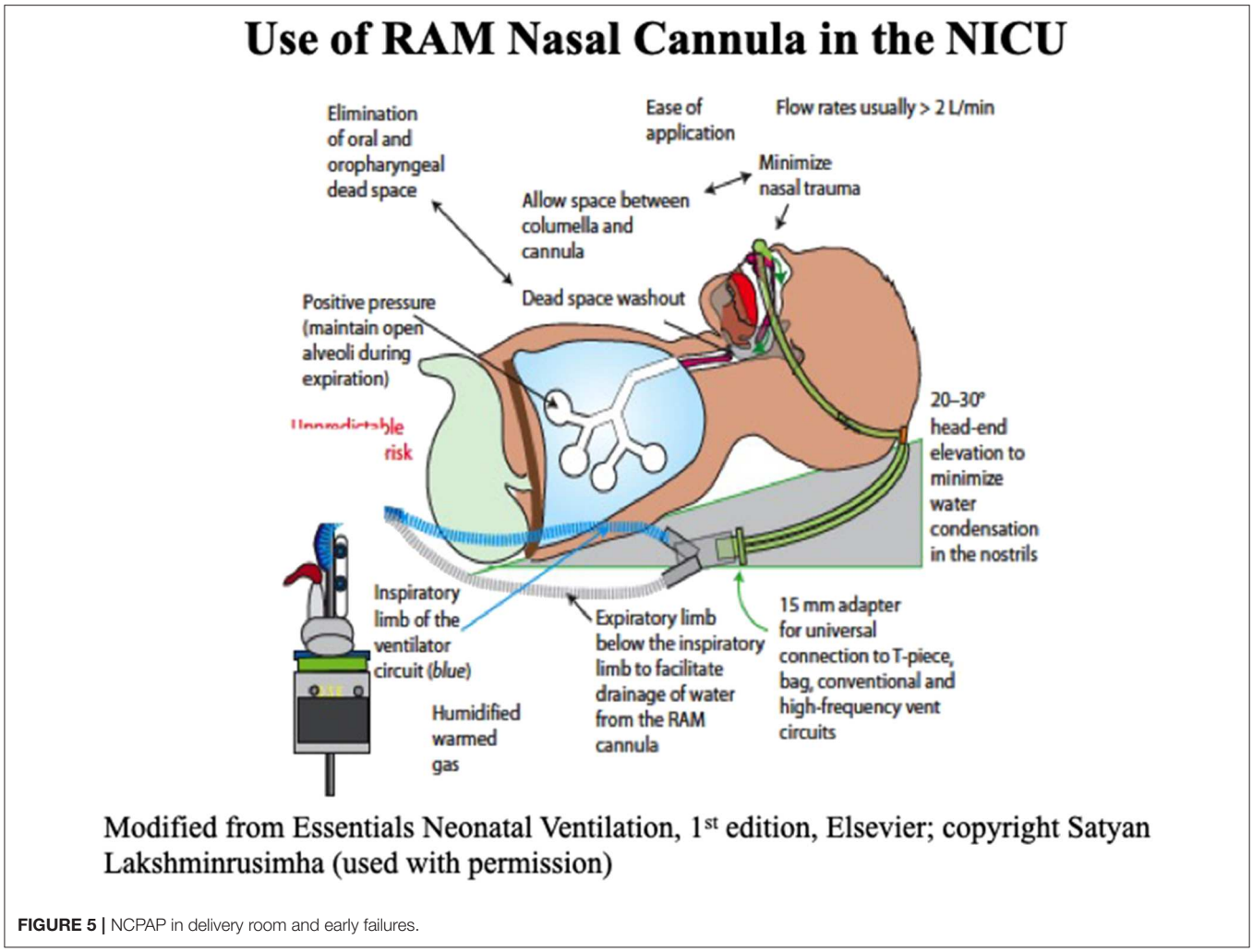


FIGURE 5 | NCPAP in delivery room and early failures.

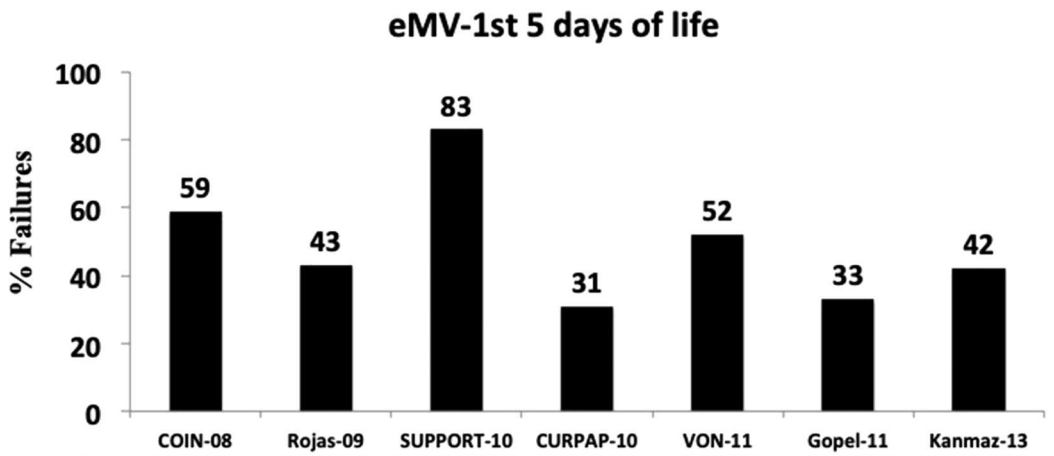
delivered in the pharynx with RAM NC or other binasal prongs. Humidification is evidenced by condensation in the tubing of RAM NC. Temperature measurement is done at the wye and beyond that, the tubing length is 11 cm to the prongs. With continuous flow of heated and humidified gas, a significant drop in temperature between the wye and the patient's nasal interface is not expected. Inspiratory gas also gets heated and humidified by the patient's nasopharynx.

NIV FOR STABILIZATION IN THE DELIVERY ROOM

Establishment of FRC during the isovolumic transformation of a fluid filled lung to an air breathing lung is critical for successful adaptation and post-natal transition (20). Extremely preterm infants are at high risk of respiratory distress and maladaptation owing to immature lungs, insufficient production of surfactant, highly compliant chest wall and immature respiratory center control (37). As a result, more than 70% of extremely preterm infants require positive pressure support (38). Strategies to optimize lung recruitment and establishing FRC at this crucial period can play a major role in decreasing respiratory morbidities and mortality in this vulnerable population. Until early 2000s, elective intubation with prophylactic administration of surfactant was the standard of care in the initial management of extremely preterm infants. After large clinical trials showing benefits of NCPAP use in the DR to decrease need for intubation and IMV (39, 40) use of NIV during stabilization and initial treatment of respiratory distress has significantly increased (4).

NCPAP IN DELIVERY ROOM

CPAP has been shown to be effective in establishing FRC (37). Two large randomized controlled trials (RCT) compared NCPAP with routine intubation in the delivery room (39, 40). The CPAP or intubation at birth (COIN) trial randomized 610 spontaneously breathing infants born at 25 to 28 weeks' gestation with signs of respiratory distress at 5 min of life to receive either CPAP or endotracheal intubation. Infants intubated due to respiratory distress before 5 min of age were excluded. NCPAP of 8 cmH_2O was used in this study. There was no difference in the primary outcome, namely, death or BPD



	COIN-08	Rojas-09	SUPPORT-10	CURPAP-10	VON-11	Gopel-11	Kanmaz-13
BW	964 (212)	1293 (324)	835 (188)	913 (200)	1053 (252)	975 (244)	1093 (270)
GA	26.9 (1.0)	29.3 (1.4)	26.2 (1.1)	27 (0.97)	28.1 (1.1)	27.5 (0.8)	28 (2)

Modified from Fischer HS, Buhrer C. Pediatrics 132:e1351-e60;2013

FIGURE 6 | Advantages of RAM NC over Bag & Mask in the delivery room.

between the two groups; however, there was a higher incidence of pneumothorax in the CPAP group (39). The surfactant positive airway pressure and pulse oximetry (SUPPORT) trial from USA randomized 1,316 infants between 24 and 28 weeks' gestational age to receive NCPAP or endotracheal intubation along with administration of surfactant. Overall mortality (47.8 and 51%, respectively) and BPD rates were similar between the NCPAP and the intubation with surfactant group (40). Evidence from these studies showed that NCPAP was as effective as routine intubation in the extremely preterm infants. To date, seven RCTs using NCPAP in the delivery room have been published. Failure rates needing intubation and IMV ranged from 31 to 83% (**Figure 6**; **Table 1**) (39–45, 47). None of individual clinical trials showed benefit in the primary outcome, namely, death or BPD. However, systematic review and meta-analysis of these studies showed a small but significant benefit in decreasing death or BPD, with a number needed to treat (NNT) of 25 (48). In a long term follow up study by Doyle et al. despite substantial increase in the use of NCPAP, there was no decrease in BPD and more importantly, no improvement in lung function was seen at 8 years of age (49). Exact reasons for the lack of benefit with NCPAP are not clear. It may be due to inability to recruit lungs with inadequate CPAP pressures due to leaks with nasal interfaces or lack of augmentation of breaths as provided during NIPPV.

NIPPV IN THE DELIVERY ROOM

There are no randomized clinical trials of using NIPPV compared to CPAP in the DR. Infants are typically placed on either CPAP or NIPPV after initial resuscitation. In a retrospective study in very low birth weight infants, comparing positive pressure ventilation (PPV) using a face mask to directly placing on NIPPV with RAM nasal cannula at birth, NIPPV use was associated with a significantly decreased need for intubation in the DR (31 vs. 85%) including among the extremely preterm infants born at 24–27 weeks of gestation, decreased need for chest compressions (11 vs. 31%), and decreased the need for IMV at 24 h of age (38 vs. 66%) (28).

USE OF SUSTAINED LUNG INFLATION IN DELIVERY ROOM

Sustained lung inflation (SLI) strategy may result in better lung recruitment immediately after birth through delivery of a PIP of 15–30 cmH_2O for a sustained period of time, typically, 10–15 s to the infant airways via a nasopharyngeal tube or mask or NC, followed by CPAP. SLI procedure creates a transepithelial pressure gradient across the alveolar-capillary membrane and helps to move fluid from the alveoli into the interstitial space and subsequent removal of this fluid via lung lymphatics

TABLE 1 | Studies comparing NCPAP and intubation with IMV.

References	Intervention (*n*)	GA, weeks	BPD (%)	Death (%)	Combined BPD and death (%)	Intubation rates in NCPAP group (%)
Morley et al. (39)	NCPAP (307) vs. IMV (303)	25–28	29 vs. 35	6.5 vs. 5.9	34 vs. 39	59
SUPPORT et al. (40)	NCPAP (663) vs. IMV (653)	24–28	40 vs. 44	14 vs. 17	49 vs. 54	83
Dunn et al. (41)	NCPAP (223) vs. INSURE (216) vs. IMV (209)	26–29	n/a	4 vs. 7 vs 7	30 vs. 28 vs. 36	52
Rojas et al. (42)	NCPAP (137) vs. INSURE (141)	27–30	59 vs. 49	9 vs. 9	62 vs. 54	53
Sandri et al. (43)	NCPAP (105) vs. INSURE (103)	25–29	n/a	n/a	21 vs. 22	31
Göpel et al. (44)	NCPAP ± LISA (108) vs. nCPAP ± INSURE (112)	26–28	8 vs. 13	n/a	14 vs. 15	46
Kanmaz et al. (45)	NCPAP + LISA (100) vs. nCPAP INSURE (100)	<30	10 vs. 20*	16 vs. 13	34 vs. 45	40
Tapia et al. (46)	NCPAP + INSURE (131) vs. MV (125)	800–1,500 g	7 vs. 10	8 vs. 9	14 vs. 19	30

*NCPAP, Nasal continuous positive pressure ventilation; IMV, Invasive mechanical ventilation; INSURE, INtubation, SURfactant and Extubation; LISA, Less invasive surfactant administration; GA, Gestational age (weeks) *P < 0.05.*

and pulmonary microcirculation. SLI superimposed on PEEP may have beneficial effects, like, maintaining adequate FRC, promoting optimal gas exchange, improving lung mechanics, and reducing the need for intubation in the DR (50). A recent large multicenter study in extremely preterm infants requiring resuscitation at birth, a ventilation strategy involving 2 SLIs at maximal PIP of 25 cmH_2O for 15 s, compared with standard intermittent positive pressure ventilation, did not reduce the risk of BPD or death at 36 weeks postmenstrual age. The study was stopped early due to safety concerns with increased rates of death in the infants receiving SLI (51). Reasons for increased mortality with SLI in this study are not clear. Updated systematic review and meta-analysis of SLI vs. intermittent positive pressure ventilation and continuous positive airway pressure for the prevention of hospital mortality and morbidity in preterm infants showed no difference in the risk of the primary outcome of death in the delivery room or before hospital discharge, although SLI was associated with increased risk of death in the first 2 days after birth, with no evidence of efficacy for SLI prevent other neonatal morbidities. Duration of mechanical ventilation was shorter in the SLI group but did not translate into better long term pulmonary outcomes. These findings do not support the routine use of SLI in preterm infants at birth in the delivery room (52, 53).

HIGH FLOW NASAL CANNULA FOR STABILIZATION IN THE DELIVERY ROOM

Only one study had evaluated HFNC during stabilization at birth. Reynolds et al. performed a pilot study evaluating use of HFNC (6–7 LPM) in stabilizing infants <30 weeks' gestation; 25 of 28 infants were successfully stabilized with HFNC, 48% of the infants received surfactant and 60% of the infants remained on HFNC at 72 h of age (54). They concluded that it is feasible to use HFNC in preterm infants. Additional studies in extremely preterm infants are needed.

EARLY USE OF NIV IN NICU

The major risk factors for BPD in extremely infants are treatment with oxygen and IMV. A meta-analysis of 7 randomized controlled trials including 3,289 patients showed that avoiding IMV reduced the combined outcome of death or BPD in preterm infants <30 weeks' gestational age (47). At present, NCPAP and NIPPV are the two most common modes used either as a primary mode or rescue mode of NIV support in the NICU.

EARLY NCPAP

Previous systematic reviews of randomized clinical trials of preterm infants found that the early use of NCPAP to avoid IMV decreased BPD, death, or both compared with the respiratory management using routine intubation (48, 55). However, one major disadvantage of using only NCPAP without intubation is a delay in the administering surfactant that is generally given via an endotracheal tube after intubation. A large multicenter study comparing early NCPAP to intubation and surfactant within 1 h of age in infants less than 28 weeks of gestation did not show any significant differences in long term morbidities (40). Several factors in extremely preterm infants including gestational age <26 weeks, birth weight < 750 g, need PPV in the DR, FiO_2 >0.30 and severe RDS on chest x-ray contribute to NCPAP failures (56). CPAP failure is associated with increased risk of mortality and major morbidities, including BPD, both in infants <29 weeks' and in infants between 29 and 32 weeks' GA (57).

USE OF NCPAP WITH SURFACTANT THERAPY

Few RCTs have evaluated routine NCPAP with NCPAP after surfactant via INSURE or LISA technique (41–46). In the DR management trial, infants 26 to 29 weeks' gestation were randomized to 3 groups: prophylactic surfactant followed by a period of mechanical ventilation for at least 6 h, prophylactic INSURE within 30 min followed by bubble NCPAP or initial management with bubble NCPAP and selective surfactant treatment. There were no differences in death or moderate to severe BPD (NCPAP 4.1% vs. INSURE 7% vs. prophylactic surfactant 7.2%), and in pneumothorax (5.4% vs. 3.2% vs. 4.8%) in these 3 groups (41). In another multicenter, RCT from the South American Neocosur Network, early bubble CPAP and selective surfactant by INSURE technique reduced the need for mechanical ventilation and surfactant; however, there were no differences in the rates of death or BPD (46). A multicenter RCT from Germany included 220 infants between 26 and 29 weeks' gestation and reported decreased need for mechanical ventilation in infants treated with NCPAP and surfactant administration via LISA technique, but no decrease in BPD (44). However, a similar study from Turkey reported decrease in both the need for mechanical ventilation and BPD (10 vs. 20%) when treated with NCPAP and LISA (45). A recent study showed SurE technique using a thin catheter for surfactant delivery resulted in decreased need for MV and less BPD (11). In a meta-analysis including majority of the above mentioned studies, Fischer et al. concluded that avoiding early IMV by using NCPAP with or without surfactant resulted in a small but significant beneficial effect on preventing BPD, with a number needed to treat (NNT) of 35 (47) (**Table 1**). Furthermore, NCPAP failures in preterm infants <29 weeks GA is associated with increase in mortality, BPD, death or BPD, and necrotizing enterocolitis (NEC) (57).

EARLY NCPAP VS. NIPPV USE IN NICU

A major reason for lack of benefit in the NCPAP trials is due to high rates of NCPAP failures, requiring intubation within 3–7 days after randomization. Most common reasons for NCPAP failures are recurrent apnea, bradycardia or desaturation episodes, hypopnea, need for higher pressures (NCPAP > 8 cmH_2O), and/or severe respiratory acidosis. NCPAP when used as a primary mode or following a period of IMV has been shown to result in failure rates of 31% to 83% (**Table 1**), requiring intubation or re-intubation. NIPPV augments NCPAP and has been shown to be more effective than NCPAP after extubation and in the treatment of apnea of prematurity (58, 59).

Several large RCTs comparing early NCPAP with early NIPPV have been published (60–69) (**Table 2**). Of the 10 studies reviewed, 6 studies enrolled patients prior to surfactant administration (60–64, 69), 2 studies had mixed enrollment (65, 66), and 2 studies enrolled after INSURE technique (67, 68). Four of these studies reported decreased rates of IMV (64, 65, 68, 69). Three studies reported decreased respiratory failure and duration of oxygen requirement (60, 61, 67). Three studies, where rescue surfactant via INSURE and LISA was provided, showed decreased rates of BPD (64, 68, 69). A recent Cochrane meta-analysis involving 10 trials enrolling 1,061 infants showed significantly decreased rates of respiratory failure [{relative risk}RR 0.61 (95% CI 0.51,0.82)], decreased need for intubation [RR: 0.78 (95% CI 0.64, 0.94)], and NNT to prevent one extubation failure was 17 with NIPPV. There were no differences in the rates of BPD (RR: 0.78; 95% CI 0.58, 1.06) and mortality (RR: 0.77 (95% CI 0.51, 1.15); however, in one study, combining surfactant with NIPPV led to a reduction in BPD. There were no differences in pneumothorax, NEC, IVH, and retinopathy of prematurity (70).

One of the largest RCT involving 1,009 patients <1 kg at birth, comparing NCPAP with Si-PAP or NIPPV, reported no difference in extubation failures (61.8 vs. 59.5%), survival with BPD (31 vs. 33.9%), and death or BPD (36.7 vs. 38.4%) (62). In this pragmatic study, more than half of the centers used IFD device to deliver "NIPPV," and in centers using a ventilator to deliver NIPPV, maximum PIP that could be used was limited to 18 cmH_2O. Even though, the authors described this study as NIPPV vs. NCPAP, this was truly a study comparing Si-PAP with NCPAP. Post-randomization failures needing intubation were very high, most likely, secondary to lower delta pressures used in the "NIPPV"

TABLE 2 | Studies comparing NIPPV and NCPAP.

References	*n*	Synchoniz-ation	Surfactant prior	GA, weeks	Intubation/respiratory failure	Death	BPD
Armanian et al. (60)	98	No	No	<35	4 vs. 2	4 vs. 2	n/a
Bisceglia et al. (61)	88	No	No	28–34	2 vs. 2	0 vs. 0	4 vs. 8
Kirplani et al. (62)	185	Some	No	<30	21 vs. 29	3 vs. 4	19 vs. 14
Meneses et al. (63)	200	No	No	26–33	58 vs. 64	22 vs. 26	26 vs. 25
Kugelman et al. (64)	84	Yes	No	24–34	25 vs. 46*	0 vs. 0	2 vs. 17*
Sai Sunil Kishore et al. (65)	76	No	Some	28–34	19 vs. 41*	13 vs. 23	3 vs. 10
Salama et al. (66)	60	Yes	Some	28–34	10 vs. 20	0 vs. 3	3 vs. 6
Lista et al. (67)	40	Yes	Yes	28–34	10 vs. 15	0 vs. 0	0 vs. 0
Ramanathan et al. (68)	110	No	Yes	26–29	17 vs. 42*	2 vs. 2	22 vs. 39
Oncel et al. (69)	200	No	No	26–32	13 vs. 29*	4 vs. 6	7 vs. 16*

*NIPPV, Nasal intermittent positive pressure ventilation; NCPAP, Nasal continuous positive pressure ventilation. *$p < 0.05$.*

TABLE 3 | Suggested settings for CPAP, Bi-PAP, NIPPV, and HFNC.

Mode of NIV	Initial settings	Max settings	Weaning parameters	Lowest settings
NCPAP	5–6 cmH_2O	8–10 cmH_2O	1 cmH_2O	4 cmH_2O
Bi-PAP	High Pressure 10 cmH_2O Low Pressure 5 cmH_2O Rate 20/min	High Pressure 15 cmH_2O Low Pressure 8 cmH_2O Rate 30/min	1 cmH_2O wean the rate by 2–4 /min every 6 h	High/Low Pressure 8/5 cm H_2O Rate 0
NIPPV	PIP 20 cmH_2O PEEP 6 cmH_2O Inspiratory time 0.5 s Rate 40/min	PIP 35-38 cmH_2O PEEP 8–10 cmH_2O Rate 50/min	wean PIP first by 1–2 until lowest possible PIP wean the rate by 2–4 /min every 6 h	PIP 12 or 15 cmH_2O PEEP 4–5 cmH_2O Rate 20/min
HFNC gas flow	4–6 L/min	8 L/min.	0.5–1.0 L/min	1–4 L/min

NIV, non-invasive ventilation; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; HFNC, high flow nasal cannula; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure.

group. However, Lemyre et al. included 185 infants from this study who were randomized prior to intubation and surfactant administration in their Cochrane review and found decreased need for intubation and respiratory failure (70).

Early NIPPV appears to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and IMV among preterm infants with RDS (70). Another important factor is related to the devices used to deliver NIPPV. NNT to decrease respiratory failure and intubation with a ventilator delivered NIPPV was 13 (70). Current evidence suggests early NIPPV delivered with a ventilator and minimally invasive technique for early, rescue surfactant therapy, like, LISA may be the most effective strategy to minimize IMV and improve outcomes in extremely preterm infants. Recommended settings for NIPPV, NCPAP, and HFNC are shown in the **Table 3**.

There are no studies comparing weaning strategies from NIPPV to CPAP. Several factors are to be considered while weaning including underlying pulmonary disease, intermittent hypoxic episodes, post-natal age, growth, oxygen requirement, and gas exchange. Individual patient specific weaning strategy is encouraged. For extremely preterm infants we (HM, MB, RR) typically wean PIP first before weaning the rate. When the PIP is around 12 or 15 cmH_2O, PEEP at 5–6 cmH_2O, and $FiO_2 < 030$, we wean the rate by 2–4 bpm every 6 h and transition to NCPAP. When patient is stable on NCPAP for 12–24 h, we wean to low flow NC (<2 lpm).

NIPPV VS. NCPAP POST-EXTUBATION

Infant receiving invasive ventilation are at high risk for developing complications such as increased hemodynamic instability, increased airway resistance, acute and chronic airway trauma, increased ventilation associated infections and reduced clearance of secretions. Minimizing IMV and extubating to NIV may aid in avoiding these undesirable side effects. Choice of post-extubation respiratory support is based on several factors including level of respiratory support at the time of extubation, duration of respiratory support, underlying lung pathology, and associated clinical problems as well as infant's hemodynamic status.

TABLE 4 | Interventions to improve rates of successful extubation in preterm infants.

Preventing extubation failures	Risk ratio [95% CI]	NNT [95% CI]
NCPAP vs. Head-Box	0.59 [0.48–0.72]	6 [3–9]
NCPAP vs. nHF	1.11 [0.84–1.47]	–
Methylxanthines	0.48 [0.32–0.71]	4 [2–7]
DOXAPRAM	0.80 [0.22–2.97]	–
NIPPV vs. NCPAP	0.70 [0.60–0.81]	8 [5–13]
NS-NIPPV or Bi-PAP vs. NCPAP	064 [0.44–0.95]	8 [4–50]
$_S$NIPPV vs. NCPAP	0.25 [0.15–041]	4 [2–5]
NS-NIPPV or sNIPPV vs. NCPAP	0.28 [0.18–043]	4 [2–5]

NS-NIPPV, non-synchronized NIPPV; sNIPPV, synchronized NIPPV; nHF, High flow nasal cannula. Ferguson et al. (75).

The 2017 Cochrane meta-analysis compared NIPPV and NCPAP for respiratory support post-extubation and included 10 studies with 1,431 infants and reported decreased rates of respiratory failure [RR: 0.70 (95% CI 0.60, 0.80)] and reintubation rates [RR: 0.76 (95% CI 0.65, 0.88)] with NIPPV without increase in gastrointestinal side effects (59). NIPPV reduced the incidence of extubation failure and the need for re-intubation within 48 h to 1 week more effectively than NCPAP; however, it had no effect on BPD or mortality (59, 71–74). In a recent systematic review, Ferguson et al. concluded that NIPPV is superior to NCPAP in preventing extubation failure [(RR 0.70, 95% CI 0.60, 0.81; NNT 8; 95% CI 5, 13)] (**Table 4**) (75).

SYNCHRONIZED NIPPV

A clinical report by the American Academy of Pediatrics concluded that synchronized NIPPV (sNIPPV) decreases the frequency of extubation failure but the evidence for non-sNIPPV or Bi-PAP is inconclusive (76). The main reason for the absence of evidence is directly attributed to the lack of approved devices to provide an effective synchronization during NIV in USA. The most studied system for synchronization during NIPPV in newborns is the Graseby capsule (77, 78), but this system is no longer available. At present, there

are no devices in the United States that are capable of providing sNIPPV, except for neurally adjusted ventilatory assist (NAVA). However, there are devices available in other parts of the world where flow synchronization as well as Graseby capsule have been successfully used to provide sNIPPV (79).

HFNC FOR PRIMARY RESPIRATORY SUPPORT IN THE NICU

In a recent international, multicenter, randomized, non-inferiority trial, 564 preterm infants with gestational age >28 weeks (HISPTER trial) were randomized to HFNC or NCPAP. When used as primary support in preterm infants with respiratory distress, HFNC use resulted in significantly higher rates of treatment failure than NCPAP (25.5 vs. 13.3%) (80). Systematic reviews including 2016 Cochrane review and a more recent systematic review reported CPAP was superior to HFNC in preventing treatment failure and intubation [RR 1.83 (95% CI 1.43, 2.35)] in favor of CPAP (81, 82). One pilot study of 76 infants <35 weeks GA and >1,000 g birth weight compared HFNC with NIPPV as a primary mode of respiratory support and found no difference in rate of intubation and MV; however, HFNC was associated with longer duration of oxygen support (83).

HFNC VS. NCPAP IN THE NICU

In one of the largest retrospective study of 2,487 extremely preterm infants, Taha et al. reported that HFNC use was associated with higher risk of death or BPD and longer length of stay when compared to NCPAP (84). The 2016 Cochrane review of HFNC compared with NCPAP to prevent extubation failure included six trials (934 infants) and found no difference in the rate of treatment failure [RR 1.21 (95% CI 0.95, 1.55)] or reintubation RR: 0.91 (95% CI 0.68, 1.20)] within 7 days, but reported a lower rate of nasal trauma [(RR 0.64 (95% CI 0.51, 0.79)] (81). A more recent systematic review included 3 more trials and found similarly no difference in rate of treatment failure [RR 1.21 (95% CI 0.97, 1.50)] and intubation rate [RR 0.98 (95% CI 0.77, 1.24)]. However, majority of the studies included infants greater than 28 weeks' gestation and currently there is insufficient evidence to support use of HFNC as primary mode or for post-extubation respiratory support in infants less than 28 weeks' gestation (82).

NON-INVASIVE NEURALLY ADJUSTED VENTILATORY ASSIST (NIV-NAVA)

Mechanism

NAVA is a newer mode of ventilation that utilizes electrical activity of diaphragm (Edi) using a special nasogastric tube embedded with electrodes to provide synchronized breaths (85). An electrical signal is generated in the respiratory center in the brainstem and travels via the phrenic nerve to stimulate the diaphragm. The Edi catheter with electrodes is inserted and adjusted in the esophagus to provide an optimal signal from diaphragm. Edi mas as well as Edi min values are detected by the electrodes and transmitted to the ventilator. The ventilator assists the spontaneous breath by delivering a proportional pressure as determined by NAVA level. The PIP delivered is proportional to the amount of Edi. Systematically increasing NAVA levels increases PIP while maintaining Edi until the breakpoint is reached. Further increases in NAVA leads to decrease in Edi. This breakpoint is increased after extubation in premature infants (86). The initiation, duration, size, and termination of breath are controlled by the patient, and thus, potentially offering full synchronization (85). Typical settings of NIV NAVA are shown in the **Table 5**. NAVA levels are typically adjusted to keep Edi peak goal of 5–15 5 μV and Edi min is kept usually between 2 and 4 5 μV. If the Peak Edi is too high, NAVA level is increased to reduce the patient's work of breathing whereas if the Peak Edi is too low, the NAVA level is reduced and weaning considered. If Edi min is too high, then additional PEEP is provided whereas for low Edi min PEEP is reduced. Weaning the patient is considered after a decline in the Edi signal and peak pressure essentially showing improvement in diaphragm performance. Detailed guide for initial set up of NIV-NAVA can be accessed at https://www.neonatologytoday.net/newsletters/nt-apr12.pdf.

Use of NIV NAVA in NICU

Stein et al. in a retrospective study reported that in preterm infants managed on NAVA mode maintained better blood

TABLE 5 | NIV NAVA suggested settings.

	Initial settings	Maximum	Wean	Minimum
NAVA level Edi max between 5–15 μV	2 cm H_2O/μV	4 cm H_2O/μV	0.2 to 0.5 cmH_2O/μV For Edi max >15 μV	0.5 cmH_2O/μV
PEEP	6 cmH_2O	8-10 cmH_2O	1 cmH_2O	5 cmH_2O
Edi Trigger	0.5 μV	2 μV	Adjust as needed	
Backup Pressure Control above PEEP	15 cmH_2O	30–35 cmH_2O	1–2 cmH_2O	Per NIPPV
Rate	40 /min	Per NIPPV	Per NIPPV	Per NIPPV
Inspiratory time	0.5 s	–	–	–
Trigger sensitivity	1 to 2	–	–	–

Edi, electrical activity of diaphragm; PEEP, positive end expiratory pressure; NIPPV, nasal intermittent positive pressure ventilation.

TABLE 6 | Studies comparing Noninvasive neutrally adjusted ventilator assist (NIV NAVA) to other forms of non-invasive ventilation.

References	Type of study	Comparison	GA (*n*)	Reintubation	CO_2 clearance	Syn	Complications	Oxygen requirement/IMV duration	Outcome (Death/BPD)
Lee et al. (90)	Retrospective	NCPAP	<30 (30)	$P = 0.04$	NS	–	–	NS	NS
Kallio et al. (91)	Prospective	NCPAP	28–36 (40)	NS	NS	NS	NS	NS	NS
Yonehara et al. (92)	Retrospective	NIPPV	<30 (34)	NS	–	–	NS	–	–
Lee et al. (93)	Observational crossover	NIV-PS	<32 (15)	–	–	$P < 0.001$	–	–	–
Gibu et al. (16)	Observational crossover	NIMV	<37 (11)	–	NS	$P < 0.01$	$P < 0.01$	$P < 0.01$	–
Yagui et al. (94)	Randomized controlled	NCPAP	Preterm <1,500 g (123)	NS	–	–	NS	$P < 0.01$	NS
Yagui et al. (95)	Retrospective	NCPAP	ELBW	$P = 0.02$	–	–	NS	$P = 0.02$	NS

NIPPV, Nasal intermittent positive pressure ventilation; NCPAP, Nasal continuous positive pressure ventilation; NIV-PS, Non-invasive ventilation-Pressure support; GA, Gestational age. IMV: invasive mechanical ventilation; Syn-synchronization.

gases with lower PIP and oxygen requirements compared to synchronized IMV plus pressure support (SIMV+PS) mode of ventilation (87). Lee et al. in a randomized crossover study also reported that NAVA lowered PIP and reduced respiratory muscle load in preterm infants when compared to SIMV+PS (88). Kallio et al. performed a randomized controlled trial in 60 infants between 28 and 36 weeks GA comparing NAVA and conventional ventilation and found no difference in duration of invasive ventilation (89). Studies using NIV-NAVA mode in extremely preterm infants are limited with some of the recent studies showing promising results (**Table 6**) (16, 90–95). Larger trials are needed to determine if NIV-NAVA is a better mode to provide sNIPPV to prevent BPD.

NASAL HIGH FREQUENCY VENTILATION (NHFV)

To decrease the need for intubation and improve ventilation in infants with hypercarbia, using NHFV modalities such as nasal high frequency flow interrupter (NHFFI), nasal high frequency oscillatory ventilator (NHFOV) (96), nasal high frequency percussive ventilator (NHFPV) or nasal high frequency jet ventilator (NHFJV) using standard nasal interfaces have been reported. Three variables that impact the delivery of tidal volume are inspiratory time (IT), amplitude, and frequency. Longer IT, higher amplitude, and lower frequency are associated with larger tidal volume delivery during NHFV. Addition of NIPPV breaths during NHFJV also improves ventilation (97). NHFV using HFFI device, Infant Star was first reported in 1998. In this observational study of 21 preterm infants, significant improvement in ventilation was seen after starting NHFFI (98). Another study describing successful use of NHFFI in 14 patients was reported in 2008 (99).

USE OF NHFV IN NICU

In a randomized, controlled trial comparing NHFPV with NCPAP in 40 term neonates delivered by cesarean section, with a diagnosis of transient tachypnea of the newborn (TTN), NHFPV was well-tolerated and more effective in improving oxygenation when compared with NCPAP (100). Using a nasopharyngeal tube to deliver NHFOV in 20 preterm neonates during weaning from IMV, NHFOV was successfully used in 91% of the patients at first attempt at extubation (101). Mukerji et al. reviewed 52 patients treated with rescue NHFOV when other NIV modes failed. Intubation was avoided in 58% of the cases (102). In a small randomized, controlled trial involving 39 patients with a birth weight <1,250 g, NHFOV was found to be not superior to Si-PAP (103). Most likely reason for lack of success in this pilot study was the use of lower MAP in the NHFOV group. In a recent meta-analysis of 8 RCTs involving 463 patients, NHFOV significantly improved CO_2 clearance and reduced the need for intubation compared with NCPAP/bi-phasic CPAP (104). There are no clinical trials using NHFJV. There is only one reported case series showing successful use of NHFJV in selected extremely preterm infants immediately after extubation from IMV (105). In a review of 6 NHFV studies involving 111 patients; different inspiratory time, amplitude, and frequency were used (96). Suggested settings for NHFV are shown in **Table 7**.

COMPLICATIONS OF USING NIV

Even if NIV offers a number of benefits over IMV some extremely preterm infants may develop complications while receiving NIV. Majority of complications are related to injury to nasal mucosa as well as nasal septum.

TABLE 7 | Suggested settings for Nasal High Frequency Ventilation.

Frequency, Hz	Start at 6–8 Hz; May decrease to 4 Hz in patients with hypercapnia; If using HFJV, start at 300 bpm (5 Hz) and may decrease to 240 bpm (4 Hz)
Amplitude, cmH_2O	MAPx2; Start at 20–30 cmH_2O; May increase to as high 70 cmH_2O. If using during weaning, set Amplitude equaling PIP prior to extubation
I: E ratio	Start at 1:1; May change to 1:2 in cases of gas trapping; If using HFJV, jet valve on time: 20 ms and may increase to 30–34 ms to improve oxygenation and increase tidal volume delivery
Mean Airway Pressure (MAP), cmH_2O	MAP: Start with the same MAP as on SIMV or 2–3 cmH_2O higher than CPAP; Start at 8–10 cmH_2O; May increase as needed based on FiO_2 and or lung expansion
NIPPV Back up rate	If available, use rates between 30 and 40 bpm; If using HFJV, keep the NIPPV settings same as before adding NHFJV

I:E ratio, Inspiration: Expiration ratio; HFJV, high frequency jet ventilator; NIPPV, nasal intermittent positive pressure ventilation; MAP, Mean Airway Pressure; SIMV, Synchronized intermittent mandatory ventilation.

NASAL INJURIES DURING NIV

One of the major problems with NIV use in the NICU in the occurrence of septal or nasal mucosal injuries resulting in nasal deformities. Snugly fit nasal prongs may put extremely preterm infants at risk for causing nasal trauma including erythema or blanching, ulceration, and columellar necrosis. Reported incidence of these complications varies from 20 to 60% in neonates. Both frequency and severity of nasal trauma has been shown to be higher in infants at lower gestational age (>90% in neonates <28 weeks of gestational age), lower birth weight, longer duration of NCPAP and longer NICU stay (106). It is important to choose the right interface with correct size of prongs as well as fittings as onset of nasal injury to the columella has been reported to occur within a mean of 2–3 days of CPAP commencement, and in some cases occurring as early as 18 h after commencement. The use of nasal barrier dressings and nasal masks as an alternative to binasal prongs may be effective interventions to reduce nasal injury. HFNC causes less nasal injury than CPAP, but it may not provide sufficient respiratory support for the smallest, sickest preterm infants (107). These complications not only have cosmetic or functional sequelae but also place the infants at risk for developing nosocomial infections. In one study nasal breakdown with the INCA prongs and subsequent use of the RAM NC did not worsen or contribute nasal injuries. Also, there were no new instances of nasal breakdown or injury reported with use of the RAM NC (108). A recent study showed skin or mucosal breakdown with RAM NC was significantly lower compared to other nasal interfaces (8 vs. 53%, $P < 0.001$) (109). Common recommendations for prevention of nasal trauma due to NCPAP in neonates include careful monitoring of the nose, avoidance of pressure, friction, and moisture.

OTHER COMPLICATIONS WITH NIV

Systemic complications related to NIV use are usually rare and account for less than 5% of patients. Pneumothorax can occur in acute phase and it is most commonly related to underlying lung disease rather than NIV itself. Also, after surfactant administration with sudden change in the compliance may lead to air leaks as well. HFNC may have reduced occurrence of pneumothorax compared to CPAP. Small pnuemothoraces usually resolves spontaneously, and one may not need to change the modality if infant is otherwise stable. Rarely an intervention is needed to evacuate the air to re-inflate the affected lung. A recent study showed a decrease risk of pneumothoraces after implementing NIV in the delivery room instead of intubation in extremely low birth weight infants (3).

It is common to observe abdominal distension with or without feeding intolerance with NIV. Some infants may need to have orogastric tube to vent the stomach and to evacuate air. There may be transient feeding intolerance. Decrease in flow may help relieve gastric distension as well. Infants who have undergone upper gastrointestinal surgery are at higher risk of complications, such as leak at the site of anastomosis if NIV is used in the immediate post-operative period (110). In a small case series, Pandita et al. reported facial palsy in 3 patients, who were on NCPAP and speculated that pressure over the stylomastoid formen by the NCPAP interface might have contributed to ipsilateral facial palsy (111).

CONCLUSIONS

In extremely preterm infants, optimal pulmonary outcomes could be achieved by minimizing the duration of IMV. NIV is currently best provided by early use of NIPPV from DR through 32 to 33 weeks postmenstrual age in the NICU. NCPAP may be used when weaning from NIPPV, followed by low flow nasal cannula (<2 LPM) in extremely preterm infants to minimize lung injury. sNIPPV could be delivered using NIV NAVA but needs more evidence to support its use in this specific population. NHFV using NHFOV as well as NHFJV have the potential as a rescue mode for use in this population especially when the lung disease is severe requiring higher pressure (PIP >30 cmH_2O) to improve gas exchange.

AUTHOR CONTRIBUTIONS

YS: Drafting of the initial manuscript, critical revision of the manuscript for important intellectual content. RR: Review of the literature, creation of tables, checking and adding references, creation of figures, drafting and subsequent revisions of the manuscript for important intellectual content. MB: Review of the literature, creation of tables, checking and adding references, drafting and subsequent revisions of the manuscript for important intellectual content. HM: Review of the literature, creation of tables, drafting and subsequent revisions of the manuscript for important intellectual content. All Authors reviewed the final version of this manuscript and approved for submission.

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Conflict of Interest: RR has a joint patent on RAM Nasal Cannula and receives royalty payments.

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CLINICAL TRIAL
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The Comparison of HHHFNC and NCPAP in Extremely Low-Birth-Weight Preterm Infants After Extubation: A Single-Center Randomized Controlled Trial

Jia Chen, Yingyi Lin, Lanlan Du, Mengmeng Kang, Xiufang Chi, Zhu Wang, Ying Liu, Weiwei Gao, Jie Yang* and Yunbin Chen**

Neonatal Department, Guangdong Women and Children Hospital, Guangzhou, China

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Linkou Chang Gung Memorial Hospital, Taiwan
Li Ma,
Children's Hospital of Hebei Province, China

***Correspondence:**
Weiwei Gao
1716107967@qq.com
Jie Yang
jasjie_yang@163.com
Yunbin Chen
yunbin_chen@hotmail.com

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Objectives: To compare the clinical efficacy of heated, humidified high-flow nasal cannula (HHHFNC) and nasal continuous positive airway pressure (NCPAP) in extremely low-birth-weight preterm infants (ELBWI) after extubation.

Methods: This trial included 94 extremely low-birth-weight infants (ELBWI), within 7 days after birth, and prepared for tracheal extubation and a change to non-invasive ventilation in the neonatal intensive care unit (NICU) admitted to our hospital from January 2015 to December 2018, with 48 infants in the HHHFNC group and 46 infants in the NCPAP group. Reintubation rate within 72 h after initial extubation, total ventilation time, non-invasive ventilation time, total oxygen inhalation time, and the time to reach full enteral feeding were the primary outcome measures. Total intestinal feeding time, average weight gain rate, days of hospitalization, costs of hospitalization, and complication rates, including nasal injury, IVH, BPD, NEC, ROP, and PDA, were used as secondary outcomes. Data were analyzed using Student's *t*-test or the Mann-Whitney *U*-test with a Chi-square test or Fisher's exact test, as appropriate, in SPSS (25.0).

Results: HHHFNC not only shortened the oxygen exposure time but also effectively reduced the incidence of nasal injury (6.25 vs. 36.96%) and NEC (10.42 vs. 28.26%) ($P < 0.05$). Additionally, HHHFNC achieved a significant advance in the time to reach full enteral feeding (31.24 ± 11.35 vs. 34.21 ± 14.09 days); increased the average weight gain rate (16.07 ± 3.10 vs. 13.74 ± 4.21) and reduced the days of hospitalization (73.45 ± 18.84 vs. 79.24 ± 19.75), with a lower cost of hospitalization (16.04 ± 3.64 vs.18.79 ± 4.13) thousand dollars (all $P < 0.05$).

Conclusions: Compared with NCPAP, HHHFNC was effective in preventing extubation failure in mechanically ventilated preterm ELBWI. HHHFNC shortens oxygen consumption time and significantly reduces the incidence of nasal injury and necrotizing enterocolitis; moreover, it can also reduce the length of stay and the hospitalization costs.

Keywords: extremely low-birth-weight preterm infants, heated humidified high-flow nasal cannula, nasal continuous positive airway pressure, preterm infant, respiratory distress syndrome

INTRODUCTION

The birth and survival rates of premature infants, especially extremely low-birth-weight infants (ELBWI), have brought about gradual increases in short- and long-term complications. The establishment of good ventilation after birth is the basis for the survival of premature infants, especially for ELBWI. Both the earlier gestational age and the lower birth weight can make it difficult to establish spontaneous breathing and may also increase the incidence of respiratory distress (1).

Invasive mechanical ventilation is widely used in neonatal intensive care units (NICUs). However, long-term invasive mechanical ventilation can lead to ventilator-related lung injuries, including pressure injuries, volume injuries, and ventilator pneumonia. In later stages, it may even lead to severe infection and bronchopulmonary dysplasia (BPD) (2), seriously affecting the long-term quality of life of infants. Therefore, extubation is recommended as soon as possible for neonates, especially premature babies, to avoid the potential damages caused by invasive ventilation as much as possible. However, early extubation is prone to extubation failure, resulting in changes in the condition of the child and more local damage. Non-invasive ventilation after extubation helps prevent possible apnoea, respiratory failure, and re-intubation.

Nasal continuous positive airway pressure (NCPAP), as the current mainstream non-invasive ventilation model, has been widely used in clinical practice to prevent tube failure in preterm infants (3, 4). However, complications (i.e., nasal injury and NEC) caused by NCPAP have a great impact on clinical outcomes (5). Humidified high-flow nasal cannula (HHHFNC) is another globally non-invasive respiratory support model for the prevention of extubation in preterm infants (6), as the use of HHHFNC may be associated with reduced respiratory function, increased ventilation efficiency, and reduced intubation requirements in children with inadequate respiratory function (7).

As primary respiratory support for preterm infants with respiratory distress, HHHFNC and NCPAP are associated with a lower incidence of nasal trauma (8). In this regard, a pilot study suggested that HHHFNC may be as effective as NCPAP in preventing endotracheal ventilation in premature infants in the primary treatment of respiratory distress syndrome (gestational age $<$ 35 weeks and birth weight $>$ 1,000 g) (9). However, there is still a lack of clinical research on the effects of the two non-invasive ventilation modes as the preferred respiratory support model for ELBWI extubation.

This study investigated the clinical efficacy of HHHFNC compared with NCPAP for ELBWI, aiming to explore a more effective mode of non-invasive ventilation for ELBWI.

Abbreviations: ELBWI, Extremely low-birth-weight preterm infants; HHHFNC, Heated, humidified high-flow nasal cannula; NCPAP, Nasal continuous positive airway pressure; IVH, Intraventricular hemorrhage; ROP, Retinopathy of prematurity; PDA, Patent ductus arteriosus; BPD, Bronchopulmonary dysplasia; NEC, Necrotizing enterocolitis; CI, Confidence interval.

METHODS

Ethics Approval

This single-institution prospective randomized clinical trial was conducted in our hospital from January 2015 to December 2018. This study was approved by the Ethics Committee and the institutional review board of the Guangdong Women and Children Hospital (Guangzhou, China). Parental written informed consent was required before delivery of the potentially eligible infants. The authors confirm that all ongoing and related trials for this intervention are registered (ChiCTR1900028092).

Participants and Design

Considering $\alpha = 0.05$, power = 80%, an attrition rate of 5% and Cohen's $d = 0.37$ (medium effect size), a 92-subject sample size was determined for the study.

We included infants who met the following criteria in this hospital. The inclusion criteria were as follows: (1) gestational age $<$ 32 weeks, body weight $<$ 1,000 g; (2) the preterm neonates were diagnosed with RDS, supported by invasive ventilation and entered the NICU within 7 days after birth and prepared for tracheal extubation and a change to non-invasive ventilation; and (3) agreement by the family to sign the informed consent form.

The standard of intubation: Infants can be intubated if they have the following conditions: severe apnea ($>$6 episodes, stimulation within 6 h, or $>$1 bag and mask ventilation); arterial carbon dioxide partial pressure (PaCO2) $>$ 65 mmHg; poor perfusion, hemodynamic instability (i.e., mean blood pressure below gestational age) or both; needing volume or vasopressor support for 4 h or more; metabolic acidosis does not respond to treatment.

The exclusion criteria were as follows: congenital airway malformations, cleft lip and palate, Pierre-Robin syndrome, congenital diaphragmatic hernia, congenital lung dysplasia, tracheoesophageal fistula, and other life-threatening congenital malformations. Infants who failed to complete the treatment were excluded from the statistical data.

After informed consent was obtained, a total of 94 VLBWI were ultimately enrolled in the study, with 48 infants in the HHHFNC group and 46 infants in the NCPAP group through block randomization. Randomization was implemented by a random number generator and a special double-sealed envelope. When an infant met the admission criteria, the envelope was opened, and the treatment was immediately initiated.

All researchers were blinded to the randomized group assignment, but the co-researcher monitored the intervention procedure. A flow diagram of the study is shown in **Figure 1**.

MATERIALS AND METHODS

The criteria for the removal of invasive ventilation were as follows: HFOV mode: mean airway pressure (MAP) of 6–8 cmH_20, oxygen concentration (FiO_2) $\leq$ 40%, and amplitude of 12–16; synchronized intermittent ventilation mode: MAP $<$ 8 cmH_20, FiO_2 $\leq$ 40%, ventilation frequency of 30 times/min; children have good spontaneous breathing; stable circulation; and less secretion.

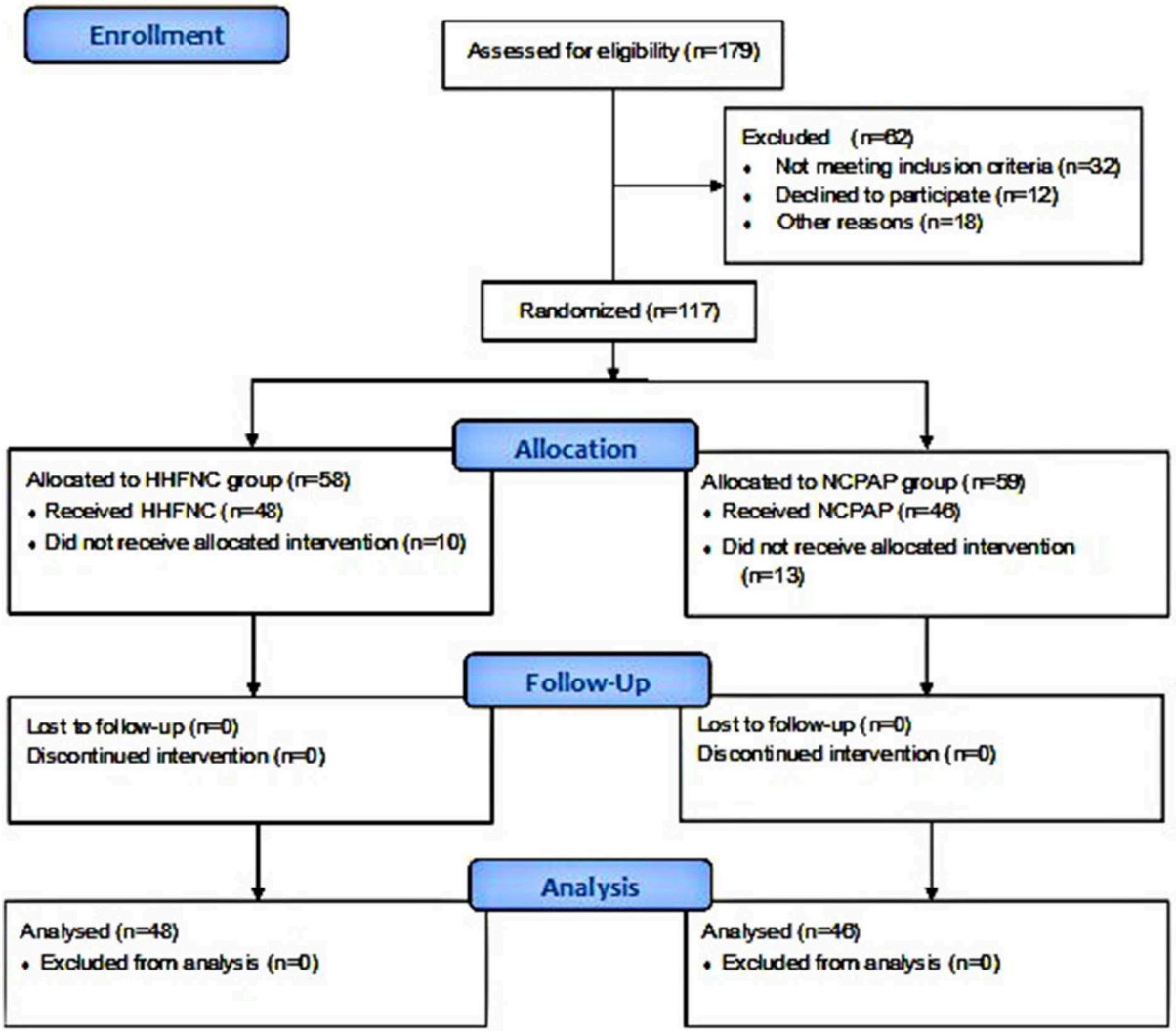

FIGURE 1 | Flow chart of participants throughout the study.

Non-invasive assisted ventilation failure was indicated by the following: (1) PEEP > 8 cmH_2O or FiO_2 > 60% still cannot maintain percutaneous $SaO_2 \geq$ 88%; (2) severe apnoea: >6 times within 24 h or >2 times of positive pressure ventilation after resuscitation; (3) the infant's breathing cycle could not be maintained or the infant was in shock; (4) severe metabolic acidosis or respiratory acidosis could not be corrected; (5) abdominal guarding and obvious abdominal distension (24-h increase in abdominal circumference greater than 1.5 cm) accompanied by one of a, b, c, d, and e: a. poor response, with blood sugar fluctuations; b. gastrointestinal bleeding; c. metabolic acidosis (BE < −10 mmol/L); d. body temperature instability; and e. significant increase in apnoea and bradycardia. In any of the above cases, tracheal intubation was performed again, and synchronized intermittent ventilation was performed. After re-intubation, the extubation was still changed to the original non-invasive ventilation mode.

The criteria for removal of non-invasive ventilation were as follows: chest X-ray and clinical improvement of the child and regular percutaneous SaO_2 and blood gas analysis. The ventilator parameters of the HHHFNC group were reduced to flow <2 L/min and FiO_2 < 25%; the ventilator parameters of the NCPAP group were reduced to flow rate PEEP < 4 cmH_2O and FiO_2 < 25%.

HHHFNC group: powered by a Bird Air Oxygen Mixer (BIRD, USA), connected to an Optiflow™ Nasal Catheter Oxygen System (Fisher & Paykel Medical, New Zealand), including an MR850 warming humidifier, an RT329 high-performance closed breathing tube, and a short nasal plug catheter; a nasal plug of the right size was chosen. Initial parameters: FiO_2 30–40%, flow 4–6 L/min, heated, humidified inhalation gas at 37°C.

NCPAP group: powered by an Infant Flow System (EME Company, the United Kingdom). Initial adjustment parameters:

flow 4–8 L/min, PEEP 5–7 cmH_2O, FiO_2 40%, when the parameter is reduced to PEEP < 4 cmH_2O, $FiO_2 < 0.25$ can be withdrawn. The ventilator parameters were adjusted based on the improvement of clinical symptoms and blood gas results to maintain PaO_2 60–80 mmHg, $PaCO_2$ 40–50 mmHg, and $TcSaO_2$ 88–92%.

Outcome Measures

Demographic and clinical characteristics were recorded, including age (weeks), birth weight (g), sex, Apgar scores, albumin (g/L), initial feeding time (d), mother's age (years), delivery, births, and antenatal use of corticosteroids.

Primary outcome measures included the reintubation rate within 7 days after initial extubation, total ventilation time, non-invasive ventilation time, and total oxygen inhalation time.

Secondary outcome measures included the time to reach full enteral feeding (day), average weight gain rate (g/day), days of hospitalization (day), and cost of hospitalization (thousand dollars).

Complications included intracerebral hemorrhage, retinopathy of prematurity, patent ductus arteriosus, bronchopulmonary dysplasia, necrotizing enterocolitis, and nasal injury.

Descriptive Statistics

Data processing was done by statisticians who were not involved in the research design and implementation. The means ± standard deviations (SDs) for numerical variables and the percentages of different categories were obtained. Student's *t*-test or the Mann-Whitney *U*-test with a Chi-square test or Fisher's exact test was selected as appropriate. Tests of normality and homogeneity of variances were performed before comparisons between the measurement data groups. All data were analyzed using SPSS version 25.0 (SPSS, Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Data Safety Monitoring Board

The board will have the following members:

Dr. Chuan Nie, Professor of Pediatrics; Neonatal Department, Guangdong Women and Children Hospital, Guangzhou.
Dr. Xiu Zhen Ye, Professor of Pediatrics; Neonatal Department, Guangdong Women and Children Hospital, Guangzhou.
Dr. Chun Shuai, Professor of Pediatrics; Neonatal Department, Guangdong Women and Children Hospital, Guangzhou.

They were arranged to conduct a simple mid-term evaluation. And they found that the trial was safe at midterm and agreed to continue.

RESULTS

Demographic and Clinical Characteristics

None of the infants in the two study groups were lost to follow-up. As shown in **Table 1**, the demographics of infants were not statistically different between the two groups. Among the 94 infants, the majority of infants were males (59/94, 62.77%), and the mean age of all infants was 27.3 ± 3.10 weeks (range 25.1–32.0 weeks).

Primary Outcomes

Compared with the NCPAP group, the total oxygen consumption time in the HHHFNC group was significantly reduced, and the difference was statistically significant ($P < 0.05$).

There were no significant differences in total ventilation time, non-invasive ventilation time, and reintubation rate within 72 h ($P > 0.05$, see **Table 2**).

Secondary Outcomes

Compared with the NCPAP group, the time to reach full enteral feeding (31.24 ± 11.30 vs. 34.21 ± 14.09 days) in the HHHFNC group was significantly earlier ($P < 0.05$). The average weight gain rate (16.07 ± 3.10 vs. 13.74 ± 4.21; g/day) was increased, the days of hospitalization (73.45 ± 18.84 vs. 79.24 ± 19.75) (days) were fewer, and the cost of hospitalization (16.04 ± 3.64 vs.18.79 ± 4.13; thousand dollars) was reduced (see **Table 3**).

Complications

The incidence rates of nasal injury (6.25 vs. 36.96%) and NEC (10.42 vs. 28.26%) in the HHHFNC group were significantly lower than those in the NCPAP group. The difference between the two groups was statistically significant ($P < 0.05$). There were no significant differences in the incidence rates of BPD, ROP, intracranial hemorrhage, PVL, and PDA between the two groups ($P > 0.05$, see **Table 4**).

DISCUSSION

NCPAP is the earliest non-invasive respiratory support for postpartum extubation (10). It can keep the airway in an expanded state, prevent alveolar collapse and improve the ventilatory blood flow ratio. Distributing an accurate pressure for variable flow through CPAP involves a tightly sealed nasal interface. However, if it is too tight, the possibility of skin rupture and mucosal damage is greater. In contrast, the key mechanism of HHHFNC is to wash out the nasopharyngeal dead space with humidified and warm gas (11); for that reason, a gap between the nasal cannula and nares is required to wash out the gas. Hence, the direct pressure effect between the proper size of the cannula of HHHFNC and the nares is much weaker than that of CPAP nasal interfaces, resulting in less nasal trauma. In the current study, as shown in **Table 4**, the incidence rates of nasal injury (6.25 vs. 36.96%) and NEC (10.42 vs. 28.26%) in the HHHFNC group were significantly lower than those in the NCPAP group. The difference between the two groups was statistically significant ($P < 0.05$).

A meta-analysis of randomized controlled trials published in 2019 showed that for respiratory support after extubation, NCPAP was associated with a lower likelihood of treatment failure than high-flow nasal cannula (HFNC) (relative risk 1.23, 95% confidence interval 1.01–1.50). The incidence rates of nasal trauma and pneumothorax in the HFNC group were significantly lower than those in the NCPAP group ($P < 0.0001$ and $P = 0.03$) (12).

TABLE 1 | Demographic and clinical characteristics of infants in the two study groups.

Demographic		Groups [*N* (%)]			
Variables		**HHHFNC group [*N* = 48]**	**NCPAP group [*N* = 46]**	**In total [*N* = 94]**	***P*-value**
DEMOGRAPHIC					
Gestational age (weeks)	Mean ± SD	27.2 ± 2.8	27.5 ± 3.2	27.3 ± 3.1	0.724[b]
	Range (Mix–Max)	25.2–32.0	25.1–31.5	25.1–32.0	
Birth weight (g)	Mean ± SD	827 ± 23.0	794 ± 31.0	814 ± 27.0	0.218[b]
	Range (Mix–Max)	740–990	720–970	720–990	
Sex	Male	30 (62.5)	29 (63.04)	59 (62.77)	0.957[a]
	Female	18 (37.5)	17 (36.96)	35 (37.23)	
Apgar scores		5.2 ± 0.6	5.4 ± 0.4	5.3 ± 0.8	0.936[b]
Albumin	(g/L)	30.9 ± 2.9	31.4 ± 3.7	31.1 ± 2.8	0.342[b]
Initial feeding time	Day	3.25 ± 1.22	3.64 ± 1.35	3.44 ± 1.31	0.054[b]
Variables	**Yes/no**	***N* (%)**	***N* (%)**	***N* (%)**	***P*-value**
CLINICAL CHARACTERISTICS					
Mother's age (years)		32.7 ± 5.1	33.1 ± 4.8	32.9 ± 5.0	0.517[b]
Delivery	Spontaneous delivery	14 (29.17)	13 (28.26)	27 (28.72)	0.923[a]
	C-section	34 (70.83)	33 (71.74)	67 (71.28)	
Births	Single	38 (79.17)	37 (80.43)	75 (79.79)	0.878[a]
	Multiple	10 (20.83)	9 (19.57)	19 (20.21)	
Small for gestational age	No	39 (81.25)	38 (82.61)	77 (81.91)	0.532[a]
	Yes	9 (18.75)	8 (17.39)	17 (18.09)	
Antenatal use of corticosteroids	No	10 (20.83)	10 (21.74)	20 (21.28)	0.544[a]
	Yes	38 (79.17)	36 (78.26)	74 (78.72)	
Extubation age (weeks)	Mean ± SD	27.8 ± 2.2	28.2 ± 2.6	31.8 ± 4.3	0.422
	Range (Mix–Max)	25.5–33.0	25.4–32.5	25.4–33.0	

SD, standard deviation; HHHFNC, Heated, Humidified High Flow Nasal Cannula; NCPAP, Nasal Continuous Positive Airway Pressure.
[a]*Chi-squared test or Fisher exact test.*
[b]*Student's t-test or Mann-Whitney U-test.*

TABLE 2 | Comparison of ventilation related factors between the HHHFNC group and the NCPAP group.

Variables		Groups			
Number of patients		**HHHFNC group [*N* = 48]**	**NCPAP group [*N* = 46]**	**Statistics test**	
		Mean ± SD	**Mean ± SD**	***U*-value**	***P*-value**
Re-intubation rate within 72 h	Yes	11 (22.91)	11 (23.91)	0.013	0.909
	No	37 (77.09)	35 (76.09)		
Total ventilation time	Day	19.4 (11.2–24.7)	17.9 (8.3–23.6)	0.102	0.645[a]
Non-invasive ventilation time	Day	12.7 (6.4–19.2)	10.8 (4.6–18.4)	0.518	0.337[a]
Total oxygen time	Day	29.7 (24.9–41.6)	32.1 (25.2–44.0)	3.074	0.030[a]

SD, standard deviation; HHHFNC, Heated, Humidified High Flow Nasal Cannula; NCPAP, Nasal Continuous Positive Airway Pressure.
[a]*Student's t-test or Mann-Whitney U-test.*

Due to the pressure produced by the cumbersome and heavy dressing of the head and face with the NCPAP, it is easy to cause the nasal compression, the nasal skin to be damaged, the nostrils to expand and deform, and the nasal mucosa to develop oedema, congestion, and other damage in infants. Nasal congestion can irritate the nostrils and increase the secretions in the nasal cavity, increasing the risk of nasal and systemic infections, especially for ELBWI. In another systematic review and meta-analysis article published in 2020, Junior et al. also showed non-inferiority in terms of therapeutic failure of HFNC in relation to NCPAP after extubation of preterm newborns. In addition, nasal trauma was significantly lower in patients submitted to the HFNC compared to those using NCPAP ($P < 0.0001$) (13).

TABLE 3 | Related factors between the HHHFNC group and the NCPAP group.

Variables		Groups			
Number of cases (%)		**HHHFNC group [*N* = 48]**	**NCPAP group [*N* = 46]**	**In total [*N* = 94]**	***P*-value**
Total intestinal feeding time	Day	31.24 ± 11.35	34.21 ± 14.09	3.591	0.019[a]
Average weight gain rate	g/day	16.07 ± 3.10	13.74 ± 4.21	−2.804	0.040[a]
Days of hospitalization	Day	73.45 ± 18.84	79.24 ± 19.75	3.047	0.036[a]
Costs of hospitalization	Thousand dollars	16.04 ± 3.64	18.79 ± 4.13	2.748	0.001[a]

SD, standard deviation; HHHFNC, Heated, Humidified High Flow Nasal Cannula; NCPAP, Nasal Continuous Positive Airway Pressure.
[a]*Student's t-test or Mann-Whitney U-test.*

TABLE 4 | Comparison of complications in infants in the HHHFNC group and the NCPAP group.

Variables	Groups						
	HHHFNC group	**NCPAP group**	**Statistics test**				
Number of cases *N* (%)	***N* = 48**	***N* = 46**	**χ2**	**OR**	**95%CI**	**Regression coefficients**	***P*-value**
Intracerebral hemorrhage	7 (14.58)	7 (15.21)	0.007	0.951	0.331–2.961	−0.050	0.931
	41 (85.42)	39 (84.79)					
Retinopathy of prematurity	17 (35.42)	18 (39.13)	0.139	0.853	0.369–1.970	−0.159	0.710
	31 (64.58)	28 (60.87)					
Patent ductus arteriosus	16 (33.33)	16 (34.78)	0.022	0.938	0.399–2.201	−0.065	0.882
	32 (66.67)	30 (65.22)					
Bronchopulmonary dysplasia	16 (33.33)	15 (32.61)	0.006	1.033	0.437–2.443	0.033	0.904
	32 (66.67)	31 (67.39)					
Necrotizing enterocolitis	5 (10.42)	13 (28.26)	4.505	0.295	0.096–0.911	−1.220	0.034
	43 (89.58)	33 (71.74)					
Nasal injury	3 (6.25)	17 (36.96)	10.529	0.114	0.031–0.423	−2.174	0.001
	45 (93.75)	29 (63.04)					

SD, standard deviation; HHHFNC, Heated, Humidified High Flow Nasal Cannula; NCPAP, Nasal Continuous Positive Airway Pressure; CI, confidence interval.

Compared with NCPAP, HHHFNC is a simple device that directly places the nasal cannula for the right side of the nose into the nasal cavity and gets rid of the external force on the head and face, thus avoiding head deformation and nasal injury (**Supplementary Figures 1–3**) (14). Similarly, these results are supported by a meta-analysis that revealed that nasal mucosa injury scores were significantly lower for HHHFNC compared to other methods of non-invasive ventilation (15). Similarly, it was also confirmed that the incidence of nasal injury in the HHHFNC group was significantly lower than that in the NCPAP group ($P < 0.05$), indicating that HHHFNC can effectively prevent nasal injury.

In addition to the low weight of the HHHFNC apparatus, HHHFNC has a relatively high oxygen humidification rate. If there is inadequate warming and humidification, a large amount of high-flow dry and cold air will enter the nasal cavity of the child, causing damage and bleeding of the nasal mucosa, which will greatly increase the chance of infection. In our study, the hollow oxygen mixed gas passed through a Fisher & Paykel MR850 heating humidifier, and the gas delivered through the closed breathing circuit was supplemented with molecular water vapor with a temperature of ∼37°C and a relative humidity of nearly 100%. As shown in **Table 2**, compared with the NCPAP group, the total oxygen consumption time in the HHHFNC group was significantly reduced, and the difference was statistically significant ($P < 0.05$).

Saslow et al. (16) found that the improvements in respiratory work and lung compliance in preterm infants were comparable to the NCPAP 6 cmH_2O when the HHHFNC flow reached 5 L/min. Moreover, some studies (17, 18) have also shown that the HHHFNC apparatus is lighter than NCPAP devices, but the pressure generated by breathing is close to the pressure generated by NCPAP. This makes it possible for HHHFNC to replace NCPAP as non-invasive respiratory support after extubation in ELBWI. Recent studies have indicated that with a flow rate of 4–6 L/min and a suitable nasal cannula size, a diameter ∼50–80% of that of the infants' nares would be safe for preterm infants (6, 19, 20). A meta-analysis also presented no differences in pulmonary air leakage or mortality between HHHFNC and other forms of non-invasive respiratory support (15). Osman et al. (21) scored pain in infants with HHHFNC and NCPAP and found that infants in the HHHFNC group had significantly less pain and improved tolerance.

This study confirmed that the use of HHHFNC for assisted ventilation after extubation was significantly shorter than that of NCPAP, and the number of infants who were reintubated was significantly less than that of the NCPAP group. This is consistent with the findings of Woodhead et al. (22) that HHHFNC can reduce respiratory work and reduce the rate of reintubation.

Abdominal distension and NEC are also important factors that cause non-invasive ventilation failure in preterm infants and that require re-intubation. This study confirmed that the incidence rates of NEC in the NCPAP group were significantly higher than those in the HHHFNC group, and the differences were statistically significant ($P < 0.05$), which resulted in a significantly longer time to reach full enteral feeding in the NCPAP group than in the HHHFNC group ($P < 0.05$). ELBWI should start drinking breast milk as soon as possible, and the time to reach full enteral feeding can promote the secretion of gastrointestinal hormones and intestinal movement, which are beneficial for the balance of enteral nutrition and protein/energy (23). Therefore, HHHFNC is more conducive to healthy infant weight gain than NCPAP, which can improve the long-term quality of life of children.

This study also confirmed that HHHFNC reduced the length of the hospital stay and significantly reduced hospitalization costs. These reductions were significantly smaller in the HHHFNC group than in the NCPAP group. The initial feeding time in the HHHFNC group was earlier than that in the NCPAP group. The daily weight gain rate was faster and the time to reach full enteral feeding was earlier in the HHHFNC group than in the NCPAP group. This study also indicated that there were no significant differences in the incidence of complications such as total ventilation and BPD, ROP, PDA, PVL, and intracranial hemorrhage ($P > 0.05$). Moreover, HHHFNC has a significantly lower unit price per hour than NCPAP, making it very beneficial for low- and middle-income families.

A possible limitation of this study is that HHHFNC cannot directly detect the actual pressure of the given flow parameters and whether the thickness of the nasal catheter used directly affects the clinical efficacy.

CONCLUSION

In summary, compared with the use of NCPAP, HHHFNC can significantly reduce the reintubation rate within 7 days, shorten the oxygen exposure time, and significantly reduce the incidence of complications such as nasal injury and NEC. HHHFNC did not increase the incidence of BPD, ROP, PDA, PVL, or intracranial hemorrhage in infants. Moreover, HHHFNC shortened the length of hospital stays for infants, greatly reduced hospitalization costs, and can greatly reduce the medical burden on low- and middle-income families. However, multi-center, large-sample randomized controlled clinical trials on the mechanism of action of HHHFNC are needed to further explore its safety and efficacy.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Guangdong Women and Children Hospital (Guangzhou, China). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JC and WG conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript. YLin and MK collected data, carried out the initial analyses, and reviewed and revised the manuscript. LD and ZW processed the experimental data. XC and YLiu mainly discussed and edited the manuscript. JY and YC designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be responsible for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00250/full#supplementary-material

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