SEDATION AND ANALGESIA CHALLENGES IN CRITICALLY ILL NEONATES AND CHILDREN

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SEDATION AND ANALGESIA CHALLENGES IN CRITICALLY ILL NEONATES AND CHILDREN

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Editorial: Sedation and analgesia challenges in critically ill neonates and children

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Editorial on the Research Topic
Sedation and analgesia challenges in critically ill neonates and children

Adequate analgesia and sedation are a precondition in the treatment of critically ill neonates and children in different clinical settings. Controlling pain and agitation enables safe mechanical ventilation and invasive procedures, decreases oxygen demand, while it also decreases accidental removal of medical devices. An appropriate sedative and analgesic approach may also promote better medical outcomes and reduce the risk of patients' complications. Both under- and over-treatment are detrimental for patients. Undersedation does not allow to obtain appropriate control of distress, with physiological and physical consequences, and does not promote optimization of mechanical ventilation. Oversedation may cause side effects, may harm the developing central nervous system, delay recovery, cause tolerance, and increase the incidence of withdrawal syndrome and pediatric delirium.

Recently, reference guidelines on analgesia and sedation were published (1, 2). However, despite these recommendations, clinical challenges and difficulties persist because many areas with weak level of evidence are reported and some decisions are left to the clinicians' expertise. Knowledge gaps for specific groups of critically ill pediatrics patients, difficult sedation and analgesia in clinical practice, neuromonitoring during neuromuscular blockade, sedation strategies in various settings, and environment optimizing bundles are all areas that need further investigation to identify the best approach. Moreover, the implementation of protocols of analgesia and sedation and their sustainability are challenging, as demonstrated by Yang et al.

The current literature is very clear on a few aspects. The presence of pain needs to be considered and treated, and the level of sedation should be titrated according to the patient's status and the clinical situation. In addition, the sedation plan should be suitable for the individual patient and flexible (1, 3).

To address pain, many molecules are suggested, depending on the intensity and level of pain. For severe pain opioids are warranted. One of these molecules, hydromorphone, has been extensively reviewed by Rodieux et al. Pharmacokinetics and pharmacodynamics of this drug at younger ages are not well-known. For this reason, current data do not support any advantage of the use of hydromorphone over morphine in children, both in terms of efficacy and safety. Regarding pain treatment in preterm neonates paracetamol/acetaminophen still is an under-evaluated analgesic therapy. In a retrospective monocentric study exploring the use of paracetamol after surgery in extremely low birth weight preterm infants, Cihlarova et al. reported its safety, although the opioid-sparing effect remains to be evaluated.

One of the key concepts of implementing analgesia and sedation in a PICU is to follow a standardized algorithm, assessing and re-assessing pain, distress and/or level of sedation, iatrogenic withdrawal syndrome and delirium. Three papers in this Research Topic discuss assessment tools, paving the way for successful use in clinical practice. Mencía et al. reported the efficacy of implementing an analgo-sedation assessment by clinical scales, which included a multicenter protocol and staff training. The effects of these interventions were measured with a survey, comparing participating and non-participating centers as well as a before-and-after analysis. In the post-intervention phase, an increased use of protocols and monitoring scales were reported. Tapia et al. analyzed the validity and the reliability of the Richmond Agitation-Sedation Scale (RASS) in a multicenter study. They showed an excellent inter-rater reliability and a good correlation between RASS and the COMFORT-B scale. Of note, these results apply to patients with adequate sedation, but also to those who are under- or over-sedated. Finally, Fazio et al. assessed the validity of the Italian translation of the Cornell Assessment of Pediatric Delirium (CAPD) scale. In this single-center study, the authors showed a high intra- and inter-rater agreement. In addition, they showed that the CAPD scale to have a higher accuracy in diagnosing delirium when compared to clinical evaluation by an intensivist.

Delirium, a well-described entity in adult patients, has become a mainstream interest in PICU research these recent years. Many studies evaluated effects of different delirium related approaches to critically ill children, not only to prevent delirium's complication, but also to increase the quality of care and to reduce the sequelae of intensive care treatments (4, 5). The ABCDEF-Bundle include: (A) assessment, prevention and management of pain, (B) spontaneous awakening and breathing trials, (C) choice of analgesia and sedation, (D) assessment, prevention, and management of delirium, (E) early mobility and exercise and (F) family engagement and empowerment. Engel et al. reviewed the literature in the field and proposed modified ABCDEF bundles for children. The authors' message is to implement these strategies in all pediatric intensive care units, advocating for pediatric studies, as today's literature is scarce.

Michel et al. conducted a single-center study to evaluate the impact of delirium bundles, comparing pre- and post-implementation data. They reported a significant reduction of the incidence of delirium, particularly in younger children and in patients after surgery for congenital heart disease.

Finally, this Research Topic addressed two long-term consequences of critical illness, at least in part due to analgesia and sedation. Neurological (including critical illness myopathy and polyneuropathy), cognitive, social, or mental health disease are well-described in adults after critical illness. Post-intensive care syndrome, or PICS, is a term used to define sequelae after intensive care. The acronym is PICS-p when affecting children, and PICS-f when affecting the family or caregivers (6, 7). A survey, conducted by Von Borell et al. in German-speaking PICUs, evaluated the staff (physicians, nurses, and psychotherapists) knowledge of PICS. The authors reported that a minority of respondents believed PICS to be of importance in their daily clinical practice.

Finally, van den Bosch et al. published a study that followed five cohorts of neonates that were exposed to pain, opioids, or anesthetics. The authors showed that while there weren't major cognitive effects eight to 19 years after exposure in early life to neonatal pain, opioid or anesthetic exposure in children, patients with the highest doses (neonates on extracorporeal membrane oxygenation and neonates with prenatal opioid exposure) had worse neuropsychological functioning.

As demonstrated by this Research Topic on *Sedation and analgesia challenges in critically ill neonates and children*, there are multiple knowledge gaps. Further efforts are warranted to establish the best strategy of analgesia and sedation in neonates and children, assessing both efficacy and safety. Protocols, based on a regular re-assessment of pain, agitation, withdrawal symptoms and delirium, are likely to be beneficial and should be implemented, even if their implementation and long-term sustainability is challenging.

Author contributions

AA wrote the first draft, which was revised and edited by OK. All authors contributed to this editorial final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MONISEDA Project: Improving Analgosedation Monitoring in Spanish Pediatric Intensive Care Units

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Background: Analgosedation (AS) assessment using clinical scales is crucial to follow the international recommendations about analgosedation. The Analgosedation workgroup of the Spanish Society of Pediatric Intensive Care (SECIP) carried out two surveys in 2008 and 2015, which verified the gap in analgosedation assessment in Spanish pediatric intensive care unit (PICUs). The objective of the study was to analyze how analgosedation assessment by clinical scales changed after a multicenter intervention program.

Methods: This is a multicenter pre–post study comparing the use of sedation, analgesia, withdrawal, and delirium scales before and after the MONISEDA project. Results were also compared with a control group formed by non-participating units. A survey about analgosedation management and monitoring was filled out before (year 2015) and after (year 2020) the implementation of the MONISEDA project in 2016. Results were compared not only between those periods of time but also between participant and non-participant PICUs in the MONISEDA project (M-group and non-M group, respectively). Data related to analgosedation of all patients admitted to a MONISEDA-participant PICU were also collected for 2 months.

Results: Fifteen Spanish PICUs were enrolled in the MONISEDA project and another 15 non-participant PICUs formed the control group. In the M-group, the number of PICUs with a written analgosedation protocol increased from 53 to 100% ($p = 0.003$) and withdrawal protocol from 53 to 100% ($p = 0.003$), whereas in the non-M group, the written AS protocol increased from 80 to 87% and the withdrawal protocol stayed on 80%. The number of PICUs with an analgosedation team increased from 7 to 47% in the M-group ($p = 0.01$) and from 13 to 33% in the non-M group ($p = 0.25$). In the M-group, routine use of analgosedation clinical scales increased from 7 to 100% ($p < 0.001$), withdrawal scales from 7% to 86% ($p = 0.001$), and delirium scales from 7 to 33% ($p = 0.125$). In the non-M group, the number of PICUs using AS scales increased from 13 to 100% ($p < 0.001$), withdrawal scales from 7 to 27% ($p = 0.125$), and delirium scales from 0 to 7% ($p = 1$).

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Conclusions: The development of a specific training program improves monitoring and management of analgosedation in PICUs.

Keywords: monitoring analgosedation, MONISEDA project, PICU, withdrawal scales, delirium scales

INTRODUCTION

Sedation and analgesia are essential in the management of critically ill children. Article 24 of the United Nations Convention on the Rights of Children addresses the rights and special demands of children in healthcare institutions, recognizing that children are especially vulnerable. It defines the right to enjoy the highest attainable standard of health and the right to avoid pain, fear, and stress.

That is why pain and anxiety abolition in children must be a priority. An adequate analgosedation diminishes emotional stress, facilitates nursing care, allows adaptation to mechanical ventilation, and improves prognosis, reducing the length of mechanical ventilation and pediatric intensive care unit (PICU) stay (1, 2). However, sedative and analgesic drugs can cause adverse effects and increase morbidity and mortality (3).

International recommendations highlight the importance of improving comfortability in critically ill children, mainly through proper analgesia, minimal possible sedation, and measures to prevent withdrawal syndrome and delirium (4, 5). For that purpose, it is necessary to assess and treat pain prior to administration of sedatives and to keep minimal sedation to allow patients to interact with the environment without agitation. It is fundamental to apply valid and reliable assessment tools to identify pain, excessive or insufficient sedation, and delirium in critically ill children and to use them on a routine basis, adjusting our procedures according to its rating (6–9).

The Analgosedation workgroup of the Spanish Society of Pediatric Intensive Care (SECIP) carried out two surveys in 2008 and 2015, which verified the gap in analgosedation assessment in Spanish PICUs. Therefore, the group decided to perform a training program called MONISEDA project. Its objectives were to create analgosedation working teams in each Spanish PICU and to promote and unify analgosedation clinical scales to improve the assessment of pain, stress, iatrogenic withdrawal syndrome, and delirium.

MATERIALS AND METHODS

A multicenter pre–post study comparing the use of sedation, analgesia, withdrawal, and delirium scales before and after the MONISEDA project was performed. The project was advertised on the SECIP website, and all the Spanish PICUs that were interested had the opportunity to participate in it. The Institutional Review Board reviewed the study and approved it (EPA-SP 02/2017), and written informed consent was waived. This manuscript adheres to the applicable STROBE guidelines.

Abbreviations: AS, analgosedation; SECIP, Spanish Society of Pediatric Intensive Care; IWS, iatrogenic withdrawal syndrome; BIS, bispectral index; PICU, pediatric intensive care unit.

The MONISEDA project was divided into different stages:

1. *Preliminary survey:* A survey was performed in 2015 to determine how pain and stress were being managed and monitored in PICUs at that moment. Two groups were included: PICUs participating in the MONISEDA project (M-group) and non-participants (non-M group).
2. *Development of MONISEDA training program* (**Table 1**): Informative and training activities with sessions and workshops for all PICU members were conducted for a period of 2 months. The project encouraged the creation of an analgosedation team in each PICU of the M-group, consisting of one or two doctors and four–six nurses.

The analgosedation working team was responsible for the training of the rest of the PICU staff through an informative clinical session and a practical training workshop on the use of clinical scales and data collection specially addressed to the nurses of the unit. Once the personnel had been formed, a training period of 1 month was carried out, during which the same data were collected as in the study. During this period, any doubts that arose during the application of the different scales were resolved.

TABLE 1 | Phases of the MONISEDA project training in each PICU.

Periods	Duration	Description
Analgosedation teams	15 days	- Creation of a team in each PICU that will be composed of 1 or 2 physicians and 4 to 6 PICU nurses. - Implementation or reinforcement of scales and analgosedation protocol.
Information period	15 days	- Presentation of the project to the rest of the PICU staff members via: • General session. • Workshops regarding clinical scales of analgesia, sedation, IWS and delirium (driven by Analgosedation team nurses).
Training period	1 month	- All nurses will assess and register analgesia, sedation, iatrogenic withdrawal syndrome and delirium using scales once per shift. - All doubts will be discussed with the Analgosedation team members.
Data collection period	2 months	- Data collection from each patient concerning analgosedation by specific team members. - Data analysis and evaluation of results.

IWS, iatrogenic withdrawal syndrome.

TABLE 2 | Initial analgosedation survey (year 2015).

Variable	Global results (%)	Moniseda (%)	Non-Moniseda (%)	*P*
Written AS protocol	67	53	80	0.123
Use of daily AS scales	10	7	13	0.5
AS working team creation	10	7	13	0.5
Sedation scale used	71	Ramsay 76	Ramsay 66	0.5
Objective monitoring: BIS	30	33	27	0.5
Written WS protocol	67	53	80	0.123
Use of daily IWS scales	3	7	0	0.5
Usual use of delirium scales	0	7	0	–

Comparison between MONISEDA group and non-MONISEDA group.
AS, analgosedation; BIS, bispectral index; IWS, iatrogenic withdrawal syndrome.

3. *Data collection phase:* For 2 months, PICUs participating in MONISEDA project filled out the data collection form. After obtaining informed consent from parents or guardians, the scores for the analgesia clinical scale (adapted to age) and sedation (COMFORT scale) for all children admitted to the PICU were registered once per shift (6 a.m., 2 p.m., and 9 p.m.). No patients were excluded. Data was sent to the coordinator center for its analysis. All study coordinators from the different PICUs were asked to complete a satisfaction survey upon completion of this phase.
4. *Subsequent survey after the project:* In 2020, the same data collection form was again completed by all the PICUS of both groups, in order to compare these results with the previous ones.

Statistical Analysis

All data was analyzed by the software package SPSS for Windows, version 19. Qualitative variables were expressed as percentages, and quantitative variables as means and standard deviation. Fisher's exact test was used to compare qualitative variables, and Mann–Whitney *U*-test for quantitative variables. The McNemar test for related samples was used to analyze the evolution of the variables of the 2020 survey with respect to that of 2015. Statistical significance was considered when $p < 0.05$.

RESULTS

Analgosedation Survey in 2015

Table 2 shows the results of the first analgosedation survey, comparing PICUs of the M-group and the non-M group. The number of PICUs that followed a written analgosedation and withdrawal protocol was higher in the non-M group, although differences were not statistically significant.

MONISEDA Project 2016

In the M-group, the project was introduced to the rest of the staff in 85% of the PICUs, and a specific analgosedation working team consisting of doctors and nurses was created in 61% of the units.

TABLE 3 | Satisfaction survey of MONISEDA group 2016.

Variable	MONISEDA Project (%)
AS working team creation	61.5
Difficulties to develop the project	40
Changes in AS daily management	69
Daily AS monitoring implementation	33
Daily IWS monitoring implementation	40

AS, analgosedation; IWS, iatrogenic withdrawal syndrome.

TABLE 4 | Final analgosedation survey (year 2020).

Variable	Global results (%)	Moniseda (%)	Non-Moniseda (%)	*P*
Written AS protocol	93	100	87	0.5
Use of daily AS scales	100	100	100	–
AS working team creation	40	47	33	0.355
Sedation scale used		COMFORT 100	COMFORT 66	
Objective monitoring: BIS	60	60	60	0.645
Written IWS protocol	90	100	80	0.241
Use of daily WS scales	57	87	27	**0.001**
Usual use of delirium scales	20	33	7	0.080

Comparison between MONISEDA group and non-MONISEDA group.
AS, analgosedation; BIS, biespectral index; IWS, iatrogenic withdrawal syndrome. The bold values mean the percentage increase in the different variables in both groups.

At the end of the project, a satisfaction survey was completed by the coordinators of each PICU (**Table 3**). Main difficulties to implement monitoring were the lack of habit and the workload, principally from the nurses' point of view (40%). There were 33% of doctors and 31% of nurses who thought that the project had significantly changed routine analgosedation monitoring, and 70% of participants considered that some monitoring aspects had changed. The most important improvement was the incorporation of the use of clinical monitoring scales in 33% of the units. A greater use of sedation scales was attained in 10 PICUs, of withdrawal scales in six units, and of analgesia scales in three units. Four PICUs started to use delirium scales.

During the 2 months of the study, data from 489 children were collected [55% were males, mean age was 4.2 years old (SD 4.7), and mean weight was 21 kg (SD 18)]. The reason for admission was medical pathologies in 53% of the cases. The mean length of stay was 6.3 days (SD 13); 30% of the patients underwent mechanical ventilation and 1.8% of the patients died.

Analgesia was monitored by scales in 97% of the patients, with a mean score of 1.5 (SD 1.4). Sedation assessment was performed by the COMFORT scale in 93% of the patients, with an average rating of 18.3 (SD 5.9). Bispectral index (BIS) monitoring of the level of consciousness was used in 8% of the patients, with a mean score of 56 (SD 14).

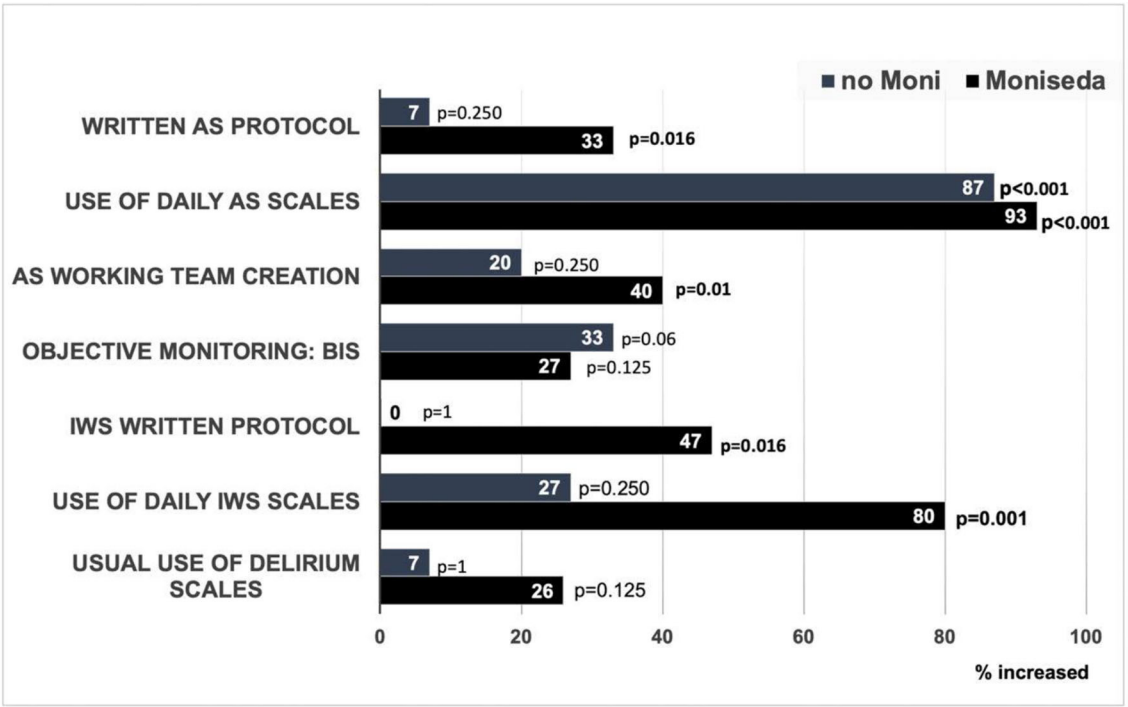

FIGURE 1 | Improvement in analgosedation survey 2020 compared to 2015 in both the MONISEDA and non-MONISEDA groups. AS, analgosedation; BIS, bispectral index, IWS, iatrogenic withdrawal syndrome.

Analgosedation Survey in 2020

Table 4 shows the results of the last analgosedation survey performed, comparing PICUs of the M-group and the non-M group. Every PICU (100%) in both groups used some analgosedation clinical scale on a daily basis. PICUs in the M-group performed analgosedation assessment more frequently than the control group. Statistically significant differences were found for withdrawal monitoring (87 vs. 27%; $p = 0.001$). Delirium assessment increased importantly too (33 vs. 7%; $p = 0.08$) but did not reach statistical significance.

Comparison Between 2015 and 2020 Surveys

Figure 1 shows the comparison between the first and the last analgosedation survey. In both groups, the use of clinical scales improved. In recent years, important morbidities have been described in patients admitted to intensive care units related to the inappropriate use of analgosedation. The scientific community has improved awareness of this problem. For this reason, most hospitals have optimized the use of analgesia, which requires adequate monitoring by means of validated scales.

The increase of analgosedation monitoring activities was higher in the M-group than in the non-M group. There was a higher increment in the creation of analgosedation working teams and written protocols for withdrawal monitoring.

DISCUSSION

This is the first multicenter project that aims to improve analgosedation monitoring in Spanish PICUs. Our study shows that a specific training project significantly improves analgesia, sedation, and withdrawal monitoring. It enhances awareness of health professionals and facilitates the creation of analgosedation working teams consisting of doctors and nurses. The patients admitted to PICU are complex patients with a high care load. The performance and the recording of the analgosedation and delirium scales can lead to an overload of work for the nursing staff. In addition, the implementation of the new work routines sometimes generates rejection, mainly related to the lack of knowledge about them. With an adequate training on their application and their importance, both points can be improved.

This leads to regular and long-term monitoring after the educational intervention. Our project could be a model for the development of new similar projects in other countries.

In the second survey, conducted 5 years after the intervention, it is important to highlight the improvement in the daily monitoring of analgosedation, withdrawal, and delirium. Creation of multidisciplinary working teams (doctors and nurses) and a better follow-up of the recommendations to homogenize the use of clinical scales in the Spanish PICUs have significantly increased too. Furthermore, the use of the COMFORT/COMFORT-b scale (specific for pediatric patients) raised compared

to the Ramsay scale, which is only validated for adults (10, 11).

The analysis showed that over the 2 months of data collection, analgosedation monitoring followed the international recommendations. The implementation of analgesia scales per shift achieved good pain control. Based on an early diagnosis and treatment adjustment according to the score, most of the patients showed no pain or mild pain and an appropriate level of sedation (4).

The second survey, conducted 5 years after the intervention, showed an improvement of analgosedation monitoring in both the M and non-M groups, which reflected a growing awareness of PICU health professionals on the importance of this monitoring (12, 13). We think that there could have been a contagion or spread effect from the PICUs included in the MONISEDA project to the rest of Spanish PICUs (14, 15).

Other studies have previously highlighted the importance of an appropriate analgosedation (AS) monitoring in order to prevent and manage the appearance of withdrawal syndrome or delirium (16–18).

Achieving an improvement on AS and withdrawal monitoring in the Spanish PICUs is challenging. The implementation of a new routine in a clinical service is difficult, especially when it is a highly complex unit and there is a high staff turnover. Both time and a great effort are essential to accomplish this task. Difficulties to introduce these types of protocols are mentioned in other studies (19, 20). We consider that the creation of working teams made up of doctors and nurses is very important. The engagement and training of the nursing staff are crucial as they are in charge of the AS monitoring and the adjustment of the treatment to the patient's condition (16). However, despite the observed improvement in the 2020 survey, there are still some aspects, such as the withdrawal and delirium monitoring (16, 21, 22), which need to be enhanced and require continuous evaluation and feedback.

Our study has some limitations. Despite every Spanish PICU being invited to participate in the project, only one third of them accepted the invitation. So, probably, those PICUs included in the project were also those with higher awareness on the importance of analgosedation and those that felt the need to implement these protocols. The hospitals that did not participate in the study did complete an online survey recording the management of analgosedation in their work units. This concern could have introduced a bias in the comparison of both groups and could explain the fact that in the initial survey only a small percentage of PICUs followed a written AS protocol.

Another limitation is that the observational study of patients was not repeated in 2020 to verify the improvements observed in the survey in the daily practice.

The study could be improved by having a longer duration. In this way, the training of the team and the different stages of the study could be repeated periodically, comparing the results after several training stages.

In conclusion, we think that the creation of multicenter training projects, like the MONISEDA project, could be an effective tool to achieve a better analgosedation assessment of critically ill children. Our project could serve as a model for other countries, adjusting it to their specific characteristics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (EPA-SP 02/2017). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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AUTHOR CONTRIBUTIONS

SM helped in manuscript writing, study design, programming, data acquisition, and data validation. RC helped as methodology advisor and with manuscript editing. JC helped with manuscript editing. JL-H helped in study design and in manuscript writing. SECIP authors helped in data acquisition and data validation. All authors contributed to the article and approved the submitted version.

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Validity and Reliability of the Richmond Agitation-Sedation Scale in Pediatric Intensive Care Patients: A Multicenter Study

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Background: There is limited data about the psychometric properties of the Richmond Agitation-Sedation Scale (RASS) in children. This study aims to analyze the validity and reliability of the RASS in assessing sedation and agitation in critically ill children.

Methods: A multicenter prospective study in children admitted to pediatric intensive care, aged between 1 month and 18 years. Twenty-eight observers from 14 PICUs (pediatric intensive care units) participated. Every observation was assessed by 4 observers: 2 nurses and 2 pediatric intensivists. We analyzed RASS inter-rater reliability, construct validity by comparing RASS to the COMFORT behavior (COMFORT-B) scale and the numeric rating scale (NRS), and by its ability to distinguish between levels of sedation, and responsiveness to changes in sedative dose levels.

Results: 139 episodes in 55 patients were analyzed, with a median age 3.6 years (interquartile range 0.7–7.8). Inter-rater reliability was excellent, weighted kappa (κ_W) 0.946 (95% CI, 0.93–0.96; $p < 0.001$). RASS correlation with COMFORT-B scale, rho = 0.935 ($p < 0.001$) and NRS, rho = 0.958 ($p < 0.001$) was excellent. The RASS scores were significantly different ($p < 0.001$) for the 3 sedation categories (over-sedation, optimum and under-sedation) of the COMFORT-B scale, with a good agreement between both scales, κ_W 0.827 (95% CI, 0.789–0.865; $p < 0.001$), κ 0.762 (95% CI, 0.713–0.811, $p < 0.001$). A significant change in RASS scores ($p < 0.001$) was recorded with the variance of sedative doses.

Conclusions: The RASS showed good measurement properties in PICU, in terms of inter-rater reliability, construct validity, and responsiveness. These properties, including its ability to categorize the patients into deep sedation, moderate-light sedation, and agitation, makes the RASS a useful instrument for monitoring sedation in PICU.

Keywords: anesthesia and analgesia, intensive care unit, pediatric, monitoring, physiologic, nursing assessment, validation studies as topic, reproducibility of results

INTRODUCTION

International clinical guidelines recommend monitoring sedation in critically ill children with a validated and age-appropriate scale (1, 2). This allows to assess the depth of sedation in a standardized way and adjust objective-guided treatment, to better avoid over and under-sedation (1–3).

A gold standard reference scale does not exist (4, 5). The COMFORT scale, its modified version COMFORT behavior (COMFORT-B), and the State Behavioral Scale (SBS) are the most recommended in the international sedation guidelines (1, 2). The COMFORT-B scale is used the most (6–9). It has shown high reliability, construct validity and responsiveness in the pediatric intensive care unit (PICU), in ventilated and non-ventilated patients (5, 10–13). It distinguishes among 3 levels of sedation/agitation, for which the authors recommend associating it to a second scale, such as the Nurse Interpretation of Sedation Score (NISS) (3, 5). The greatest disadvantage of the COMFORT-B scale is the time required to perform it (14). The other recommended scale, the SBS, is only valid for ventilated patients (15). For these reasons, it would be useful to have a simpler alternative, capable of quickly differentiating between different levels of sedation, which would not require the use of other complementary scales, and apt to intubated and non-intubated patients.

The RASS (Richmond Agitation-Sedation Scale) is commonly used in adults admitted to critical care (16, 17). In critically ill children, RASS is used as a starting point for delirium diagnosis along with the Pediatric Confusion Assessment Method for the ICU (pCAM-ICU), Preschool Confusion Assessment Method for the ICU (psCAM-ICU) and Cornell scales, which require a RASS score $\geq$-3 to start assessment (18–20).

Although the RASS has not been sufficiently validated in critically ill children, some PICUs use it for sedation monitoring, due to the simplicity and quickness of the procedure (3, 21, 22). Only two previous studies have analyzed RASS inter-rater reliability in critically ill children, obtaining good results in this population (21, 22). However, these studies have their limitations, as they are single-center studies. RASS construct validity has also been explored in one of them, using the University of Michigan Sedation Scale (UMSS) as the comparator instrument, a validated sedation scale for pediatric procedures which does not include agitation (21). Agitation was only analyzed based on the expert opinion, using a visual analog sedation-agitation scale (VAS) (21).

The aim of our study was to analyze the measurement properties of the RASS in children admitted to PICU, in terms of inter-rater reliability, construct validity and responsiveness, in a prospective multi-center study.

MATERIALS AND METHODS

A prospective multi-center study was carried out, with the participation of 14 Spanish PICUs. The study was approved by the Research Ethics Committee of the promoting center. Written informed consent of parents and mature minors subjects was obtained.

Study Period

Ethics committee approval in July 2016, video recording of the episodes from August to November 2016, theoretical training in June 2018, and video evaluation (training and final) from July 2018 to February 2019.

Patients

Patients admitted to the PICU of the promoting hospital were enrolled until a minimum of 100 episodes from 50 patients was reached (following the COSMIN recommendations for an adequate sample size) (23). Patients between ages 1 month and 18 years with any level of sedation were included. Exclusion criteria were uncontrolled pain, severe psychomotor impairment, auditive or visual impairment, neuromuscular diseases, and treatment with muscle relaxants.

Research Team

The research team consisted of 14 intensive pediatric doctors, including the principal investigator, and 14 PICU nurses. The pediatricians belonged to the Analgesia and Sedation Group of the Spanish Society of Pediatric Intensive Care (SECIP). The nursing staff had more than 10 years of experience in the PICU. Eighty-four percent of the researchers had previous experience using the COMFORT-B scale.

The research team received a training course in the application of the RASS and COMFORT-B scales, following the instructions published by their authors (24, 25). The training course consisted of an in-person theoretical-practical section of 2 h, and a second non-attendance part in which every researcher applied the scales in 20 video recorded clinical cases.

Video Recordings of the Episodes

The principal investigator carried out the patients' video recordings according to the following protocol: (1st) observation of the patient without stimulation, including all parts of the body; (2nd) broadcast of auditory stimulus, calling the patient by their name, telling them to open their eyes and to look at the interlocutor; (3rd) muscle tone assessment, holding and dropping one arm; (4th) application of a tactile stimulus of increasing intensity, from a gentle touch to the shoulder to a potentially painful stimulus, following the RASS instructions. The ventilator screen and the vital signs monitor were also recorded. In order not to influence the observers, the stimulation sequence was done until the end, even if a response appeared in the first steps, except if the patient's agitation prevented it. The same patient could be analyzed once a day for several days or several times in the same day, if any change in sedation was made.

Scales Assessment

The researchers were randomly divided into 7 groups of 4 members each (2 nurses and 2 pediatricians), equally dividing the total number of episodes to be analyzed among the 7 groups, so as not to overburden the collaborators. The same episode was independently assessed by the 4 researchers. Each researcher scored the RASS (**Supplemental Appendix 1**) first, the COMFORT-B scale (**Supplemental Appendix 2**) second, and the NRS third, of their corresponding episodes.

The RASS consists of 10 levels of sedation/agitation: 5 of sedation, one of calm alertness and 4 levels of agitation (24). Each value on the RASS scale is defined in 2 complementary ways: by a term/epigraph for each sedation-agitation level and by a specific description of the expected behavior at that level. The researchers gave 2 values for the RASS scale: one based solely on the epigraph (RASSe), which corresponds to the observer's subjective opinion, and the other according to the objective description of the patient's behavior or conduct (RASSc). As the scale is based on expected behaviors in adults (RASSc), an attempt was made to see whether differences with pediatric behavior affect the level at which a child is classified, observing if they coincide with the expert's opinion (RASSe) or not. A previously published Spanish version of the RASS was used (**Supplemental Appendix 3**) (26).

The COMFORT-B scale is composed of 6 items (25). Each one is scored from 1-5, obtaining a minimum score of 6 points and a maximum of 30. It distinguishes among 3 levels of sedation/agitation, for which the authors recommend associating it to a second subjective scale, such as the NISS: over-sedation (6–10 points), optimum sedation (included in the range 11–22, combined with NISS = 2), and under-sedation (23–30) (3, 5). The NISS is a 3-point scale based on the nurse expert opinion, where score 1 corresponds to insufficient sedation, 2 = adequate sedation, and 3 = oversedation (5).

The NRS is a subjective scale of 11 points which represents the expert opinion of the observer, ranging 0–10: 0 corresponds to the deepest sedation state imaginable for the patient, and 10 to the maximum agitation state.

Analgosedation

The analgosedation protocol of the leading hospital was followed, based on prioritizing the adjustment of analgesia first sedation. Drugs and dosages were prospectively registered. The analgesics used were fentanyl, morphine, paracetamol, metamizole, ketorolac, and gabapentin. The sedatives used were propofol, dexmedetomidine, clonidine, midazolam, sevoflurane, ketamine, chlorpromazine, and levomepromazine.

Statistical Analysis

A descriptive analysis was performed. Qualitative variables were described by absolute and relative frequencies and quantitative variables by median and interquartile range (IQR) as they did not have a normal distribution (measured by the Kolmogorov-Smirnov test). The observations which weren't assessed by the 4 observers in each group were not included in each specific analysis.

The validation stages and their statistical analysis were made following the Consensus-based Standards for the selection of health Measurement Instrument (COSMIN) criteria (23).

Reliability

Inter-rater reliability was measured using the intraclass correlation coefficient (ICC) two-way mixed-effects model for the COMFORT-B and NRS scales, or the quadratic weighted kappa (κ_w) index for the RASS scale (RASSe and RASSc), among all the researchers and between the group of nurses, pediatricians, and nurses-pediatricians. Additionally for the RASS, we analyzed separately patients younger and older than 12 months. The same was done with the subgroup of restless and/or agitated patients (RASS +1 to +4), since there could be differences between anxious or agitated behavior of adults and pediatric patients. An ICC value of >0.8 and a kappa index >0.8 were considered excellent, >0.6 satisfactory or good and >0.4 moderate, according to the Landis and Koch criteria (27).

Construct Validity

To test construct validity, we explored the degree to which the RASS score was consistent with the following hypotheses: (1) The RASS score increases and decreases in the same direction as the COMFORT-B and the NRS do. This correlation was measured using the Spearman correlation coefficient (rho), expected to be ≥0.5. This analysis was repeated in the subgroup of children under 12 months of age. Following COSMIN criteria, rho ≥0.5 was considered as indicating that both instruments measure a similar construct, rho 0.3–0.5 as the construct is related but dissimilar, and rho <0.3 as measuring unrelated constructs (23). (2) The RASS can distinguish between 3 different categories of sedation-agitation, similar to those of the COMFORT-B scale. We considered the ranks (−5 to −4, deep sedation), (−3 to +1, moderate and light sedation) and (+2 to +4, agitation) of the RASS to be similar to the ranks (6–10), (11–22) and (23–30) of the COMFORT-B. We used the Kruskal-Wallis test to analyze the ability of the RASS to discriminate among the 3 categories, and κ and κ_w indices to measure the agreement between RASS and COMFORT-B. (3) RASSe and RASSc measure the same construct (sedation-agitation). Spearman correlation coefficient was calculated, expected to be ≥0.5. (4) RASSe and RASSc scores match when rating an episode of sedation-agitation. The agreement between RASSe and RASSc was calculated using κ and κ_w.

Responsiveness

A responsiveness analysis to sedative changes was carried out, rating the differences in RASS values before and after a required intervention of increase or decrease of sedatives using the Wilcoxon test for paired samples.

All analyses were performed with SPSS and STATA statistical package and a p value < 0.05 was considered significant.

RESULTS

Patient Characteristics and Episodes

Fifty-five patients (58% female) with a median age of 3.6 years (IQR: 0.7–7.8), ranging from 44 days to 16 years of age were enrolled. We obtained 146 episodes, 7 of which were excluded due to recording failures, so that 139 episodes were finally included. The characteristics are shown in **Table 1**. The distribution of the scores according to the different scales used is shown in **Figure 1**. Ten different observations were missed for every scale. There were 5

TABLE 1 | Patient characteristics and episodes.

Category	Variations	*N* (%)
Number of patients		55
Age distribution	<12 months	17 (30.9%)
	12–24 months	5 (9.1%)
	2–5 years	15 (27.3%)
	6–12 years	11 (20%)
	13–19 years	7 (12.7%)
Diagnosis	Sedation for procedures	19 (34.5%)
	Respiratory Failure	10 (18.2%)
	Postoperative of cardiac surgery	9 (16.4%)
	Postoperative of otorhinolaryngological surgery	7 (12.7%)
	Postoperative of orthopedic surgery	4 (7.3%)
	Severe infections	4 (7.3%)
	Post cardiac catheterization	3 (5.4%)
	Endocrine failure	1 (1.8%)
Number of episodes		139
Number of episodes per patient	1	14 (25.5%)
	2	23 (41.8%)
	3	9 (16.4%)
	4	2 (3.6%)
	5	4 (7.3%)
	6	1 (1.8%)
	8	1 (1.8%)
	10	1 (1.8%)
Median of episodes per patient (range)		2 (1–10)
Episodes with invasive mechanical ventilation		52 (37.4%)
Episodes without sedation (%)		19 (13.7%)
Number of observations	RASS[a]	546
	COMFORT-B[b]	546
	NRS[c]	546

[a]*Richmond Agitation-Sedation Scale;* [b]*COMFORT Behavior Scale;* [c]*Numeric Rating Scale.*

investigators who did not assess all their corresponding episodes: 1 observer missed 4 episodes, 2 observers missed 2 episodes each, and 1 observer missed 1 episode, making a total of 10 episodes in 6 patients. The patients belonged to different age groups, with 12.8, 0.6, 16.1, 1.2, 0.8, and 6.4 years, respectively.

The assessments carried out in each Unit are shown in the (**Supplementary Table 1**).

Inter-Rater Reliability

For the RASS, 538 observations were analyzed, 528 for the COMFORT-B scale, and 532 for the NRS.

The median (IQR) RASSe and RASSc scores was −2 (−4 to 0), for both global nursing and global pediatrician groups (**Supplementary Table 2**).

For the COMFORT-B scale, it was obtained an ICC = 0.910 (95% CI, 0.883–0.931) among all researchers. Between nurses and pediatricians, the result was an ICC = 0.901 (95% CI, 0.876–0.92). For the NRS scale, an ICC = 0.913 (95% CI, 0.888–0.934) was obtained among all observers, and an ICC = 0.919 (95% CI, 0.898–0.935) between nurses and pediatricians (**Supplementary Table 3**).

RASS inter-rater reliability among all researchers and between nursing and pediatric groups is shown in **Table 2**. A similar result was achieved when taking a unique first observation of each patient (n = 55), with a κ_w = 0.954 (95% CI, 0.93–0.98) for RASSe, and κ_w = 0.961 (95% CI, 0.94–0.98) for RASSc, between nurses and pediatricians. There were no differences in inter-rater reliability between patients younger and older than 12 months [RASSe κ_w = 0.941 (95% CI, 0.90–0.98) vs 0.932 (95% CI, 0.914–0.949) and RASSc κ_w = 0.951 (95% CI, 0.917–0.985) vs. 0.944 (95% CI, 0.926–0.961)] (**Supplementary Table 4**).

There were 27 and 28 episodes classified as restless or agitated according to RASSe and RASSc (108 and 111 observations, respectively, with RASS +1 to +4). In analyzing these observations, the inter-rater reliability of the RASS was only moderate. For RASSe, we obtained a κ_w = 0.527 (95% CI, 0.374–0.671), with no differences between children younger and older than 12 months [0.561 (0.637–0.755) vs. 0.478 (0.286–0.671)]. For RASSc, we observed a κ_w = 0.511 (95% CI, 0.345–0.678) with no differences between those younger and older than 12 months [κ_w = 0.509 (95% CI, 0.260–0.759) vs. 0.487 (95% CI, 0.282–0.692)].

Construct Validity

The results of the analyses undertaken to test construct validity are shown below:

The Spearman rho correlation between the COMFORT-B scale and RASSe and RASSc was analyzed in 544 observations. The results, with rho = 0.935 (p < 0.001) in the global population and in the subgroups of children younger and older than 12 months, are shown in **Table 3**. The correlation was also statistically significant both in nursing staff (rho = 0.927 and 0.938; p < 0.001) and among pediatricians (rho = 0.939 and 0.931; p < 0.001), for RASSe and RASSc, respectively.

The Spearman rho correlation between RASS and NRS, in 544 observations, is shown in **Table 3**. It was statistically significant among nurses (rho = 0.949 and 0.948; p < 0.001) and pediatricians (rho = 0.973 and 0.970; p < 0.001), for RASSe and RASSc, respectively.

To check whether the fact that the same observer applied the 3 scales simultaneously could have facilitated the correlation between them, a randomized representative

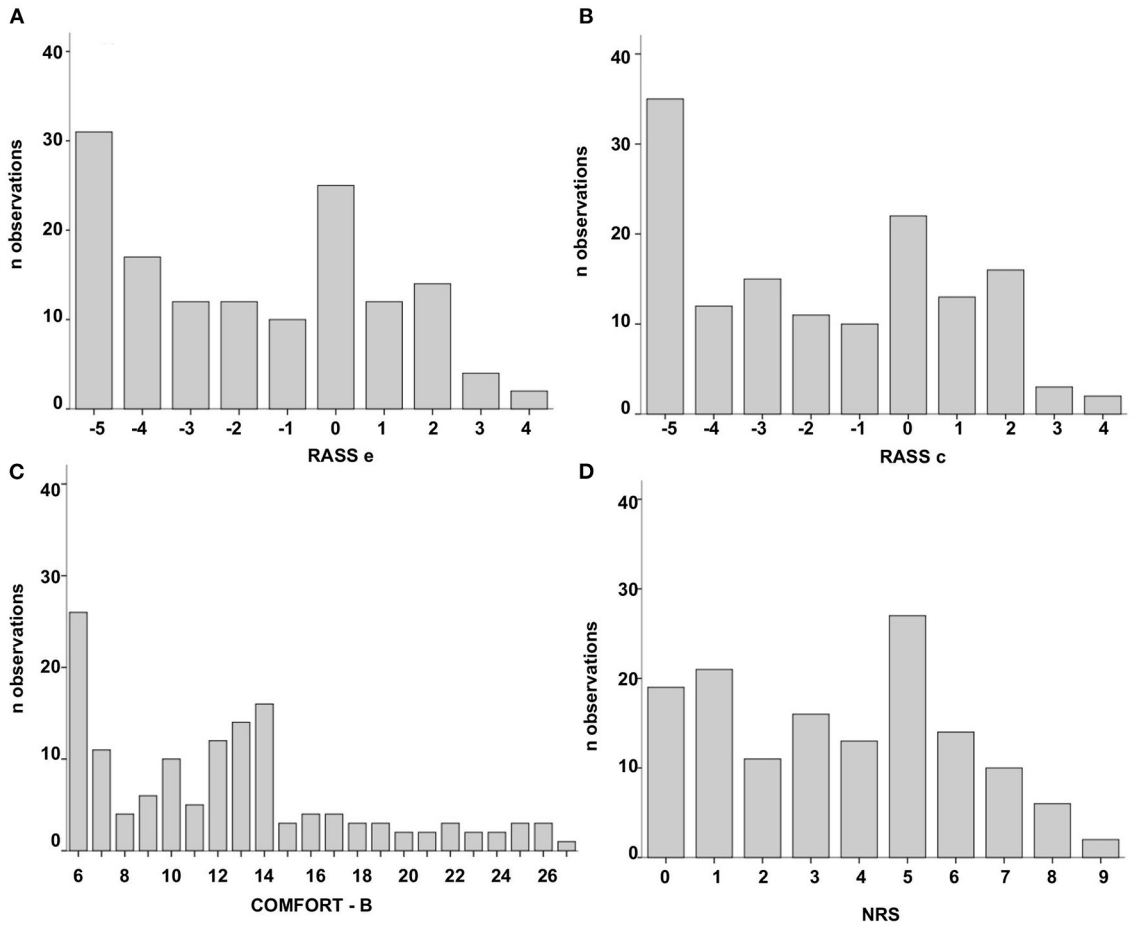

FIGURE 1 | Scores of the 546 observations in 139 patient episodes according to the scale used: **(A)** Richmond Agitation-Sedation Scale based on the epigraph (RASSe). **(B)** Richmond Agitation-Sedation Scale based on the description of the conduct (RASSc). **(C)** COMFORT Behavior Scale (COMFORT-B). **(D)** Numeric Rating Scale (NRS).

TABLE 2 | Inter-rater reliability of the Richmond Agitation-Sedation Scale ($p <$ 0.001 in all cases).

Observers group	κ_w (95 CI%)[a]	
	RASSe[b]	RASSc[c]
Between nurses	0.927 (0.894–0.961)	0.948 (0.917 - 0.979)
Between pediatricians	0.943 (0.913–0.973)	0.942 (0.911–0.973)
Between nurses and pediatricians	0.933 (0.908–0.959)	0.946 (0.924–0.969)
Global ($n = 538$ observations)	0.934 (0.917–0.951)	0.946 (0.929–0.962)

[a]*Weighted kappa (95% confidence interval);* [b]*Richmond Agitation-Sedation Scale based on the epigraph;* [c]*Richmond Agitation-Sedation Scale based on the description of the conduct.*

sample of procedures was analyzed ensuring that the same observer had only applied one of the scales. Similar data were obtained for all correlations (data not shown).

RASSe and RASSc scores were significantly different for the 3 sedation-agitation categories of the COMFORT-B scale (Kruskal-Wallis, $p < 0.001$) (**Supplementary Table 5**).

The agreement between RASS and COMFORT-B scores in classifying the patients into the 3 COMFORT-B categories is shown in **Table 4**, with a $\kappa = 0.762$ (95% CI, 0.713–0.811), in 544 observations. There were 26 observations that RASSe scored +2 to +4, and COMFORT-B scored 11 to 22. Among them, 88.4% (23/26) had a score of 17 or higher on the COMFORT-B scale.

Between RASSe and RASSc, a statistically significant correlation and agreement were observed: Spearman rho = 0.985 ($p < 0.001$), $\kappa = 0.802$ (95% CI, 0.766–0.839) and $\kappa_w = 0.986$ (95% CI, 0.984–0.90), in 546 observations (**Supplementary Figure 1**). This agreement was maintained considering the 3 sedation-agitation categories before mentioned, $\kappa = 0.894$ (95% CI, 0.859–0.928) and $\kappa_w = 0.927$ (95% CI, 0.902–0.951) (**Supplementary Table 6**).

Responsiveness

To test responsiveness, 45 interventions were analyzed before and after a change in the sedative dose (18 episodes of diminishing or

TABLE 3 | Spearman rho correlation between RASS and COMFORT-B and between RASS and NRS, in the global population and in children < or > 12 months ($p <$ 0.001 in all cases).

Scale	RASS[a]	Global	*N*	≤12 months	*n*	>12 months	*n*
COMFORT-B[d]	RASSe[b]	0.932	544	0.938	147	0.931	397
COMFORT-B	RASSc[c]	0.935	544	0.941	147	0.932	397
NRS[e]	RASSe	0.960	544	0.963	147	0.957	397
NRS	RASSc	0.958	544	0.967	147	0.953	397

[a]Richmond Agitation-Sedation Scale; [b]Richmond Agitation-Sedation Scale based on the epigraph; [c]Richmond Agitation-Sedation Scale based on the description of the conduct; [d]COMFORT Behavior Scale; [e]Numeric Rating Scale.

TABLE 4 | Agreement between the Richmond Agitation-Sedation Scale and the COMFORT behavior scale categories ($p < 0.001$ in all cases).

Scale	RASS[a]	COMFORT-B[d]			
	Sedation-agitation category	6–10	1–22	23–30	*n* observations
RASSe[b]	−5 to −4	183	3	0	186
	−3 to +1	46	238	1	285
	+2 to +4	0	26	47	73
	n observations	229	267	48	544
	κ (95% CI)[e]	0.762 (0.713–0.811)			
	κ_w (95% CI)[f]	0.835 (0.799–0.871)			
RASS c[c]	−5 to −4	182	9	0	191
	−3 to +1	47	238	2	287
	+2 to +4	0	20	46	66
	n observations	229	267	48	544
	κ (95% CI)[e]	0.754 (0.703–0.804)			
	κ_w (95% CI)[f]	0.827 (0.789–0.865)			

***Sedation-agitation categories: Deep sedation**: RASS −5 to −4 and COMFORT-B 6 to 10. **Moderate to light sedation**: RASS−3 to +1 and COMFORT-B 11 to 22. **Agitation:** RASS +2 to +4 and COMFORT-B (23 to 30). [a]Richmond Agitation-Sedation Scale; [b]Richmond Agitation-Sedation Scale based on the epigraph; [c]Richmond Agitation-Sedation Scale based on the description of the conduct. [d]COMFORT Behavior Scale; [e]kappa (95% confidence interval); [f]weighted kappa (95% confidence interval).*

TABLE 5 | Median scores (IQR) of the 45 episodes assessed before and after an intervention of increase or decrease in sedatives.

Scale	Score[e] Intervention							
	Sedative increase (*n* episodes = 27)				Sedative decrease (*n* episodes = 18)			
	Before	After	Difference	*p*	Before	After	Difference	*p*
RASSe[a]	0 (0–2)	−4 (−5 to −3)	−4 (−5 to −3.8)	<0.001	−5 (−5 to −3)	−1 (−2 to 0)	3 (2–4)	<0.001
RASSc[b]	1 (0–1)	−5 (−5 to −3)	−5 (−6 to −3.8)	<0.001	−5 (−5 to −3)	−1 (−8 to 0)	3 (2–4.8)	<0.001
COMFORT-B[c]	15 (13–19)	7 (6–15)	−8 (−11 to −6)	<0.001	7 (6–9)	1 (12–15)	6 (3–8)	<0.001
NRS[d]	5 (5–7)	1 (0–3)	−4 (−5 to −3)	<0.001	1 (0–2)	5 (3.5–5)	4 (2–4)	<0.001

[a]Richmond Agitation-Sedation Scale; [b]Richmond Agitation-Sedation Scale based on the epigraph; [c]Richmond Agitation-Sedation Scale based on the description of the conduct; [d]COMFORT Behavior Scale; [e]Numeric Rating Scale; [e]Median score.

stopping sedation and 27 of increasing or initiation of sedation). Most of them were carried out during sedation for procedures. There was a significant modification in sedation-agitation scores following both types of intervention (**Table 5**; **Figure 2**). Doses were collected but not statistically analyzed because of the large variability in the type of drugs and dose received by each patient due to the heterogeneity of the sample and are not shown in the study.

DISCUSSION

Our study shows that the RASS has good measurement properties in assessing sedation in critically ill children, with and without mechanical ventilation, in terms of inter-rater reliability, construct validity and responsiveness.

It confirms some of the findings of two previous studies conducted in PICU (21, 22). Furthermore, our study has certain

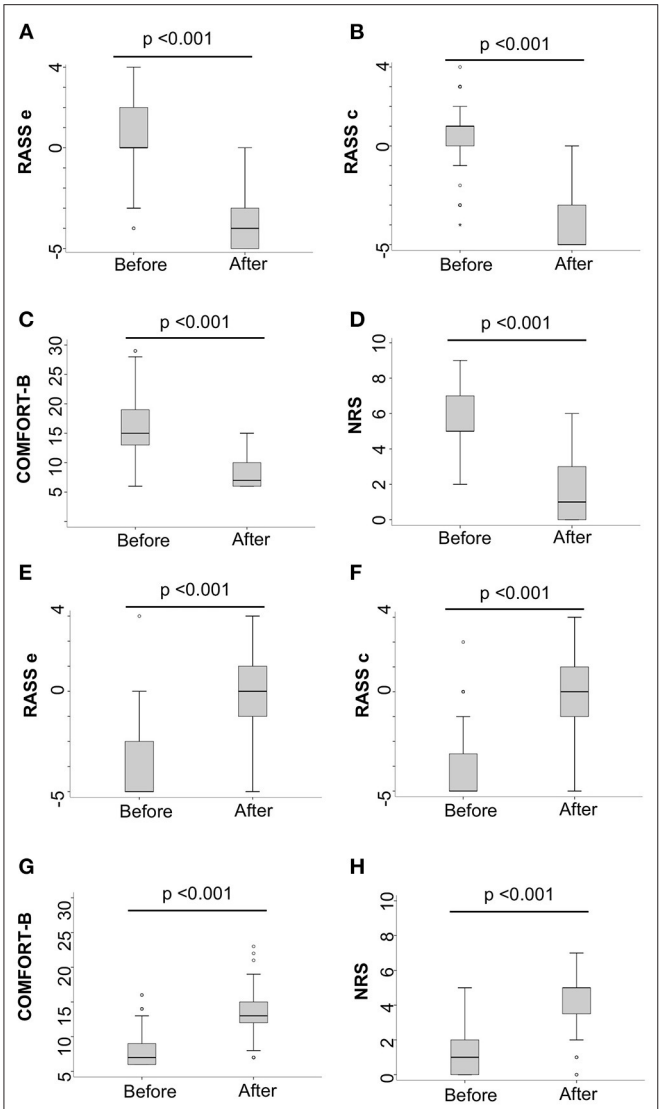

FIGURE 2 | Responsiveness of the RASS: Modification in sedation-agitation scores of the different scales used, before and after a sedative intervention. **Increasing/initiation of sedatives (A)** RASSe; **(B)** RASSc; **(C)** COMFORT-B; **(D)** NRS. **Diminishing/stopping of sedatives (E)** RASSe; **(F)** RASSc; **(G)** COMFORT-B; **(H)** NRS. RASSe, Richmond Agitation-Sedation Scale based on the epigraph; RASSc, Richmond Agitation-Sedation Scale based on the description of the conduct; COMFORT-B, COMFORT Behavior Scale; NRS, Numeric Rating Scale.

characteristics that strengthen our results. Firstly, a multicenter study reduces the risk of bias in the application of the results. Secondly, a video recording format ensures total independence in assessments among researchers. Third, a validated scale has been used as a comparative tool of the agitation range. And lastly, a responsiveness study has been included.

We found RASS inter-rater reliability to be excellent among health professionals from different PICUs, with similar results between pediatricians and nurses, and between patients younger and older than 12 months. These findings coincide with the two previous studies, where it was found a κ_w of 0.825 ($p <$ 0.0001) and 0.86 (95% CI), respectively (21, 22). The inter-rater reliability, however, resulted lower in our subgroup of agitated patients.

Inter-rater reliability among the research team was also excellent in the scales chosen as references, COMFORT-B and NRS, demonstrating the ability of the collaborators to participate in the study. The researchers were experienced PICU personnel, and all had previously received a training course to use the RASS and COMFORT-B scales. This fact coincides with that observed by Kihlstrom et al. who found an improvement in the inter-rater reliability after an educational intervention for the use of the RASS in their PICU (22).

We obtained a high correlation between COMFORT-B and RASS scales, which was similar in children younger and older than 12 months. In the study by Kerson et al. a good correlation was also obtained between the RASS and the UMSS, which exclusively includes sedation levels (21). Our study is the first to validate the agitation area of the RASS with a recommended and validated tool such as the COMFORT-B scale. A high correlation with the expert's subjective opinion was observed in both studies, using a VAS in the former and a NRS in ours (21).

This study has demonstrated the RASS capacity to classify PICU patients into 3 different categories of sedation-agitation (deep sedation: RASS−5 to−4, moderate to light sedation: RASS−3 to +1, and agitation: RASS + 2 to + 4), based on the 3 levels established by the COMFORT-B scale: over-sedation (score 6–10), optimum sedation (included in the range 11–22) and under-sedation (23–30). Good agreement was observed between the 2 scales when categorizing the patients into these 3 levels. Interestingly, 9.7% of the patients who were considered as adequately sedated according to the COMFORT-B scale (scores 11–22) were assessed as agitated by the RASS. Most of these patients (88.4%) had COMFORT-B scores ≥17. This data is consistent with the pain management algorithm published by van Dijk et al. and the results obtained by Valkenburg et al., in a study conducted to validate the COMFORT-B scale to assess pain and distress (25, 28). These authors found that the cut-off point for agitation due to pain on the COMFORT-B scale was 17 and not 22 (28). Moreover, Ista et al., in a validation study of the levels of sedation of the COMFORT-B, observed that patients classified within the range of 11–22 had a 15% probability of being under-sedated, and that the correlation with the expert opinion (using the NISS) was low in this range (5). These authors conclude that the score range from 11 to 22 on the COMFORT-B scale is a "gray area," in which "optimal sedation" would be included, but for which final interpretation is necessary to associate a second scale, to include the subjective opinion of the professional in charge of the patient (5).

The RASS has the advantage of integrating this second subscale, which we have called RASSe in this study, and that would correspond to the expert's subjective opinion. Comparing RASSe (subjective scale) with RASSc (objective description of the behavior of the patient for each level), an excellent agreement and correlation was observed.

The percentage of agitation episodes in this study (11% in RASSc and 13% in RASSe) was similar to other studies in critically ill children, which resulted in around 10% of the total

(5, 13). Our results of RASS inter-rater reliability were worse in this agitation area. This may be due to an insufficient number of patients in this range, to the difficulty in assessing agitation for professionals, or to a limitation of the scale to assess agitation in children. In the present study the RASS has demonstrated its ability to distinguish whether the child is agitated or not, but this scale may not be accurate enough in designating the exact level of agitation in the pediatric population.

Finally, our study has been the first to analyze the responsiveness of the RASS in critically ill children, showing that the scale scores varied significantly after a required intervention of increase or decrease of sedatives, which makes it useful for controlling sedation modifications in PICU.

Limitations

Our study has several limitations. The recruitment of patients was carried out according to the availability of the PI and not randomly. The sample size was not sufficient to perform an analysis by pediatric age groups. The number of patients under 9 weeks was insufficient for drawing conclusions in this age range, which is particularly important as sustained eye contact maturation is achieved at 6–9 weeks of age (29, 30). The fact that the same observer applied the 3 scales simultaneously could have facilitated the correlation between them.

Future Research

Since the duration of eye contact, greater or <10 s, is the criterion that discriminates between RASS levels−1 and−2, it would be convenient to study infants under 9 weeks of age in more detail, assessing the need to modify the scale to adapt it to their normal psychomotor development, as Kihlstrom et al. did for neonates (22).

Regarding our results in the subgroup of distressed patients, that could be interpreted as an only moderate ability of the RASS to assess the exact degree of agitation in children future research may be needed at this range of the scale. We believe a RASS modification in the agitation area, including more typical pediatric agitation behaviors, could improve distress evaluation in critically ill children.

CONCLUSIONS

In this multi-center study, we found a high inter-rater reliability, excellent construct validity and adequate responsiveness to change in sedative doses, of the RASS in PICU patients. The RASS also proved its ability to categorize the patients' level of sedation into deep sedation, moderate to light sedation, and agitation, enabling its use in a target-level of sedation-based protocol. This good measurement properties makes the RASS a useful instrument for monitoring sedation in PICU.

As inter-rater reliability was only moderate in the subgroup of agitated children, it may be necessary to extend future validation studies in this range.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética de la Investigación del Hospital Universitario Ramón y Cajal (code RASS-UCIP-01). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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AUTHOR CONTRIBUTIONS

RT: this author helped with conception, design, acquisition, analysis, and interpretation of data for the work, drafting the work, giving the final approval of the version to be published, and agrees to be accountable for all aspects of the work. JL-H: this author helped with the interpretation of data for the work, drafting and revising the work critically for important intellectual content, giving the final approval of the version to be published, and agrees to be accountable for all aspects of the work. ÁA: this author helped with the statistical analysis and interpretation of data for the work, drafting the work, giving the final approval of the version to be published, and agrees to be accountable for all aspects of the work. JC: this author helped with interpretation of data, English language editing, giving the final approval of the version to be published, and agrees to be accountable for all aspects of the work SM: this author helped with acquisition and interpretation of data for the work, drafting and revising the work critically for important intellectual content, giving the final approval of the version to be published, and agrees to be accountable for all aspects of the work. All authors contributed to the article 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.2021.795487/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

NOMENCLATURE

CI, Confidence interval; COMFORT-B scale, COMFORT behavior scale; COSMIN: Consensus-based Standards for the selection of health Measurement Instruments; ICC, Intraclass correlation coefficient; IQR, Interquartile range; κ, Kappa; κ_w, Weighted kappa; NISS, Nurse Interpretation of Sedation Score; NRS, Numeric rating scale; pCAM-ICU, Pediatric Confusion Assessment Method for the ICU; psCAM-ICU, Preschool Confusion Assessment Method for the ICU; PICU, Pediatric intensive care unit; RASS, Richmond Agitation-Sedation Scale; RASSe, RASS by epigraph; RASSc, RASS by description of the patient conduct/behavior; rho, Spearman correlation coefficient; SECIP, Spanish Society of Pediatric Intensive Care; UMSS, University of Michigan Sedation Scale; VAS, visual analogue sedation-agitation scale.

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Implementation of a Delirium Bundle for Pediatric Intensive Care Patients

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Background and Objective: Delirium represents the most common form of acute cerebral dysfunction in critical illness. The prevention, recognition, and treatment of delirium must become the focus of modern pediatric intensive care, as delirium can lead to increased morbidity and mortality. The aim of this study is to evaluate the impact of a delirium bundle consisting of mainly non-pharmacological measures.

Material and Methods: This is a pre-/post-implementation study in an interdisciplinary pediatric intensive care unit of a tertiary care university hospital. In the pre-implementation period, pediatric intensive care delirium was monitored using the Sophia Observation withdrawal Symptoms and Pediatric Delirium scale. After introduction of a delirium bundle consisting of non-pharmacological prevention and treatment measures a period of 4 months was interposed to train the PICU staff and ensure that the delirium bundle was implemented consistently before evaluating the effects in the post-implementation period. Data collection included prevalence of delirium and withdrawal, length of PICU stay, duration of mechanical ventilation, and cumulative dose of sedatives and analgesics.

Results: A total of 792 critically ill children aged 0–18 years were included in this study. An overall delirium prevalence of 30% was recorded in the pre-implementation group and 26% in the post-implementation group ($p = 0.13$). A significant reduction in the prevalence of pediatric delirium from was achieved in the subgroup of patients under 5 years of age (27.9 vs. 35.8%, $p = 0.04$) and in patients after surgery for congenital heart disease (28.2 vs. 39.5%, $p = 0.04$). Young age, length of PICU stay, and iatrogenic withdrawal syndrome were found to be risk factors for developing delirium.

Conclusions: Based on a validated delirium monitoring, our study gives new information regarding the prevalence of pediatric delirium and the characteristics of intensive care patients at risk for this significant complication. Especially young patients and patients after surgery for congenital heart disease seem to benefit from the implementation of non-pharmacological delirium bundles. Based on our findings, it is important to promote change in pediatric intensive care—toward a comprehensive approach to prevent delirium in critically ill children as best as possible.

Keywords: PICU, sedation, analgesia, withdrawal, critical care, delirium, post-intensive care syndrome, PICU delirium bundle

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INTRODUCTION

Delirium in pediatric intensive care unit patients (PICU delirium) is a complication of critical illness affecting attention, cognition, and awareness and is associated with a poor outcome. PICU delirium can develop within a short period of time. The hypoactive delirium is distinguished from the hyperactive and the mixed form, and symptoms can fluctuate throughout the day (1). Delirium is a result of pre-existing risk factors, underlying disease and medical conditions, iatrogenic drug exposure, and environmental factors during the intensive care stay (2). Independent risk factors are young age, developmental delay, benzodiazepine exposure, and mechanical ventilation (3). The prevalence of PICU delirium is reported to range from 17 to 66% (2, 4). In children, hypoactive delirium and the mixed form are most common, and last for several days (5–8). There are significant associations between PICU delirium, increased duration of mechanical ventilation, length of stay, used resources, and medical costs (2, 5, 8, 9). Delirium is also independently associated with mortality in children (2). Data to long-term outcomes associated with pediatric delirium are rare. Two authors found an association between delirium during the PICU stay with decline in health-related quality of life (10, 11). Evidence on measures to prevent and manage delirium is urgently needed. There are few reports of low quality on pharmacological management of pediatric delirium with typical and atypical antipsychotic drugs which led to improvement in delirium symptoms, but side effects such as extrapyramidal symptoms, heavy sedation, and prolonged corrected QT (QTc) interval were common (12–14). It remains unclear if antipsychotic use reduces overall delirium prevalence or effectively treats hypoactive or mixed delirium (15). The risks associated with antipsychotic management may not outweigh the risks in all patients, however, in hyperactive delirium the benefits may outweigh the risks. As alternative to pharmacological management, the bundle approach, multicomponent delirium interventions, seems to be promising. Based on evidence of delirium bundle in the adult population, bundle intervention may decrease the incidence of delirium as well in the pediatric population (16, 17). Nevertheless, a recent published meta-analysis failed to support that bundle interventions are effective in reducing ICU delirium prevalence and duration, although, it supported that bundle interventions are effective in reducing the proportion of patient-days with coma, hospital length of stay, and 28-day mortality (18).

When creating developmentally appropriate bundle for the pediatric population, caregivers should focus on modifiable risk factors. Modifiable risk factors are clinical variables such as mechanical ventilation, choice of sedating medications, especially reduction of benzodiazepine exposure, reduction of anticholinergic drugs, administration of red blood cells, physical restraints, and good nutrition (2, 5, 6, 8, 9, 11, 17). A structured approach to introduce delirium bundle at the PICU may prevent delirium. We have sustainably implemented a functioning nurse-driven analgesia and sedation protocol on our PICU, that was feasible and safe and reduces length of PICU stay, cumulative dose of benzodiazepines and withdrawal symptoms (19–23).

The aim of this study was to evaluate the impact of a delirium bundle consisting of mainly non-pharmacological measures in a pediatric intensive care unit of a tertiary center.

MATERIALS AND METHODS

Study Design

This is a non-randomized, monocentric, pre-/post-implementation study. In the pre-implementation period (January 2016–February 2017), PICU delirium was monitored using the Sophia Observation withdrawal Symptoms and Pediatric Delirium (SOS-PD) scale (24, 25). In March 2017 a delirium bundle consisting of non-pharmacological prevention and treatment measures was introduced. A period of 4 months was interposed to train the PICU staff and ensure that the delirium bundle was implemented consistently by verifying that delirium scoring as well as bedside documentation of non-pharmacologic measures were regularly used and filled out before evaluating the effects in the post-implementation period from July 2017 to May 2018 (**Figures 1**, **2**). Clinical data of our patients including age, gender, weight, diagnosis, length of PICU stay, duration of mechanical ventilation, levels of sedation and analgesia, incidence and duration of delirium and withdrawal, cumulative dose of sedatives and analgesics, and safety-relevant events due to the application of the bundle were collected from the patient data management system (IntelliSpace Critical Care and Anesthesia, Koninklijke Philips N.V., the Netherlands). All parameters were routinely assessed and automatically calculated by the patient data management system in intervals of 8 h. At the end of the study, the data were extracted from the patient data management system. The study protocol was approved by the local ethics committee (650/2015BO1).

Study Location and Population

The study was conducted at a 14-bed interdisciplinary PICU at a University Children's Hospital. The ratio of registered nursing staff to patients was between 1:1 and 1:2, the ratio of registered medical doctors to patients was between 1:5 and 1:7. The hospital is a tertiary referral center including active departments of pediatric cardiovascular surgery, pediatric surgery, pediatric neurosurgery, transplantation, trauma, as well as hematology and oncology services. All patients between 0 and 18 years of age admitted to the PICU with a length of stay of at least 24 h were enrolled in this study. Exclusion criteria were diagnosed encephalitis, or death. In addition, periods of very deep sedation defined by a COMFORT Behavior Scale (COMFORT B) (26) < 11, coma, or continuous neuromuscular blockade were not considered.

Nurse Driven Analgesia, Sedation and Withdrawal Protocol, and Drugs and Routes

During the entire study period, sedation and analgesia medication was titrated to attain a COMFORT-B level of 12–18 and a nurse interpretation sedation scale (NISS) level of 2 (adequate sedation) following the updated version of our institutional standardized, goal-directed nurse-driven

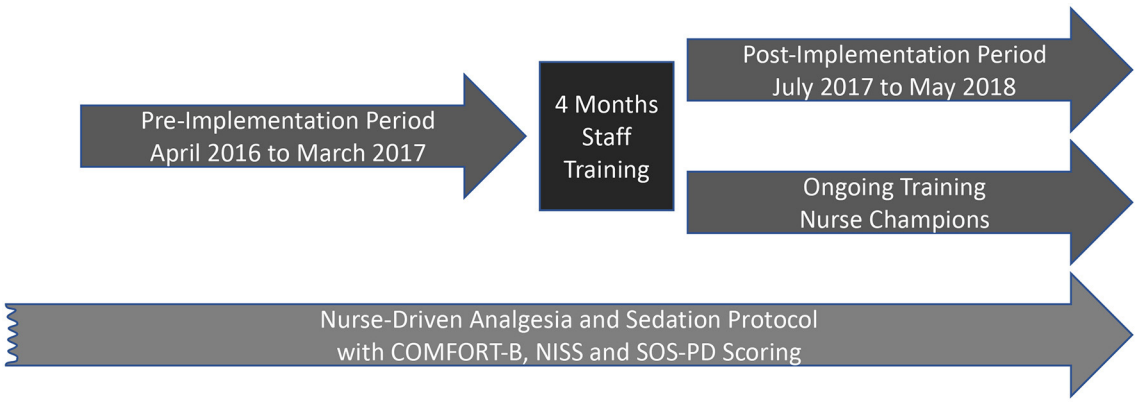

FIGURE 1 | Conceptual design of the study.

analgesia, and sedation protocol, which has been described in detail previously (20). The standard therapy during the study period consisted of continuous i.v. infusion of opioids (morphine [5–100 $\mu g \cdot kg^{-1} \cdot h^{-1}$; starting dose 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$] $\leq$ 2 years of age and fentanyl [0.1–6.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$; starting dose 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$] $>$ 2 years) and continuous i.v. infusion of clonidine (0.5–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The updated version of the analgesia and sedation protocol did not involve the routinely administration of midazolam. Oral/rectal chloral hydrate (up to 6 $\times$ 25 $mg \cdot kg^{-1} \cdot day^{-1}$) and oral melatonin (3–7 $mg \cdot day^{-1}$) were administered additionally according to our PICU guideline. However, to protect patients' safety in case of undersedation the attending intensivist could deviate from the updated sedation protocol at any time. During weaning from analgesia and sedation medication, children were monitored regarding withdrawal symptoms and delirium using the SOS-PD scale (24, 25, 27). The medication tapering plan provided reduction of opioids and benzodiazepines by 50% of the dose every 24 h in case of therapy lasting 5 days or less, and by 10–20% every 24 h in case of therapy longer than 5 days. A SOS score of $\geq$4 indicates withdrawal, and the medication tapering plan was paused for 24 h.

Delirium Scoring and Management Pre-implementation Period

We had decided in advance to use the SOS-PD scale in this study and in daily clinical practice because this scale, in contrast to Cornell Assessment of Pediatric Delirium (CAP-D), measures both delirium and withdrawal and discriminates between them. Delirium screening was performed and documented in the patient data management system (PDMS) at least every 8 h. The SOS-PD scale, the SOS scale, extended with a pediatric delirium (PD) component, has promising validity, and reliability (24, 25). The intraclass correlation coefficient (ICC) of paired nurse-researcher observations was 0.90 (95% CI: 0.70–0.96) (28). The sensitivity was 96.8% (95% CI: 80.4–99.5%) and the specificity was 92.0% (95% CI: 59.7–98.9%) (25). Pearson coefficient between the SOS-PD scale and the CAP-D was 0.89 (CI 95%, 0.82–0.93; $p < 0.001$). A very good agreement (Kappa = 1; $p < 0.001$) between the two scales was identified (29). Compared to the psychiatrist diagnosis, the overall sensitivity was 92.3% with a specificity of 96.5% (25). No prophylaxis measures were routinely performed, delirium management was carried out according to the decision of the responsible physician.

Delirium Scoring and Management Post-implementation Period

An interprofessional team consisting of nurses, intensivists, psychiatrists, and pharmacists developed the PICU delirium bundle and a training plan to improve PICU staff education. The team first conducted a review of literature regarding evidence-based assessment and management of PICU delirium to develop the non-pharmacologic delirium bundle. Little literature was available on detection, prevention, and management of delirium in children in the intensive care unit at the time the bundle was designed. Most studies recommended family support and family presence in the ICU, operational, and environmental modifications and improving communication with families. We have selected the following as the most important measures for our setting: Providing a calm and reassuring environment (30–34), providing pictures of the family of home and personal cuddly toys, having favorite toys, music and personal items ready, like a mother's t-shirt (33, 35–37), avoiding physical restraints (37, 38), children who need glasses or hearing aids should wear them when possible (34, 39), creating an schedule of daytime activities and nighttime sleep, placing bed in a upright position when child tolerates, discourage sleep during the daytime except for scheduled naps or quiet rest times (40), having a calendar and clock for date and time identification (37), using a dim light at night (41), using eye masks to block light during sleep and earplugs to block noise (40, 42), allowing the view outside to determine the time of day (36), and guidance for parents to reorient their child to person, place, time, and reason for being in the hospital (43–45). In addition to the existing pain, sedation, withdrawal and delirium assessment instruments, the designed bundle comprises non-pharmacologic prevention strategies, identification of potential etiologies, and treatment measures. To identify and reverse the underlying etiology of pediatric delirium

A

Possible causes of delirium.

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Treatment of delirium should always include identification and reversal of the underlying etiology. Screening and measures during the morning noon and evening rounds

Possible causes of delirium	
Worsening or new disease	Sepsis, infection
Drugs	Remove drugs, stop sedatives/narcotics, evaluate the use of opioids and medication with anticholinergic activity
Environment	Immobilization, sleep, day/night rhythm, hearing aids, glasses, transfer to a quieter room
Labs	Including electrolytes, BUN, NH3+, hyperbilirubinemia
Respiratory status	ABGs, paO2, paCO2
Hemodynamic status	Hypotension, hypertension, anemia, stroke, arrhythmia, shock
New organ failure	Renal failure, liver failure, heart failure
Withdrawal	Discontinuation of tapering plan for 24 hours, symptomatic therapy
New CNS pathology	CNS ultrasound, check intracranial perfusion
Deficiencies	Vitamin B12, folate, niacin, thiamine
Endocrinopathies	Hyper-/hypoadrenocorticism, hyper-/hypoglycemia, hyperparathyroidism
Iatrogenic exposure	Consider any diagnostic procedure or therapeutic intervention
Developmental delay	Check for preexisting impairments
Use of restraints and catheters	Reevaluate restraints, central lines and catheters daily
Urinary/fecal retention	Consider urinary retention or fecal impaction

B

Bedside documentation sheet for the use of the nonpharmacologic PICU Delirium Bundle

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Screening and measures at least 1x/shift

Documentation of nonpharmacologic Delirium Bundle measures															
Shift	**ES**	**LS**	**NS**	**ES**	**LS**	**NS**	**ES**	**LS**	**NS**	**ES**	**LS**	**NS**	**ES**	**LS**	**NS**
Scoring-Result SOS-PD-Scale															
Shielding Phase (deeply sedated for medical reasons)															
Minimal handling and shielding Eye and ear protection, low-noise backdrop, no glaring light															
Active Bundle Phase (awake, tube-tolerant, actively participating in the treatment)															
Day-night rhythm Natural light during the day, no bright light in the evening, darken Do not talk loudly or make noise in the evening and at night															
Early mobilization Upper body elevation, place bed in an upright position, kangarooing, physiotherapy twice a day, mobilization in and out of bed															
Cognitive stimulation Presence of the family, guidance for the activation of the child by the parents (drinking, eating, playing, personal hygiene)															
Reference person creating of a familiar environment, encourage regular visits from parents or relatives, Introduce home habits on ward, e.g. favorite music on headphones, photos and cuddly toys from home															
Re-orientation to time, place and person Provide a clock, hearing aids and glasses if necessary; place bed in an upright to allow a look on the clock and the outside world															
Parents information brochure handed out															

FIGURE 2 | (A) Possible causes of pediatric delirium. **(B)** Bedside checklist and documentation sheet for the non-pharmacologic measures of the PICU Delirium Bundle (ES, Early Shift; LS, Late Shift; NS, Night Shift).

we developed a checklist, based on the mnemonic "I WATCH DEATH," to screen for possible causes during the morning, noon, and evening rounds (**Figure 2A**) (46). Pharmacologic treatment is not part of the bundle. A period of 4 months was interposed to train the PICU staff and ensure that the delirium bundle was implemented consistently. Nursing and physician staff participated in several 1-h educational sessions about delirium causes, consequences, prevention, identification, and management. PICU staff received training on how to conduct and document delirium scoring. During the sessions, sample videos of patients with delirium symptoms and patients with withdrawal symptoms were demonstrated, which were used to practice scoring and explain the differentiation between withdrawal symptoms and delirium. Furthermore, the documentation forms

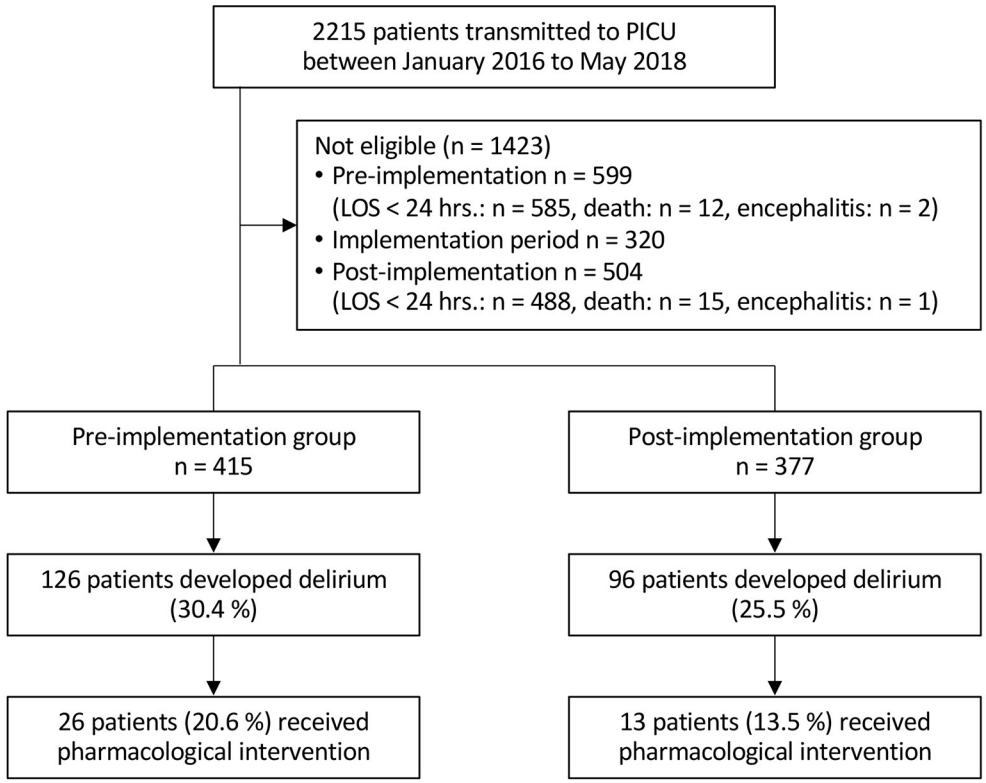

FIGURE 3 | CONSORT flow diagram (LOS, Length of stay).

of the non-pharmacological measures, the differences between the shielding phase and the active bundle phase, and the measures in these two phases were explained. The SOS-PD scale had been introduced and trained before the study. SOS-PD scale and PICU delirium bundle were available on the PDMS, and on bedside charts. Nurse champion were available to answer questions, provide assistance and solve problems. Resident physicians participated in 1-h educational sessions at the beginning of their PICU rotation. The bundle is divided into two phases. The "shielding phase" is used for children who need to be deeply sedated for medical reasons and involves the complete shielding of noise and light through eye and ear protection. The second phase is applied to all other children who may be awake and tube-tolerant. This phase includes the creation of a day-night rhythm, mobilization in bed and, if possible, out of bed, cognitive stimulation by parents after guidance, choosing of reference persons in the team, and involvement of the parents in the care of their children. Required hearing aids and glasses were provided at an early stage. Parents were encouraged to bring along music, photos, and cuddly toys from home. To improve the children's ability to reorient themselves, care was taken to ensure that the head of the bed was placed in an upright position and that they had a view of a clock and the outside world. At the beginning of the intensive stay, the parents were given a brochure explaining withdrawal and delirium and providing advice on how to deal with their children (**Supplementary Material**). A printed version of the brochure was available at each patient's bedside. The bedside documentation sheet of the non-pharmacological PICU delirium bundle measures is shown in **Figure 2**. If delirium with severe agitation or hyperactive symptoms persisted despite interventions to address potential causes, pharmacologic antipsychotic treatments was started in individual cases with low-dose levomepromazine, an aliphatic phenothiazine neuroleptic drug (0.1 $mg{\cdot}kg^{-1}$) (47).

Statistical Analysis

Statistical analysis and the creation of charts were performed using SigmaPlot (Version 13 for Windows, Systat Software, Inc., San Jose, CA, US) and SPSS (Version 24, IBM, Armonk, NY, US). Normality was assessed using the Shapiro-Wilk test. Data are presented as median [interquartile range (IQR)]. For statistical analysis Student's *t*-test and the Mann–Whitney Rank Sum test was applied, depending on whether the data were normally distributed. Categorical variables were compared using Two-tailed Fisher's exact test. A probability of $p < 0.05$ was defined as statistically significant. To compare the amount of opioids given in patients $\leq$2 years of age and patients >2 years of age, we converted opioids to morphine equivalents; the equipotency ratio of i.v. fentanyl to i.v. morphine was calculated as 1:80.

TABLE 1 | Differences of patients' characteristics between the pre-implementation group and post-implementation group.

Parameter		Pre	Post	*p*-value
Sex (m/f)	*n* (%)	224/191 (54.0/46.0%)	205/172 (54.4/45.6%)	0.94
Age (mo)	Median [IQR]	11.6 [2.6–55.8]	15.1 [2.8–64.7]	0.15
Weight (kg)	Median [IQR]	8.4 [4.0–17.0]	9.0 [4.0–17.0]	0.51
Ventilator days	Median [IQR]	2.8 [0.7–11.6]	2.3 [0.6–9.6]	0.33
Length of PICU stay (d)	Median [IQR]	4.0 [1.9–12.8]	3.9 [1.9–11.0]	0.25
Cumulative opioids (μg/kg)	Median [IQR]	968 [269–3,939]	580 [78–3,685]	0.09
Patients w/o opioids	*n* (%)	59 (14.2%)	83 (22.0%)	0.01
Cumulative midazolam (mg/kg)	Median [IQR]	2.2 [0.0–14.2]	0.0 [0.0–3.5]	0.55
Patients w/o midazolam	*n* (%)	157 (37.8%)	229 (60.7%)	<0.01
Cumulative clonidine (μg/kg)	Median [IQR]	0.0 [0.0–152.9]	0.0 [0.0–126.6]	<0.01
Patients w/o clonidine	*n* (%)	213 (51.3%)	191 (50.7%)	0.89

IQR, interquartile range; PICU, pediatric intensive care unit.

TABLE 2 | Prevalence of delirium and withdrawal symptoms in all patients, in patients grouped by age, and in patients grouped by disease.

Parameter	Pre	Post	*p*-value
All patients			
Patients with withdrawal symptoms	63/415 patients (15.2%)	40/377 patients (10.6%)	0.06
Patients with delirium	126/415 patients (30.4%)	96/377 patients (25.5%)	0.13
Duration of delirium (d)	0.44 [0.0–6.6]	0.46 [0.0–3.1]	0.29
Patients with delirium needing pharmacological intervention	26 patients (20.6%)	13 patients (13.5%)	0.07
Age < 60 months			
Patients with withdrawal symptoms	60/318 patients (18.9%)	32/276 patients (11.6%)	0.02
Patients with delirium	114/318 patients (35.8%)	77/276 patients (27.9%)	0.04
Duration of delirium (d)	0.8 [0.0–7.1]	0.4 [0.0–3.0]	0.21
Age > 60 months			
Patients with withdrawal symptoms	3/97 patients (3.1%)	8/101 patients (7.9%)	0.21
Patients with delirium	15/97 patients (15.5%)	18/101 patients (17.8%)	0.71
Duration of delirium (d)	0.1 [0.0–1.9]	1.1 [0.0–3.7]	0.66
Patients with CHD			
Patients withdrawal symptoms	34/185 patients (18.4%)	18/131 patients (13.7%)	0.29
Patients with delirium	73/185 patients (39.5%)	37/131 patients (28.2%)	0.04
Duration of delirium (d)	0.3 [0.0–7.2]	0.7 [0.0–4.3]	0.91
Patients after surgery (other than CHD)			
Patients withdrawal symptoms	22/130 patients (16.9%)	15/168 patients (8.9%)	0.05
Patients with delirium	35/130 patients (26.9%)	41/168 patients (24.4%)	0.69
Duration of delirium (d)	2.3 [0.0–10.0]	0.0 [0.0–1.8]	0.01
Patients with other diseases (e.g., hematological, oncological, neuropediatric, and nephrological)			
Patients withdrawal symptoms	7/100 patients (7.0%)	7/78 patients (9.0%)	0.78
Patients with delirium	18/100 patients (18.0%)	18/78 patients (23.1%)	0.45
Duration of delirium (d)	0.12 [0.0–2.6]	1.7 [0.0–5.2]	0.30

CHD, congenital heart disease.

RESULTS

A total of 792 critically ill children aged 0–18 years were included in this study (415 in the pre-implantation group, 377 in the post-implantation group) (**Figure 3**). **Table 1** summarizes the patients' characteristics. There were no significant differences between the two groups in gender (m/f 224/191 vs. 205/172, $p = 0.94$), age (11.6 [2.6–55.8] vs. 15.1 [2.8–64.7] months, $p = 0.15$), weight (8.4 [4.0–17.0] vs. 9.0 [4.0–17.0] kg, $p = 0.51$), duration of ventilation (2.8 [0.7–11.6] vs. 2.3 [0.6–9.6] days, $p = 0.33$), and length of PICU stay (4.0 [1.9–12.8] vs. 3.9 [1.9–11.0] days, $p = 0.25$). In the post-implementation group, significantly fewer patients received midazolam (72.2 vs. 39.3%, $p < 0.01$) and opioids (85.8 vs. 78%, $p = 0.01$). An overall delirium prevalence of 30.4% with a median duration of 0.44 [0.0–6.6] days was recorded in the pre-implementation group and 25.5% with a median duration of 0.46 [0.0–3.1] days in the post-implementation group (prevalence $p = 0.13$; duration $p = 0.29$) (**Table 2**).

In the subgroup analysis of patients younger than 5 years, a significant reduction in the prevalence of delirium was recorded after the introduction of delirium bundles (35.8 vs. 27.9%, $p = 0.04$) (**Table 2**). The median duration of delirium also showed a decreasing trend, but was not statistically significant (0.8 [0.0–7.1] vs. 0.4 [0.0–3.0], $p = 0.21$). In this subgroup, there were no significant differences between the pre-implementation and post-implementation group in (m/f 175/143 vs. 146/130, $p = 0.62$), age (5.8 [0.8–23.7] vs. 5.9 [0.8–20.5] months, $p = 0.61$), weight (5.7 [3.5–11.0] vs. 6.0 [3.5–11.1] kg, $p = 0.94$), duration of ventilation (4.3 [0.9–13.9] vs. 3.1 [0.7–11.6] days, $p = 0.16$), and length of PICU stay (5.4 [2.5–15.1] vs. 4.0 [1.9–11.8] days, $p = 0.10$) (**Table 3**).

TABLE 3 | Differences of patients' characteristics between the pre-implementation group and post-implementation group in patients aged 60 months and younger.

Parameter		Pre	Post	*p*-value
Sex (m/f)	*n* (%)	175/143 (55.0/45.0%)	146/130 (52.9/47.1%)	0.62
Age (mo)	Median [IQR]	5.8 [0.8–23.7]	5.9 [0.8–20.5]	0.61
Weight (kg)	Median [IQR]	5.7 [3.5–11.0]	6.0 [3.5–11.1]	0.94
Ventilator days	Median [IQR]	4.3 [0.9–13.9]	3.1 [0.7–11.6]	0.16
Length of PICU stay (d)	Median [IQR]	5.4 [2.5–15.1]	4.0 [1.9–11.8]	0.10
Cumulative opioids (μg/kg)	Median [IQR]	1,372 [474–5,643]	710 [139–4,096]	0.04
Patients w/o opioids	*n* (%)	40 (12.6%)	53 (19.2%)	0.03
Cumulative midazolam (mg/kg)	Median [IQR]	3.1 [0.0–19.1]	0.0 [0.0–5.1]	0.52
Patients w/o midazolam	*n* (%)	100 (31.4%)	158 (57.2%)	<0.01
Cumulative clonidine (μg/kg)	Median [IQR]	19.3 [0.0–249.6]	13.9 [0.0–137.9]	<0.01
Patients w/o clonidine	*n* (%)	141 (44.3%)	129 (46.7%)	0.56
Performed scorings per day	Median [IQR]	3.0 [2.0–3.9]	2.3 [1.8–2.8]	<0.001

IQR, interquartile range; PICU, pediatric intensive care unit.

TABLE 4 | Differences of patients' characteristics between the pre-implementation group and post-implementation group in patients with congenital heart disease.

Parameter		Pre	Post	*p*-value
Sex (m/f)	*n* (%)	104/81 (56.2/43.8%)	73/59 (55.3/44.7%)	0.91
Age (mo)	Median [IQR]	4.7 [0.6–25.0]	5.7 [0.8–30.8]	0.22
Weight (kg)	Median [IQR]	5.4 [3.5–10.9]	6.0 [3.5–10.2]	0.74
Ventilator days	Median [IQR]	2.8 [0.8–13.9]	2.2 [0.7–12.0]	0.81
Length of PICU stay (d)	Median [IQR]	5.0 [2.4–15.9]	4.8 [1.9–13.0]	0.64
Cumulative opioids (μg/kg)	Median [IQR]	1,347 [481–4,971]	899 [212–4,652]	0.59
Patients w/o opioids	*n* (%)	9 (4.9%)	21 (16.0%)	<0.01
Cumulative midazolam (mg/kg)	Median [IQR]	2.9 [0.0–16.8]	0.0 [0.0–6.3]	0.36
Patients w/o midazolam	*n* (%)	60 (32.4%)	72 (55.0%)	<0.01
Cumulative clonidine (μg/kg)	Median [IQR]	26.0 [0.0–187.5]	24.0 [0.0–132.7]	0.12
Patients w/o clonidine	*n* (%)	78 (42.2%)	53 (40.5%)	0.82

IQR, interquartile range; PICU, pediatric intensive care unit.

The prevalence of delirium was also significantly reduced in the subgroup of patients after surgery for congenital heart disease from 39.5 to 28.2% ($p = 0.04$) (**Table 2**). Again, there were no significant differences between both groups in (m/f 104/81 vs. 73/59, $p = 0.91$), age (4.7 [0.6–25.0] vs. 5.7 [0.8–30.8] months, $p = 0.22$), weight (5.4 [3.5–10.9] vs. 6.0 [3.5–10.2] kg, $p = 0.74$), duration of ventilation (2.8 [0.8–13.9] vs. 2.2 [0.7–12.0] days, $p = 0.81$), and length of PICU stay (5.0 [2.4–15.9] vs. 4.8 [1.9–13.0] days, $p = 0.64$) (**Table 4**).

Using logistic regression analysis, young age (OR = 0.995; 95% CI: 0.992–0.999; $p = 0.02$), length of PICU stay (OR = 1.035; 95% CI: 1.010–1.061; $p < 0.01$), and iatrogenic withdrawal syndrome (OR = 54.052; 95% CI: 19.096–152.999; $p < 0.01$) were found to be risk factors for developing delirium (**Table 5**). Patients with delirium were significantly younger (7.3 [1.9–33.4] vs. 22.0 [3.0–78.5] months, $p < 0.01$), had lower weight (6.5 [3.8–13.0] vs. 10.7 [4.1–19.0] kg, $p < 0.01$), had longer duration of ventilation (10.2 [3.4–22.9] vs. 1.2 [0.3–5.0] days, $p < 0.01$) and longer length of PICU stay (12.9 [6.0–26.3] vs. 2.9 [1.7–5.9] days, $p < 0.01$). They received more opioids (cumulative dose 4,851 [1,600–12,073] vs. 491 [56–1,409] $\mu g \cdot kg^{-1}$, $p < 0.01$) midazolam (cumulative dose 13.3 [1.9–56.6] vs. 0.0 [0.0–2.5] $mg \cdot kg^{-1}$, $p < 0.01$), and clonidine (cumulative dose 211.9 [55.6–728.2] vs. 0.0 [0.0–28.1] $\mu g \cdot kg^{-1}$, $p < 0.01$) (**Table 6**). In the pre-implementation group, 26 patients (20.6%) who developed delirium and showed severe agitation or hyperactive delirium symptoms despite non-pharmacological measures received pharmacologic therapy, compared with 13 patients (13.5%) in the post-implementation group ($p = 0.07$). Patients who received pharmacologic delirium therapy had longer duration of ventilation (21.1 [10.4–50.7] vs. 7.0 [1.9–17.3] days, $p < 0.001$), longer length of PICU stay (25.9 [14.3–66.1] vs. 11.0 [4.7–22.7] days, $p < 0.001$), longer duration of delirium (9.6 [3.7–44.5] vs. 0.1 [0.0–2.0] days, $p < 0.001$), and a higher prevalence of iatrogenic withdrawal syndrome (33/39 [84.6%] vs. 66/183 [36.1%], $p < 0.0001$). No difference was observed in age (12.3 [3.8–37.0] vs. 6.2 [1.5–32.2] months, $p = 0.14$) and weight (7.2 [5.0–12.0] vs. 6.1 [3.7–13.0] kg, $p = 0.29$). Scoring was performed a median of 3.0 [2.0–3.9] times per patient day during the pre-implementation phase and 2.3 [1.8–2.8] in the post-implementation period ($p < 0.001$, **Figure 4**). During the post-implementation period, the adherence to the bundle was randomly checked and showed an average compliance rate of 72% for the bundle. No adverse events associated with the PICU delirium bundles were reported.

DISCUSSION

Delirium in critically ill children is a serious problem that affects short- and long-term morbidity and mortality, among other outcomes (2, 5, 6, 9, 11). Many studies are now available on

TABLE 5 | Odds ratios for effects of sex, age, length of PICU stay, duration of mechanical ventilation, and withdrawal symptoms on development of delirium.

Variable	Regression coefficient	Standard error	Odds ratio	95%-CI	*p*-value
Sex (male/female)	0.110	0.211	1.117	0.738–1.690	0.60
Age (mo)	−0.005	0.002	0.995	0.992–0.999	0.02
Length of PICU stay (d)	0.035	0.013	1.035	1.010–1.061	<0.01
Mechanical ventilation (d)	0.009	0.013	1.009	0.984–1.036	0.48
Withdrawal symptoms	3.990	0.531	54.052	19.096–152.999	<0.01

CI, Confidence interval; PICU, pediatric intensive care unit.

TABLE 6 | Differences of patients' characteristics between patients with delirium and patients without delirium.

Parameter		Pre	Post	*p*-value
Sex (m/f)	*n* (%)	123/99 (55.4/44.6%)	306/264 (54.6/45.4%)	0.69
Age (mo)	Median [IQR]	7.3 [1.9–33.4]	22.0 [3.0–78.5]	<0.01
Weight (kg)	Median [IQR]	6.5 [3.8–13.0]	10.7 [4.1–19.0]	<0.01
Ventilator days	Median [IQR]	10.2 [3.4–22.9]	1.2 [0.3–5.0]	<0.01
Length of PICU stay (d)	Median [IQR]	12.9 [6.0–26.3]	2.9 [1.7–5.9]	<0.01
Cumulative opioids (μg/kg)	Median [IQR]	4,851 [1,600–12,073]	491 [56–1,409]	<0.01
Patients w/o opioids	*n* (%)	9 (7.4%)	133 (23.3%)	<0.01
Cumulative midazolam (mg/kg)	Median [IQR]	13.3 [1.9–56.6]	0.0 [0.0–2.5]	<0.01
Patients w/o midazolam	*n* (%)	46 (20.7%)	340 (59.6%)	<0.01
Cumulative clonidine (μg/kg)	Median [IQR]	211.9 [55.6–728.2]	0.0 [0.0–28.1]	<0.01
Patients w/o clonidine	*n* (%)	31 (14.0%)	373 (65.4%)	<0.01

IQR, interquartile range; PICU, pediatric intensive care unit.

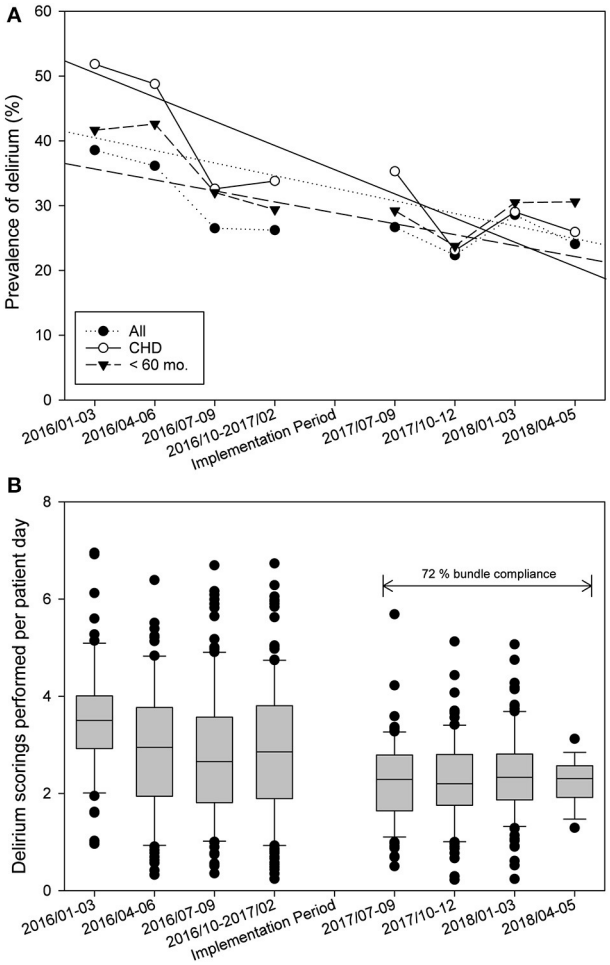

FIGURE 4 | Statistical process control chart of time [**(A)** prevalence of delirium in all patients, in patients after surgery for congenital heart disease and in patients aged 60 months and younger. **(B)** Delirium scorings performed per day].

modifiable and non-modifiable risk factors for pediatric delirium. Although, the efficacy of multicomponent delirium interventions has been demonstrated in adult intensive care patients, there have been few studies on the efficacy of delirium bundles in pediatric intensive care patients (16, 17, 48). One challenge is certainly to adapt and implement these interventions in PICUs (48). Pediatric delirium screening is not being performed consistently in most PICUs internationally, regular monitoring of delirium with validated assessment tools is practiced in only 25–40% of PICUs (49, 50). Knowledge about delirium among PICU staff is still insufficient, and sustainably designed training programs are urgently needed (51). Interventions should focus on validated sedation, pain, withdrawal, and delirium screening tools, identification of potential delirium risk factors, analgesia, and sedation protocols, avoidance of deliriogenic medications, reorientation measures, modification of environmental factors, early mobilization, family empowerment and engagement, and sleep promotion (16, 17).

We have successfully implemented and use a nurse-controlled analgesia and sedation protocol in our clinical routine for several

years with validated scoring instruments for sedation, pain, withdrawal, and delirium (20). Building on this, we created a delirium bundle in a multi-professional team, developed a sustainable training concept and named nurse champions. This is one of the first prospective studies addressing the implementation of a delirium bundle in critically ill children in a before and after study design. The overall prevalence of delirium showed a statistically non-significant reduction from 30% before implementation to 26% after implementation. Compared with other studies, the prevalence of delirium is somewhat lower in our collective, possibly influenced by our analgesia and sedation protocol, and the routine scoring of sedation, pain, withdrawal, and delirium. The reported prevalence of delirium in PICU patients is up to 57% in pediatric postoperative cardiac surgery patients (4, 6, 8, 9, 11, 52). The most vulnerable patient group appears to be young children after cardiothoracic surgery, and in this group our non-pharmacological delirium bundle was most effective (9, 53). In patients under 5 years of age and especially in patients after surgery for congenital heart disease a significant reduction in the prevalence of pediatric delirium from 36 to 28% and from 40 to 29% was found. In agreement with other studies, we found length of PICU stay, iatrogenic withdrawal, and young age to be risk factors for developing delirium (2, 4, 6, 8, 9).

Simone et al. (17) described that the prevalence of delirium can be reduced in a subgroup of young patients and patients after surgery for congenital heart disease by implementing non-pharmacological prevention and therapy measures during sequential implementation of delirium, sedation, and early mobility protocols over a 22-month period. Delirium screening compliance was 95% throughout the study, compliance rates for bundle components were not reported (17). Delirium scoring was performed a median of 3.0 [2.0–3.9] times per patient day during pre-implementation period and 2.3 [1.8–2.8] during post-implementation period. The average compliance rate for the bundle was 72%, single components of the bundle were not examined. The high compliance rate of delirium scorings and for the bundle could be the result of the extensive ongoing training program and the presence of nurse champions. In another study, Franken et al. (48) found no difference in average CAP-D scores following a non-pharmacologic nursing bundle implementation, compared to a retrospective control group. Screening compliance was low with 6–9%, with only few positive CAP-D screening results, compliance rates for bundle components were not reported (48). Implementing delirium screening and delirium bundle in a complex environment like a PICU is a great challenge, but universal delirium screening, prevention, and management are feasible and sustainable and can become standard care on a PICU, if you involve all PICU team members and have a long breath.

Important limitations of this study are the single-center and the study design, the absence of randomization in our study population, and missing blinding of the involved health care professionals. Therefore, we cannot exclude, that the delirium prevalence would have decreased without the bundle over time, due to the improvement of intensive care and implementation of fast track procedures, for example. In addition, there were significant differences between the two groups in the administration of midazolam, opioids, and clonidine. The lower use of analgesia and sedation was not explicitly listed as a component in the delirium bundles (**Figure 2**). However, the association between high and prolonged doses of sedatives and analgesics and the occurrence of delirium was highlighted during staff training, so the reduced use of the medication may be attributed to this. A correlation of high-dose and prolonged use of sedatives and analgesics can be observed in our collective: Patients with positive delirium scoring had significantly higher use of opioids, benzodiazepines, and clonidine than patients without delirium. Pediatric delirium is related to the use of sedation medication, including benzodiazepines, opioids, propofol, and ketamine (31). Benzodiazepines have been shown to trigger or prolong delirium, especially in children (54). However, causality cannot be inferred from our data. Patients with critical illness, long ventilation time and long PICU stay are inevitably exposed to increased sedatives and analgesics due to the complex intensive care treatment. From our study, it is not possible to conclude the degree to which critical illness, complex intensive care treatment, and the use of medications contribute to the development of delirium. This raises the need for further research to better understand the risk factors for the development of delirium. The single-center design limited generalization to other PICUs. Another problem with pediatric delirium studies is the variation in delirium screening, which makes comparability difficult. The SOS-PD scale used in this study for assessment of pediatric delirium was validated in children between 3 months and 18 years of age admitted to a PICU. Patients with neurological abnormalities (e.g., encephalitis, coma) and periods of deep sedation (COMFORT behavior score < 11) or neuromuscular blockade were excluded (25). To our knowledge, there was no delirium score available for children with developmental delay at the time of the study. Since the Cornell Assessment for Pediatric Delirium tool (CAPD) also has a limited informative value with children with developmental delay, Kaur et al. (55) found the combination of the CAPD with fluctuation in level of awareness over the course of a 24-h period as measured by the Richmond Agitation-Sedation Scale (RASS) to be valid and reliable for the diagnosis of delirium in children with developmental delay. This recent knowledge should be considered for future research, as a presumably relevant proportion of patients in a pediatric intensive care unit have diagnosed and undiagnosed developmental delay. We have not analyzed the data by delirium subtype. We must assume that some cases with hypoactive delirium were not detected. We cannot determine which measure of the PICU delirium bundle had the greatest impact on the decrease in delirium prevalence. Because the data were collected automatically using our patient data management system at the end of the observation period, we cannot exclude possible documentation errors. In addition, we observed a significant decrease in the frequency of scoring in the post-implementation phase. It confirms the conclusion of other authors that if protocols are implemented without training and regular monitoring of staff, there is a risk that quality will not be sustainably improved (56). Furthermore, it must be pointed out that compliance with the bundles was only checked on a random

basis. Compliance could certainly be improved by continuous monitoring with the possibility of immediate intervention and motivation of the PICU staff. As also described by Ubeda Tikkanen et al. (57), we had significant problems during this study in diagnosing delirium in children with acquired brain injury due to overlapping symptoms of delirium and acquired brain injury.

Further studies are needed to understand the long-term effects of pediatric delirium and the impact on Post Intensive Care Syndrome (PICS), assessing medications, and their effect on development of delirium and to determine the efficacy and safety of interventions for delirium prevention and management in large randomized studies.

CONCLUSION

Based on a validated delirium monitoring, our study gives new information regarding the prevalence of pediatric delirium and the characteristics of intensive care patients at risk for this significant complication. According to our data, the prevalence of delirium was reduced in a subgroup of pediatric intensive care patients after implementing non-pharmacological prevention and therapy measures. Especially young patients and patients after surgery for congenital heart disease seem to benefit from the implementation of delirium bundles. However, the overall delirium prevalence did not decrease significantly, and we cannot specify the impact of the improvement of critical care and change in PICU culture on this. Further research is needed for a better understanding. Based on our findings, it is important to promote change in pediatric intensive care—toward a comprehensive approach to prevent delirium in critically ill children as best as possible.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Tübingen. 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

JM, ES, and FN designed the study, contributed to data collection, data analysis, and data interpretation. JM wrote the first draft of the manuscript. All authors contributed to the article 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.2022.826259/full#supplementary-material

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REVIEW
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Hydromorphone Prescription for Pain in Children—What Place in Clinical Practice?

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While morphine is the gold standard treatment for severe nociceptive pain in children, hydromorphone is increasingly prescribed in this population. This review aims to assess available knowledge about hydromorphone and explore the evidence for its safe and effective prescription in children. Hydromorphone is an opioid analgesic similar to morphine structurally and in its pharmacokinetic and pharmacodynamic properties but 5–7 times more potent. Pediatric pharmacokinetic and pharmacodynamic data on hydromorphone are sorely lacking; they are non-existent in children younger than 6 months of age and for oral administration. The current data do not support any advantage of hydromorphone over morphine, both in terms of efficacy and safety in children. Morphine should remain the treatment of choice for moderate and severe nociceptive pain in children and hydromorphone should be reserved as alternative treatment. Because of the important difference in potency, all strategies should be taken to avoid inadvertent administration of hydromorphone when morphine is intended.

Keywords: hydromorphone, opioids, children, safety, pain

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INTRODUCTION

Pain is an important public health problem. In pediatrics, it is the most common symptom in the emergency setting (1) and can affect up to 50–75% of children during their hospitalization (2).

Although pain management in children has improved dramatically, many challenges remain and prescribing analgesics in this population can be complex for several reasons. First, due to ontogeny, the response to most medications when used in children, especially neonates, differs from that of adults. Due to the physiological maturation and development of their different organs, transporter and enzyme systems, the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs are different in children compared to adults. All stages of PK are affected: the degree of protein binding is usually decreased, the volume of distribution (Vd) of many drugs is modified according to changes in body composition, and the activities of many enzymes and drug transporters involved in drug metabolism and disposition are significantly decreased during the first years of life which impacts not only hepatic and renal clearance, but also their passage through biological barriers such as the blood-brain barrier (BBB). Besides this, the capacity of the target organ to respond to medications may also differ in children compared to adults. For analgesics in particular, assessment of their effect may be limited in young children with little or no verbal communication, leading to a risk of ineffectiveness or intoxication. Finally, the therapeutic choice is limited by the lack of efficacy and safety data and approved indications for many analgesic drugs.

Despite these obstacles, effective pain management in children is essential, not only for the child's comfort, daily life and activities but also to avoid development of a chronic pain syndrome related to central sensitization and altered quality of life in the medium and long term (3–7). Pain management should be a multimodal approach, including medications from different analgesic classes, procedural interventions and rehabilitation. Pharmacological treatment in children still follows the World Health Organization's three-step approach, i.e., non-opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, for mild nociceptive pain; non-opioids and weak opioids, such as tramadol and codeine, for moderate nociceptive pain; and non-opioids and strong opioids for severe nociceptive pain. A two-step approach is increasingly advocated today: NSAIDs and paracetamol for mild pain, and non-opioids and strong opioids for severe pain, omitting, weak opioids (8). Despite the lack of formal comparisons between the two-step and three-step treatment in children, the risks associated with strong opioids appears to be more acceptable than the uncertainty associated with the variability in drug response observed with codeine and tramadol (9, 10).

Among strong opioids, morphine is the one for which most data are available in children. Morphine has been shown to be effective and safe when used appropriately in children (11, 12). It can be used in children of all ages and is available in a variety of dosage forms (13). Morphine is thus the gold standard for treating severe pain in children.

Hydromorphone is another strong opioid which can be administered both intravenously (IV) and orally, and whose administration appears to be increasing in children of all ages, including infants (14). We are also seeing this increase in our practice, and although some prescribers claim that nausea-vomiting and pruritus are less common with hydromorphone, the rational for prescribing hydromorphone in children instead of morphine is not always known.

In order to better understand whether hydromorphone is a safe option and an alternative to morphine for severe pain treatment in children, this article aims to review the available literature on hydromorphone in children, particularly on its PK and safety.

Relevant articles in the PubMed and EMBASE databases, published until September 2021, were identified using the following keywords: "neonates", "infant", "children", "pediatric", "hydromorphone", "pharmacokinetics". The following article types were eligible: original articles, PK/PD reviews, epidemiologic studies and case reports. Our search was limited to English-language studies published in peer-reviewed journals. Additional publications were identified by reviewing references of these original. The Swiss (SwissmedicInfo), American (Food and Drug Administration, FDA), English (British National Formulary for children, BNFc) and French (Vidal) summary of product characteristics were consulted.

DISCUSSION

Hydromorphone

Hydromorphone is a semi-synthetic opioid analgesic with potent mu-agonist activity. It was first marketed in the U.S. in the 1920s.

Hydromorphone is structurally very similar to morphine (**Figure 1**); differing by the presence of a 6-keto group and the hydrogenation of the double bond at the 7–8 position of the molecule (15).

It is marketed in various formulations, including injection solution, (extended-) tablet, oral solution and suppository.

Pharmacokinetics

The PK of hydromorphone is well described in adults. In this population, after oral administration hydromorphone is rapidly absorbed and is subject to a significant first-pass effect, leading to a mean systemic oral bioavailability of 32% with wide interindividual variation (17–62%) (16–19); the maximum serum concentration (Cmax) is reached in less than an hour for immediate-release forms. After intranasal administration of the injection solution, a bioavailability of 50–60% is described (20, 21). Rectal administration has also been evaluated in small studies ($n < 10$) and has been found to have a bioavailability of around 30% (10–65%) (17, 18). Hydromorphone is a lipophilic molecule with a limited protein binding capacity of 7–19%, and its apparent Vd is relatively small, estimated to be approximately 1.22-4 L/kg. It is extensively metabolized (>95%) in the liver by uridine 5'-diphospho-glucuronosyltransferase 2B7 (UGT2B7) to hydromorphone-3-glucuronide (H3G), which has no intrinsic pain-relieving effects but is thought to have neuroexcitatory adverse effects (22–25). Other metabolites are dihydromorphine (<1%), dihydroisomorphine (1%) and their glucuronides. The involvement of P-glycoprotein (P-gp) in hydromorphone transport is not clearly established to date and rapid membrane crossing, including the BBB, is observed due to the liposolubility of hydromorphone (26).

Hydromorphone is therefore not only structurally but also pharmacokinetically very similar to morphine. Both molecules have interindividual variation in oral bioavailability, undergo glucuronidation primarily by UGT2B7, are metabolized to a 3-glucuronide metabolite and are eliminated by renal route. Response to both hydromorphone and morphine treatments may be influenced by polymorphisms in the μ-receptor gene (*OPRM1*), as well as drug interactions involving the UGT2B7 (27, 28). In adults, their key PK parameters such as bioavailability, Vd and half-life, are comparable (**Table 1**). Their differences are mainly for hydromorphone (i) a less well-defined role of the P-gp efflux transporter in the BBB penetration and brain disposition (26, 31, 32) and (ii) the lack of active 6-glucuronide metabolite formation. For this last reason, hydromorphone use in patients with severe renal impairment is often viewed as a safer alternative to morphine. However, evidence of a larger safety margin in renal failure is limited and both molecules should be used with caution due to the accumulation of their 3-glucunonide metabolites.

All mentioned data and observations are from studies in adults. In young children, ontogenic changes and other age-related differences can significantly alter the PK of drugs, for both morphine and hydromorphone, making simple extrapolation of adult data inappropriate.

Regarding morphine, the effect of ontogeny is well described. It is thus known that the estimated oral bioavailability is higher

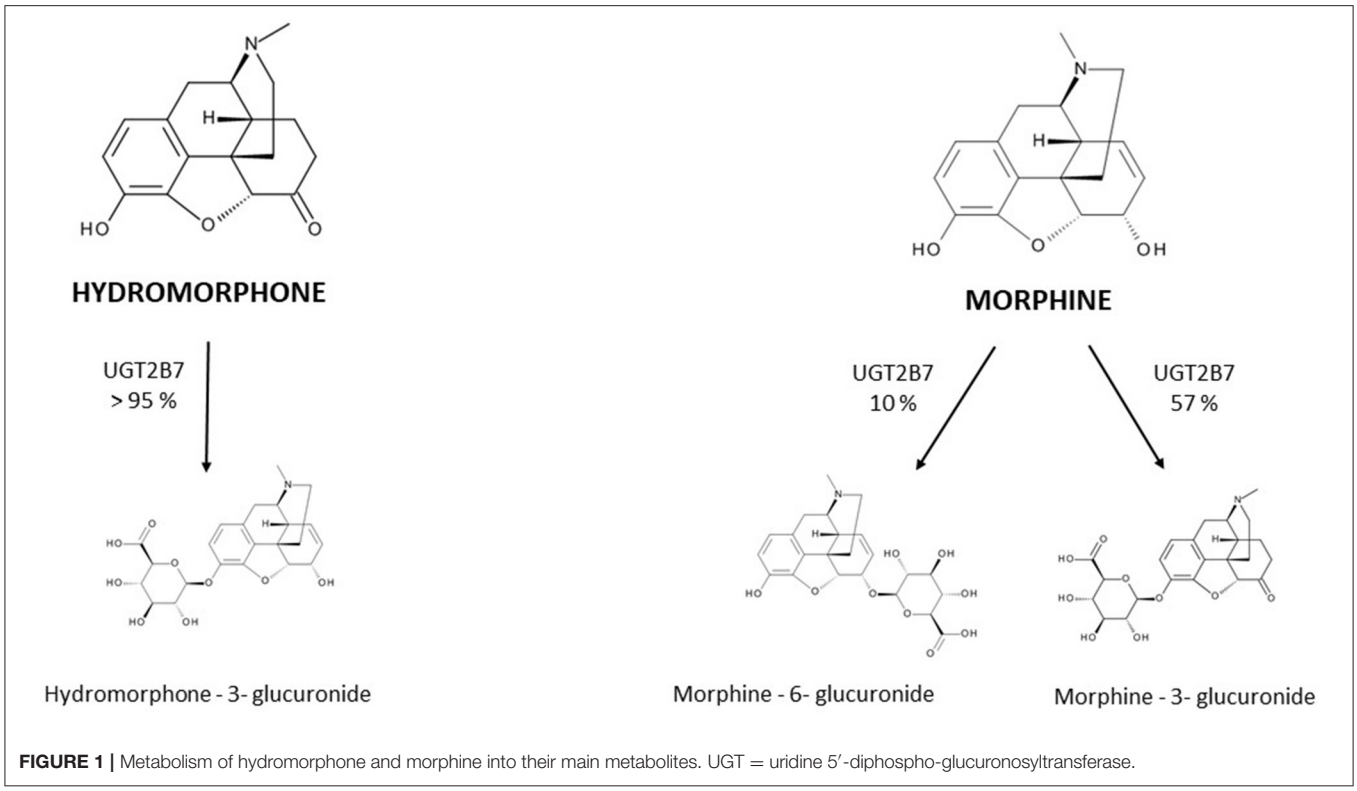

FIGURE 1 | Metabolism of hydromorphone and morphine into their main metabolites. UGT = uridine 5′-diphospho-glucuronosyltransferase.

TABLE 1 | Main PK parameters of hydromorphone and morphine.

	Bioavailability (%)	Tmax (h)	Protein binding (%)	Volume of distribution (L/kg)	Metabolism (Main pathway)	Main metabolites	Excretion (Main pathway)	Half-life (h)
Hydromorphone	17–62	1	7–19	1.2–4.0	UGT2B7	H3G	Kidney	1.5–4.0
Morphine	20–40	1	20–35	3–4	UGT2B7	M6G (10–15 %) + M3G (50–57 %)	Kidney	2.0–4.0

PK, Pharmacokinetics; Tmax, Time to reach maximum concentration; h, Hour; L, Liter; kg, Kilogram; UGT, Uridine 5′-diphospho-glucuronosyltransferase; M6G, Morphine-6-glucuronide; M3G, Morphine-3-glucuronide; H3G, Hydromorphone-3-glucuronide; T1/2, Plasma half-life time (16, 17, 19, 29, 30).

in very young infants than in healthy adults (33). Data on the ontogeny of UGTs are scarce, but UGT2B7 isoenzyme activity is reduced at birth and seems to reach adult activity levels between 1 and 12 months of age (34). Consistent with the immaturity of hepatic glucuronidation by UGT2B7, the limited ability of neonates to glucuroconjugate morphine is well documented (35, 36). Renal function which is represented by glomerular filtration rate (GFR) changes quickly with the maturation of young children, reaching adults' capacity between 6–12 months (37). Morphine clearance is typically slower in infants and approaches adult values by 6 months of age (38); therefore, the half-life is longer in the earliest stages of life and decreases as metabolic pathways develop (39). The neonatal BBB shows a lower barrier capacity than in adults, due to lower expression of barrier-related proteins and lower function of the P-gp, which reaches adult activity between 3 and 6 months of age (32, 40). This increase in permeability contributes, amongst others factors, to the increased sensitivity of neonates and young infants to the central depressant effects of morphine (32, 41).

As hydromorphone is pharmacokinetically very similar to morphine, the same changes, as described above, could be expected. However, data on the PK of hydromorphone in children are much sparser. We found only two studies that evaluated hydromorphone PK in the pediatric population (42, 43). The first study by Collins et al. included 10 children randomly assigned to receive either morphine or hydromorphone by patient-controlled analgesia (PCA) (mean ages 13.7 and 15.3 years respectively) to manage mucositis pain. Blood samples were drawn 2, 4, and 6 h after the start of a continuous infusion and only clearance was determined (51.7 mL/min/kg; range, 28.6–98.2). In the second, more

recent prospective study by Balyan, 34 children [mean age 13.5 (4–18 years), bodyweight 56.7 (23–89.6 kg)] undergoing elective surgery (spine, neurological, or abdominal surgery) were treated with IV hydromorphone boluses followed by PCA. The PK profile was determined by measuring hydromorphone concentrations before and 3, 10, 30, and 90 min after the first dose and by using nonlinear mixed-effects modeling. The study demonstrated that body weight was a significant covariate for clearance while gender, race and type of surgery were not. Vd was comparable to the one described in prior adult studies (33 L/70kg vs. 3.35–42.7 L/70kg) and clearance value was smaller (0.738 L/min/70kg vs. 1.02-1.81 L/min/70kg) (17, 44, 45). Therefore, these two studies give us no information regarding other relevant PK properties, such as bioavailability or time to reach maximum concentration (Tmax), and above all, they provide no PK data for young children, particularly for infants younger than 6–12 months in whom the effect of ontogeny is the most expected.

Pharmacodynamics

Hydromorphone is a non-selective opioid receptor agonist with predominant affinity for μ-receptors and lower affinity for k- and d-receptors.

The efficacy and safety of hydromorphone are documented in adults, regardless of route of administration (46–48). As with all opioids, there is a large interindividual variability in the dose-efficacy-toxicity relationship. The "appropriate" dose for a given patient varies depending on many factors, including individual factors (gender, weight, comorbidities, organ function, previous exposure to opioids, ontogeny...) as well as genetic and environmental factors (comedications, diet...). The recommended initial dose often needs to be adjusted according to individual pain intensity, efficacy and occurrence of adverse drug reactions (ADRs). The most commonly described ADRs of hydromorphone are related to its binding to the μ-opioid receptors and are therefore, at equianalgesic doses, similar to the ADRs of other opioids. They consist mainly of dizziness, nausea, confusion, drowsiness, vomiting, constipation, pruritus and dry mouth; more rarely, respiratory depression and impaired consciousness. In adults, no study has demonstrated a different ADR profile, including nausea and pruritus, between hydromorphone and morphine at equianalgesic doses (48–50). The higher affinity for μ-receptors makes hydromorphone a more potent analgesic than morphine. The equianalgesic dose ratio between parenteral hydromorphone and morphine, calculated from adult studies, is approximately 1:5–7 (48, 51, 52). The same is true for the oral equianalgesic dose (52, 53).

In children, the efficacy of hydromorphone to treat perioperative pain has been demonstrated in a small number of studies when administered IV, either in bolus, continuous or PCA (14, 43, 54–60). The efficacy of epidural administration has also been established (61–67) and a recent study showed the efficacy of intranasal administration (68). Hydromorphone appears to be as effective as morphine, fentanyl and sufentanyl. These studies, whatever the route of administration, primarily included children and adolescents. Only two of them included infants (54, 59). These studies showed good tolerance of hydromorphone in infants, children and adolescents. Adverse effects were comparable to those described in adults, mainly nausea, vomiting and pruritus (14, 43, 57, 58, 60–68).

Spénard et al. recently published an excellent systematical review that sought to compare the efficacy and safety of hydromorphone and morphine in children (69). Among 754 abstracts reviewed, they found only four randomized controlled trials that compared the PD of hydromorphone and morphine in children (43, 56, 57, 61). In three of them, treatment was administered IV (43, 56, 57), in bolus or PCA doses, with equianalgesic dose ratio ranging from 5:1–7:1. The last of the four studies involved epidural administration and none involved oral administration. More than 150 children and teenagers were included, but none were younger than 3 years of age. Two of the studies involving IV administration showed no statistically significant difference in pain scores with morphine compared with hydromorphone. Only the study by Chen et al. showed that significantly more patients in the morphine group required extra fentanyl for pain relief, however with no significant difference in analgesia satisfaction score between the two groups (56). The three studies reporting the use of the IV route showed no significant difference in adverse effects, including nausea, sedation and pruritus (43, 56, 57). Only the study in which hydromorphone and morphine were administered epidurally found a higher incidence of pruritus related to the use of morphine (8% for hydromorphone vs 35% for morphine) (61). These findings should be taken with caution, as the relatively low (8%) incidence of pruritus on hydromorphone described in this study does not corroborate with the 30% to almost 70% incidence of pruritus reported in other studies (64, 65, 67).

Regarding the hydromorphone to morphine equianalgesic dose ratio, only one pediatric study has assessed the equipotence of hydromorphone vs. morphine (43). In this double-blind three-period crossover study, 10 children (mean ages 13.7 and 15.3 years for group 1 and 2, respectively) with mucositis pain received morphine or hydromorphone by PCA in a 7:1 ratio. Analysis of variance of total opioid doses indicated that patients used 27% more hydromorphone than expected, suggesting a mean equipotence of 5:1, comparable to that derived from adult's studies. No study has determined the equianalgesic dose ratio between oral hydromorphone and morphine in children and the same ratio is used in children of all ages, including infants, without taking into account the ontogenic considerations described above.

Dosing Recommendations

Marketing authorization for hydromorphone administration in children is restricted and varies from country to country (**Table 2**). Due to the few studies available on its epidural or intranasal administration, the only routes of administration approved by the majority of national regulatory authorities are oral, SC and IV injection (bolus, continuous or via PCA). In the United States (US), there is no labeled indication in children, regardless of the route of administration.

Various international expert opinions and formularies (70–79) have issued dosing recommendations for IV and oral

hydromorphone in children. These recommendations vary widely and their scientific evidence is not described (**Table 3**).

As summarized in **Table 3**, the majority of IV recommendations tend to agree on a dosage of 0.01–0.02 mg/kg/dose every 3–4 h or 0.003–0.006 mg/kg/h for continuous infusion regardless of patient's age, but most often specifying an age older than 6 months or a weight higher than 10 kg. The Dutch Kinderformularium, a database developed by the Dutch Knowledge Centre for Pediatric Pharmacotherapy (Nederlands Kenniscentrum Farmacotherapie bij Kinderen: NKFK), available online at www.kinderformularium.nl, provides specific dosing for

TABLE 2 | Labeled authorization (non-exhaustive list).

Country	Authorized routes of administration in adults	Authorized routes of administration in children	Therapeutic indications
US labeled authorization	IV, SC and IM (bolus injection)	**No authorization**	moderate to severe pain
	Rectal	**No authorization**	moderate to severe pain
	Oral	**No authorization**	moderate to severe pain
Swiss labeled authorization	IV and SC (bolus injection, infusion)	from **1** year of age	moderate to severe pain
	PCA (IV and SC)	from **12** years of age	moderate to severe pain
	Oral	from **12** years of age	moderate to severe pain
UK labeled authorization	IV and SC (bolus injection, infusion)	from **12** years of age	severe pain in cancer
	PCA (IV and SC)	from **12** years of age	severe pain in cancer
	Oral	from **12** years of age	severe pain in cancer
French labeled authorization	Oral	from **7** years of age	severe pain in cancer

IV, intravenous; SC, subcutaneous; IM, intramuscular; PCA, patient-controlled analgesia.

TABLE 3 | Examples of pediatric dosing recommendations.

(A) IV bolus

Source	"Age category" as mentioned in the referenced source	Recommended starting dose		
		Dose (mg/kg/dose)	Dose (mg/dose)	Interval (h)
FDA	-	-	-	-
Swissmedicinfo (70)	≥12 months and <12 years	0.015	-	3–4
	>12 years and <50 kg	0.015	-	3–4
	>12 years and >50 kg	-	1–1.5	3–4
BNFc (72)	-	-	-	-
Kraemer and Rose (73)	Infants and children	0.010–0.020	-	3–4
Zernikow et al. (74)	>6 months and >10 kg	0.010 (max 0.5 mg/dose)	-	3
Friedrichsdorf and Kang (75)	Children ≤ 50 kg	0.015	-	3–4
	Children >50 kg	-	1–1.5	3–4
Berde and Sethna (76)	<6 months	*	*	*
	>6 months and <50 kg	0.020	-	2–4
	>6 months and ≥50 kg	-	1	2–4
Lexicomp (77)	Infants >6 months and >10 kg	0.010–0.015	-	3–6
	Children <50 kg	0.015	-	3–6
	Children ≥50 kg	-	0.2–0.6	2–4
Pediatrics, in Micromedex (78)	≥6 months and <50 kg	0.010–0.020 (max 0.5 mg/dose)	-	3–4
	≥6 months and ≥50 kg	-	1–1.5	3–4
Kinderformularium (79)	≥1 month and <10 kg	0.003–0.005	-	3–4
	≥1 month and <50 kg	0.010–0.015	-	3–4
	≥1 month and ≥50 kg	-	1.0–1.5	3–4

IV, intravenous; -, no data.

**The author recommends in a comment note "In infants under six months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended" in older infants (76).*

TABLE 3B | IV, Continuous infusion.

Source	"Age category" as mentioned in the referenced source	Recommended starting dose	
		Dose (mg/kg/h)	Dose (mg/h)
FDA	-	-	-
SwissmedicInfo (70)	≥12 months and <12 years	0.005	-
	>12 years and <50 kg	0.005	-
	>12 years and >50 kg	0.004	0.15–0.45
BNFc (72)	-	-	-
Kraemer and Rose (73)	Infants and children	0.003–0.005	-
Zernikow et al. (74)	>6 months and >10 kg	0.005 (max. 0.2 mg/h)	-
Friedrichsdorf and Kang (75)	Children ≤ 50 kg	0.003−0.005	-
	Children >50 kg	-	-
Berde and Sethna (76)	<6 months	*	*
	>6 months and <50 kg	0.006	-
	>6 months and ≥50 kg	-	0.3
Lexicomp (77)	>6 months and >10 kg	0.003–0.005 (max 0.2 mg/h)	-
	Children <50 kg	0.003–0.005 (max 0.2 mg/h)	-
	Children ≥50 kg	-	0.3
Pediatrics, in Micromedex (78)	≥6 months and <50 kg	0.003–0.006 (max 0.2 mg/h)	-
	≥6 months and ≥50 kg	-	0.3
Kinderformularium (79)	≥1 month and <10 kg	0.001–0.002	-
	≥1 month and <50 kg	0.003–0.005	-
	≥1 month and ≥50 kg	0.003–0.005 (max 0.45 mg/h)	-

IV, intravenous; -, no data.

**The author recommends in a comment note "In infants under six months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended" in older infants (76).*

young infants, distinguishing between infants under or over 10 kg. They recommend a much lower dosage in infants under 10 kg: 0.003–0.005 mg/kg/dose every 3–4 hours (Kinderformularium.nl). Berde et al., in a small comment note under their guidelines table, specify that "in infants under 6 months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended" in older children (76).

In line with the oral bioavailability of hydromorphone described in adults, the most commonly recommended oral pediatric dose is 0.03–0.06 mg/kg/dose every 3–4 h. For young infants under 10 kg, the Dutch Kinderformularium recommends a dosage of 0.01–0.02 mg/kg/dose every 3–4 h. As with IV administration, Berde et al. recommend that "in infants under 6 months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended" in older children (76).

CONCLUSION/RECOMMANDATION

Hydromorphone is a morphine derivative with significantly greater analgesic potency than morphine. Except for its higher potency, hydromorphone does not differ substantially from morphine in PK, analgesic efficacy and ADRs.

Available data on the use of hydromorphone in children is very limited and non-existent for oral administration and for children under 6 months of age. Current data do not support an advantage of hydromorphone over other opioids, particularly over morphine, in terms of both efficacy and safety. Despite its increasing use, until more studies examining the use of hydromorphone are available in children, morphine remains the drug with the strongest evidence of efficacy and safety and should remain the opioid of first choice in the pediatric population for the management of severe nociceptive pain. IV hydromorphone is a valuable alternative when morphine is poorly tolerated.

The prescriber should be aware that the use of hydromorphone in children is an off-label prescribing in most situations. The prescriber should have specific knowledge and experience with this drug in children and should also take into account the conditions that the European Academy of Paediatrics and the European Society for Perinatal and Developmental Paediatrics Pharmacology (ESDPPP) have recently defined to facilitate rational and safe prescribing of off-label drugs (80). When prescribing hydromorphone, whatever the route of administration, in young infants under 6 months or 10 kg, dosing should consider the possible impact of ontogeny, such as decreased clearance and increased permeability of the BBB. The simple weight-adjusted dosing recommendation used in older children is probably not safe enough, and to minimize

TABLE 3C | PCA.

Source	"Age category" as mentioned in the referenced source	Recommended starting dose				
		Demand dose (mg/kg)	Demand dose (mg)	Lockout interval (min)	Basal infusion (mg/kg/h)	Rescue dose (mg/kg)
FDA	-	-		-	-	-
SwissmedicInfo (70)	≥12 months and <12 years	-	-	-	-	-
	>12 years and <50 kg	-	-	-	-	-
	>12 years and >50 kg	-	0.2	5–10	-	-
BNFc (72)	-	-	-	-	-	-
Kraemer and Rose (73)	Infants and children	0.004		8–10	0–0.004	0.01
Zernikow et al. (74)	>6 months and >10 kg	0.004 (max. 0.2 mg)	-	-	-	-
Friedrichsdorf and Kang (75)	-	-	-	-	-	-
Berde and Sethna (76)	-	-	-	-	-	-
Lexicomp (77)	Children ≥5 years and <50 kg	0.003–0.004	-	6–10	0–0.004	–
	Children ≥50 kg	0.1–0.2		6		
Pediatrics, in Micromedex (78)	≥6 years	0.004 (max. 0.2 mg)	-	5–10	0.0014–0.004	0.01
Kinderformularium (79)	≥1 month and <10 kg	-	-	-	-	-
	≥1 month and <50 kg	0.003-0.004	-	5–10	0.003–0.005	-
	≥1 month and ≥50 kg	-	0.2	5–10	0.003–0.005	-

PCA, Patient-controlled analgesia; -, no data.

TABLE 3D | Oral, immediate release.

Source	"Age category" as mentioned in the referenced source	Recommended starting dose		
		Dose (mg/kg)	Dose (mg)	Interval (h)
FDA	-	-	-	-
SwissmedicInfo (71)	≥12 years	-	1.3–2.6	4
BNFc (72)	≥12 years	-	1.3	4
Kraemer and Rose (73)	Infants and children	0.04–0.08	-	4
Zernikow et al. (74)	>6 months and >10 kg	0.03 (max 1.3 mg)	-	4
Friedrichsdorf and Kang (75)	Children ≤ 50 kg	0.03–0.06	-	3–4
	Children >50 kg	-	1- 2	3–4
Berde and Sethna (76)	<6 months	*	*	*
	>6 months and <50 kg	0.04–0.08	-	3–4
	>6 months and ≥50 kg	-	2–4	3–4
Lexicomp (77)	Infants >6 months and >10 kg	0.03	-	4
	Children and adolescents <50 kg	0.03–0.08	-	3–4
	Children and adolescents ≥50 kg	-	1–2	3–4
Pediatrics, in Micromedex (78)	≥6 months and 10-50 kg	0.03–0.08 (max 1.3 mg)	-	3–4
	≥6 months and ≥50 kg	-	1–4	3–4
Kinderformularium (79)	≥1 month and <10 kg	0.01–0.02	-	3–4
	≥1 month and ≥10 kg	0.03–0.08 (max 2.6 mg)	-	3–4

-, no data.

**The author recommends in a comment note "In infants under six months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended" in older infants (76).*

the risk of ADR, a lower starting dose, as proposed by the Dutch Kinderformularium and Berde et al., seems warranted. Great caution is required when administering an oral form to infants and young children due to the lack of data. Attention should be paid to the choice of age-adapted dose formulation. As with other opioids, regular and close assessments of efficacy and ADRs are essential and should allow prompt dosage adjustments in children of all ages. Adverse events should be reported to the national pharmacovigilance agencies.

Because of its higher potency, inadvertent prescription and administration of hydromorphone when morphine is intended can have severe, potentially fatal, consequences, in particular in children. Caregivers prescribing or administering hydromorphone should be aware of this difference in potency, and standard strategies such as Tall Man lettering (which uses capital letters to help differentiate between look-alike drug names) and color coding should be implemented.

Further clinical studies describing the PK and PD of hydromorphone in children are needed. Given the real-world difficulty of including children in PK studies, physiologically-based pharmacokinetic (PBPK) modeling may help acquire data on the influence of age-dependent physiological differences on hydromorphone PK.

AUTHOR CONTRIBUTIONS

FR wrote the manuscript. CS, AI, MB, and JD revised the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

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REVIEW
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Modified ABCDEF-Bundles for Critically Ill Pediatric Patients - What Could They Look Like?

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Background and Significance: Advances in pediatric intensive care have led to markedly improved survival rates in critically ill children. Approximately 70% of those children survive with varying forms of complex chronic diseases or impairment/disabilities. Length of stay, length of mechanical ventilation and number of interventions per patient are increasing with rising complexity of underlying diseases, leading to increasing pain, agitation, withdrawal symptoms, delirium, immobility, and sleep disruption. The ICU-Liberation Collaborative of the Society of Critical Care Medicine has developed a number of preventative measures for prevention, early detection, or treatment of physical and psychiatric/psychological sequelae of oftentimes traumatic intensive care medicine. These so called ABCDEF-Bundles consist of elements for (A) assessment, prevention and management of pain, (B) spontaneous awakening and breathing trials (SAT/SBT), (C) choice of analgesia and sedation, (D) assessment, prevention and management of delirium, (E) early mobility and exercise and (F) family engagement and empowerment. For adult patients in critical care medicine, research shows significant effects of bundle-implementation on survival, mechanical ventilation, coma, delirium and post-ICU discharge disposition. Research regarding PICS in children and possible preventative or therapeutic intervention is insufficient as yet. This narrative review provides available information for modification and further research on the ABCDEF-Bundles for use in critically ill children.

Material and Methods: A narrative review of existing literature was used.

Results: One obvious distinction to adult patients is the wide range of different developmental stages of children and the even closer relationship between patient and family. Evidence for pediatric ABCDEF-Bundles is insufficient and input can only be collected from literature regarding different subsections and topics.

Conclusion: In addition to efforts to improve analgesia, sedation and weaning protocols with the aim of prevention, early detection and effective treatment of withdrawal symptoms or delirium, efforts are focused on adjusting ABCDEF bundle for the entire pediatric age group and on strengthening families' decision-making power, understanding parents as a resource for their child and involving them early in the care of their children.

Keywords: pediatric critical care, post intensive care syndrome, PICS, ABCDEF-bundles, family centered care, PICUs (pediatric intensive care unit)

INTRODUCTION

Within the last decade, long term complications after intensive care therapy have moved further into focus for both adult and, in later years, pediatric patients (1).

Measurement of outcome parameters in pediatric intensive care patients has been performed for decades, including the development of different scales and questionnaires like the Pediatric Overall and Cerebral Performance Categories (POPC, PCPC) and Functional Status Scale (FSS) (2, 3).

Using these tools, assessment of outcome after pediatric intensive care has shown a decrease in mortality from 5.8% in 1989/1990 to 4.6% published in 2000 down to 2.4% in 2014 (1, 3, 4).

In that same study, Pollack et al. (1) found the rate of significant new morbidities to be 4.8%, double that of mortality, and concluded "that pediatric critical care may have exchanged mortality for morbidity over the last several decades".

In light of these developments, long-term survival and health related quality of life have moved further into focus.

Both the event leading up to the ICU-stay (congenital or acquired, traumatic or medical) and the repeated trauma caused by necessary interventions and therapies have long lasting effects on patients and their families. In adult patients, long-term consequences of intensive care treatment have been recognized as a relevant problem with an increasing focus on its prevention during treatment (5, 6). Lately, research and knowledge regarding pediatric patients and their families is increasing in this regard, reliable methods for prevention and treatment however are still lacking (7, 8).

The associated combination of debilitating symptoms following long-term or deep sedation, mechanical ventilation and forced immobilization has been identified and described by Needham et al. (5) as post intensive care syndrome (PICS). It includes significant physical (pulmonary, neuromuscular, and physical function), cognitive ("critical illness–related brain injury," memory loss, lack of concentration, learning impairment) and mental/emotional (PTSD, fear, or anxiety disorder) problems and disorders which last long after discharge. Up to 64% of surviving adult ICU-patients without preexisting impairment suffer from one or more of these aspects (9). Extremely relevant for long-term outcome for instance is ICU-acquired weakness, characterized by symmetric myo-and polyneuropathy. It affects up to 67% of patients on mechanical ventilation at time of awakening and oftentimes persists after discharge (10).

Critically ill patients can present with problems from all categories. Additionally, relatives and caretakers often suffer from mental or emotional long term impairment such as anxiety or post-traumatic stress disorder (11). This phenomenon is described as PICS-F for "family" and affects relatives of up to 75% of patients (5, 12).

PICS in adult patients has been studied in depth and several projects have made it their goal to improve treatment and avoid its development altogether. A collaboration of intensive care professionals has developed the so called ABCDEF-Bundles, a number of measures meant to prevent PICS in both patients and their families (6).

They consist of several evidence-based treatment options meant to prevent or, if necessary, treat symptoms of PICS.

The ABCDEF-Bundles include (A) assessment, prevention and management of pain, (B) spontaneous awakening and breathing trials (SAT/SBT), (C) choice of analgesia and sedation, (D) assessment, prevention, and management of delirium, (E) early mobility and exercise and (F) family engagement and empowerment.

Since their first description, the bundles have emerged as a well-founded system for liberating patients from mechanical ventilation and improving long-term outcome.

Their implementation has been shown to be very effective in caring for critically ill adult patients, showing, among others, improvement in survival and disposition at time of discharge, reduction in time on mechanical ventilation, use of physical restraints and occurrence of delirium (13, 14).

As all elements are overlapping or interconnecting at some point, they have shown to be most effective when implemented together (13).

The successful implementation of these bundles and their increasing incorporation in routine adult critical care leads to the assumption that a similar paradigm shift in pediatric critical care is urgently needed.

A well-known problem in pediatrics is a delay in the introduction of new therapies for children (15).

Studies on ABCDEF-Bundles in children are still rare. Reliable recommendations for prevention and treatment of PICS in children have not been developed.

Studies show the effect of one to three bundles for use in children, confirming that scoring and treatment for delirium

and early mobility can be successfully implemented with positive results (16).

A survey conducted in 15 European countries shows a high variation by region concerning implementation of individual bundles in pediatric intensive care units (17).

In 2020 Walz et al. (18) published a review regarding ABCDEF-Bundles for use in children. They conclude that ABCDEF-Bundles are suspected to be of similar use in children as in adults, even though clinical studies to their effect still need to be conducted. For all aspects they recommend establishing protocols and multidisciplinary teams for implementation of bundles in pediatric critical care. There are no further recommendations on changes that might need to be made in order to adapt the bundles for use in children (18).

The prevalent use of deep sedation and prolonged immobilization in treating critically ill children contributes to physical impairment like ICU-acquired weakness, mental problems following delirium and poor neurocognitive outcome.

In addition, Manning et al. (8) described one difference in PICS between adult and pediatric patients concerning the involvement of families. Besides known emotional and mental disorders such as PTSD or anxiety, which occur in families of adult patients as well, families of critically ill children suffer severe challenges to social interactions which affect both parents and siblings in their daily life.

Following the well-known adage "children are not small adults," ABCDEF-Bundles like any new therapies and methods, need to be adjusted for use in children, taking into account flexibility for a broad range of developmental stages.

There is scientific evidence for some aspects of the Bundles for use in children, for others further research is needed. In this publication, an overview of existing literature and methods is given as well as suggestions for further development.

MATERIALS AND METHODS

Based on a narrative review of the existing literature on PICS and ABCDEF-Bundles in adult and pediatric patients, ABCDEF-Bundles are reevaluated and adapted for use in children by adjusting them as much as possible according to existing scientific evidence.

Taking into consideration current scientific evidence on analgesia and sedation, mechanical ventilation, management of delirium, mobilization and family involvement, pediatric ABCDEF-Bundles are being developed for implementation in the treatment of critically ill children.

Data sources: A systematic search of PubMed database was undertaken for full articles pertaining to ABCDEF Bundle and PICS, case series, observational and cohort studies and randomized controlled trials were included.

Study selection: No language or date barriers were set. Studies that met the following eligibility criteria were included: The study design aimed to describe the prevalence of PICS and the causes resulting from critical care treatment, as well as the description and effectiveness of ABCDEF Bundle on outcome.

Data extraction: Data were extracted by the primary researcher and accuracy checked by coauthors.

Data synthesis: A narrative synthesis was undertaken.

RESULTS AND DISCUSSION

For adult patients in critical care medicine, research shows significant effects of ABCDEF- bundle-implementation on survival, mechanical ventilation, coma, delirium, and post-ICU discharge disposition.

For children, a recent survey showed an implementation of all aspects in only 9% of 161 PICUs in the US, Canada, Brazil and Europe (19). Although there are calls for implementation of these measures in pediatric intensive care, as with most medical developments, the use of adult therapies in children without crucial changes beyond adaptation for size and body weight has not been effective (18).

Therefore, adjustments are necessary where proven methods in adults do not show the same results in pediatrics.

Before addressing each of the elements, a framework for implementation needs to be established. In analyzing adherence to ABCDE-Bundles (not including "F" for family involvement and empowerment) the complexity of combined ABCDE-Bundles has been identified as one major obstacle to adherence to bundles. On first impression, bundles are associated with an increased workload within an already stressful work environment. Studies and reports to this effect are difficult to compare, as variables are not clearly defined and success or adherence is rated differently across publications (20).

Other aspects identified include concerns over patient stability or safety, providers lack of knowledge regarding reasons and goals behind bundles, unclear or difficult to follow protocols and lack of coordination within inter-professional teams (21).

In order to improve compliance with guidelines and facilitate implementation of bundles in daily critical care routines, structured and repeated training of all professionals involved is a necessity. Continuous reinforcement can be assured by establishing champions within the team, taking on responsibility for adherence to protocols and acting as intermediaries in case of doubt or questions as to the procedures. Protocols need to clearly define methods for assessment, prevention and treatment of symptoms, assign responsibility for different aspects to all professions involved and therefore dividing the burden of perceived increase in workload on many shoulders (20).

Clearly structured documentation within already established patient records without need for additional systems help monitor adherence as well as results and enable reevaluation and adjustment of bundles.

An analysis of ABCDEF-Bundle use in critically ill adult patients showed a dose and response effect, with an increase in effect dependent on the amount of bundle aspects implemented. While all aspects are at some point connected and have synergistic effects when used in combination, we therefore stipulate, that use of just some aspects should always be preferred over not using any at all because of limited resources (13, 16).

In 2016, Yaghmai et al. (22) demonstrated a deterioration in adherence to nurse-controlled sedation protocols after initial successful implementation, showing the need for continuous efforts in training and monitoring.

Considering the widely acknowledged problem of a "theory-to-practice gap" in all fields of academic study, including medical research, nursing science and others, the process of implementing some or all bundles should be guided by current recommendations from implementation science in order to reach permanent use and effectiveness (23, 24).

Assessment, Management, and Prevention of Pain and Choice of Sedation

Guidelines on analgesia and sedation differ according to regions and availability of substances and protocols should be adjusted accordingly.

Disoprivan, for instance, is recommended for use in children for up to 48 h within the United States but its use is not allowed for long-term sedation in Europe because of risk for propofol infusion syndrome in children under the age of 16 (25, 26).

We advocate for nurse-controlled protocols primarily using opioid infusion supplemented by alpha-2-agonists. Additionally, non-opioid drugs should be used for mild to moderate pain without the need for further sedative effect (25). Spinal anesthesia has been shown to effectively reduce opioid use in pediatric postoperative patients and has a significant benefit in providing hemodynamic stability in infants after surgery (27, 28).

In both adult and pediatric care, assessment of pain can best be accomplished by self-reporting using the numeric rating scale or visual analog scale. Unfortunately, in pediatric intensive care patients are oftentimes unable to participate due to either severity of illness or physiological developmental stages. There are several Scores available for use in such cases, i.e., the FLACC-Score or, in German speaking countries, the so called KUS-Skala (kindliche Unbehagens- und Schmerzskala) (29). They are validated for use in children <4 years and can also be used in older children with neurologic or developmental impairment (30, 31). All these scales are scored with points between 0 and 10 with any score ≥ 4 being seen as a reason for intervention. For postoperative assessment of sedated and even intubated children of all ages the Comfort-B-Scale is also available (32).

In general, the choice of scoring tool is not as important as the fact of scoring at all. It is recommended to evaluate pain regularly, we suggest every 8 h or more often in case of manifest pain and after intervention. Additionally, children under continuous analgesia and sedation can be scored using non-verbal scales in an attempt to differentiate between pain and undersedation for more appropriate intervention (33).

Prevention of pain should be achieved by using analgesia before any kind of potentially painful procedures, including endotracheal suction, blood draws, or other routine interventions.

Closely connected to bundle "A" is bundle "C," Choice of sedation, which can also be achieved by implementing a protocol for analgesia and sedation.

In order to reduce stress and anxiety of patients as well as the safety risk to patients dependent on mechanical ventilation and catheters, undersedation needs to be avoided. On the other hand, oversedation carries the risk of prolonged mechanical ventilation, hemodynamic difficulties and an increase in withdrawal and delirium.

The goal should be sedation by continuous drug infusion which provides for patients in comfort, who are tolerating mechanical ventilation but are awake enough to perceive some of their environment and to communicate any discomfort which may be eliminated without the need for further sedation. In older children and adolescents, communication via drawing or writing should be made possible if tolerated by the patients.

The goal in both children and adults is the prevention of over- and undersedation with the long-term effect of reduction in withdrawal and delirium. For children, midazolam has been shown to increase delirium, decrease quality of sleep and prolong both length of mechanical ventilation and length of stay in the PICU. Most importantly, they have emerged as an independent risk factor for the development of pediatric delirium (34). While not all studies show a reduction in length of mechanical ventilation after implementation of sedation protocols, they do show a decrease in days with pain, withdrawal or delirium (35, 36). Use of sedation protocols has been shown to help in reducing use of benzodiazepines, support the interdisciplinary communication in order to set and manage goals of sedation and to lessen the presentation of iatrogenic withdrawal symptoms (37).

Several studies have shown alpha-2-agonists like dexmedetomidine and clonidine to have a sedative effect leading to a reduction in opioid- and benzodiazepine-requirement. At the same time, they prove to be less neurotoxic than other substances and lead to a lower occurrence in withdrawal and delirium (38, 39).

Protocols therefore should call for the sparing use of benzodiazepines in critically ill children, using opiates and alpha-2-agonist clonidine for firstline treatment (25, 33). Even with our knowledge of side effects and negative long-term effects, there are still patients who are sedated using benzodiazepines. In 2018 Shildt et al. could show that even with successful implementation of a benzodiazepine-sparing protocol, 30% of patients received midazolam infusion after sedation was found to be insufficient. The authors discuss whether some of those patients might have suffered from undetected delirium and question the influence of the practitioners' comfort with established routines using midazolam (40).

For any protocol based on titration of dosage to the effective level, there can be a reluctance in timely reduction. Therefore, regular scoring should involve active reevaluation of possible oversedation and protocols should call for attempted reduction in calm children.

The problem of iatrogenic withdrawal syndrome after long-term sedation is not included within the original ABCDEF-Bundles for adult patients. In 2019, Arroyo-Nonoa et al. (41) found only 8 works on IWS in adult critical care patients, with two published between 1998 and 2016 and 6 between 2017 and 2019. In contrast, this is one aspect where pediatric research is

more advanced, having introduced and validated scoring tools for early detection (42, 43), after showing it to lead to relevant stress for both patients and parents (19). Additionally, IWS has been shown to be an independent risk factor for development of delirium, which in turn factors heavily within the long-term effects of critical care treatment (see bundle D below).

Nurse driven protocols for analgesia and sedation including tapering schedules contribute to the reduction in IWS (44). We therefore recommend using standardized IWS-scoring at least every 8 h, for instance using the Sophia observation of withdrawal score (Sophia observation and withdrawal score—pediatric delirium in conjunction with delirium screening) (43).

A possible strategy for the avoidance of oversedation might lie within increased family involvement in taking care of mechanically ventilated patients where nurse-to-patient ratios do not suffice for individualized care.

Both Spontaneous Awakening and Spontaneous Breathing Trials

A significant deviation occurs in adjusting bundle "B" for use in pediatric patients. In the original ABCDEF-Bundles for adult patients, "B" stands for "both spontaneous awakening and spontaneous breathing trials," therefore tying it in closely between bundles A and C. It describes a standardized protocol for pauses in sedation and mechanical ventilation for assessing the patient while alert for any extubation readiness (6). In pediatric patients, a careful risk-benefit-analysis has to be performed. While mechanical ventilation is a vital part of critical care medicine, prolonged use brings with it risks such as need for deeper sedation, followed by hemodynamic instability, immobilization and infection, in turn leading back to a prolonged mechanical ventilation and length of PICU-stay (45–47).

Regular spontaneous awakening and breathing trials with pause in all sedation have been successful in reducing time on mechanical ventilation, length of PICU-stay and cumulative dosis of sedatives (45), but have not been proven effective in terms of short-term health related quality of life (48). Instead, compared to use of standardized sedation protocols with continuous reduction in sedation (40, 49), Vet et al. (50) showed daily sedation interruption in addition to protocolized sedation to increase mortality in critically ill children when compared to those under protocolized sedation only. There were no added benefits for clinical outcome in the combined group.

On the other hand, continuous titration of sedation might lead to a hesitancy in reducing sedatives after reaching a comfortable dosage and prolonging sedation, mechanical ventilation and length of stay (22). Likewise, it has been found that protocols for weaning from mechanical ventilation should include clear instructions for when to start reducing parameters in order to avoid unnecessary delay (51).

An early study on weaning and extubation readiness has shown a high percentage of children to be ready for extubation on their first extubation readiness test, suggesting a lack of extubation readiness tests in early stages of treatment and the danger of unnecessarily prolonged ventilation (52). Additionally, upper airway obstruction ranged as a main factor for extubation failure, which cannot be detected by spontaneous breathing trials (52).

However, for patients with congenital heart disease, spontaneous breathing trials and daily extubation readiness tests proved effective in reducing extubation failure and length of PICU-stay (53, 54).

We therefore propose focusing any aspects concerning analgesia and sedation within bundle A and renaming bundle B as "Breathing and mechanical ventilation" for use in pediatric critical care. We advocate for a proactive and continuous weaning protocol with standardized daily reevaluation of mechanical ventilation and assessment for weaning, regular reduction of ventilator parameters in conjunction with protocolized reduction in sedation once feasible and daily extubation readiness tests for identification for extubation as early as possible in hopes of further reducing time on the ventilator and maybe even length of stay on the PICU (52). In support of this goal, early use of non-invasive ventilation should be considered.

Assessment, Management and Prevention of Delirium

Delirium is a significant complication in critically ill children consisting of several symptoms of acute cerebral dysfunction. It has been found in up to 66% of patients in PICUs and is associated with prolonged time on mechanical ventilation, higher use of sedatives and physical restraints and leads to an increase in mortality as well as a reduction of health-related quality of life (55–57).

As with pain and sedation, regular assessment by using validated tools is the key for adequate management. Delirium remains underdiagnosed and misinterpreted in children and therefore undertreated, especially as children in hypoactive delirium are often seen as just especially calm and "easy" to comfort (58). All children admitted to a PICU should be subject to routine screening for withdrawal and early detection of symptoms and diagnosis of both hypo- and hyperactive as well as mixed forms of delirium in children

Although there are several possible scoring systems, such as the widely used tools of the Cornell Assessment of Pediatric Delirium (CAPD) or the Pediatric Confusion Assessment Method—Intensive Care Unit (pCAM-ICU) (59, 60), there is advantage in using the Sophia observation withdrawal—pediatric delirium assessment (SOS-PD). It has been validated for use in all pediatric age groups and, more importantly, differentiates between symptoms of withdrawal and delirium (61).

There are several modifiable risk factors for delirium in critically ill children, including mechanical ventilation, use of benzodiazepines as long-term sedatives, physical restraints, noise pollution and a lack of adequate nutrition which need to be considered in treatment (55, 57, 62, 63). On the other hand, we have no influence on independent factors such as age, sex, or severity and type of illness (34).

Delirium bundles have already been developed and described in detail.

Early use of non-pharmacological measures such as helping the children to reorient themselves after sedation, providing

glasses and hearing aids and toys from home can prevent development of delirium or go a long way in treating symptoms that have already manifested (64). One most promising aspect in prevention of delirium presents standardized analgesia and sedation, which aims at a reduction in dosage (especially concerning benzodiazepines and anticholinergic substances) and a shortening in length of sedation (65).

The most important factors include treatment within a calm and comforting environment, including the presence of pictures or toys from home and the continuous care by a parent or other close caregiver. Orientation (or reorientation) in space and time should be encouraged by use of hearing aids and glasses, clocks and calendars and upright positioning in bed where tolerated (66, 67).

In severe cases, using low dose antipsychotic drugs as off-label medication (i.e., Quetiapine, Levomepromazine) might be feasible, but high quality studies to their affect are still lacking. Available studies show a high risk of side effects like extrapyramidal symptoms and changes in corrected QT-time (68–70). After close consideration in each case, benefits may outweigh the risks and should not be discounted completely. Nevertheless, these results emphasize the importance of non-pharmacological treatment of delirium and the necessity of a change of culture in pediatric intensive care toward prevention of delirium in critically ill children (67).

Child life specialists and other specialists should be present on the ward in order to treat patients, support and educate families and help train all other staff in dealing with delirium in critically ill children.

Early Mobility and Exercise

"E" stands for early mobilization in critically ill patients. It has been shown to have a positive effect on body function, reducing limitations on activity and improving muscle strength and ability to walk (71).

While literature shows a solid scientific foundation for adult patients, implementation in PICUs is lacking (19). Interestingly, within this field of study there are more reviews available than clinical studies (72).

Additionally, in a recent review Nydahl et al. analyzed 33 reviews concerning early mobilization in critically ill patients. Out of these, only 3 were analyzing studies concerning pediatric patients (72).

Restrictions in time and space, lack of personnel and fear of adverse events such as dislodging of endotracheal tubes or central venous catheters all present (real and perceived) barriers to mobilization of critically ill children (17, 73, 74).

Throughout the available literature, a timeframe for early mobilization is not clearly defined (75). For children however, both Wieczorek and Choong have defined early mobilization as starting within 72 h of admission, starting with assessment for mobilization within 24 h (76, 77).

Depending on severity of illness, state of sedation and clearly indicated restrictions in movement or instabilities because of trauma or surgery, mobilization can be implemented as passive, assisted active or active mobilization (72, 76).

As with all other bundles, key is establishing a reliable protocol for daily review of the patients' goals, clear documentation of reached milestones for continuity of care and a multidisciplinary approach including rehabilitation specialists, nurses, doctors and parents, communicating different perspectives and defining common goals in daily rounds. Having a standardized protocol instead of individualized plans is associated with improved outcome and lessens the risk of implicit bias in planning the therapeutic approaches (76, 78).

Reinforcing the importance of the last of the bundles, F for "Family", family presence has shown a marked influence on successful out-of-bed-mobilization for children (aOR 7.83). Unfortunately, the same study showed about one quarter of patients in pediatric intensive care to be completely immobilized (17).

Several international initiatives advocate for standardized early mobility in children, making a solid case for implementation in all PICUs, showing it to be safe and feasible, even in low resource regions (17, 77).

Family Engagement and Empowerment

Family education and empowerment are listed last within the concept of pediatric ABCDEF-Bundles but represent a key element. While PICS is relevant in critically ill children, trauma, or sudden illness of a child has a significant impact on all members of the household and other close relatives. Post-traumatic stress disorder, anxiety and sleep disorders in parents can disrupt daily life for the whole family for a long time after discharge, including for patients who leave the hospital without permanent impairment (8, 79).

In adult critical care, family engagement includes participation in rounds, ethics and palliative care consultations as well as the offer of being present during traumatizing situations such as CPR. All aspects have been shown to be beneficial for patients and family as well as staff (6).

A common reason for psychological long-term difficulties of family members is the parents' feeling of helplessness and lack of information experienced when coping with their child's illness (80).

In 2020 the EU PARK-PICU study evaluated family centered care by questioning if 24-h-presence by family members at bedside was possible (17). However, Meert et al. (81) described a much broader approach to family centered care in pediatric intensive care based on the recommendation by the American Academy of Pediatrics, calling for "an innovative approach to the planning, delivery, and evaluation of health care that is grounded in a mutually beneficial partnership among patients, families and providers that recognizes the importance of the family in the patient's life".

Among the core aspects are open visitation hours for parents and individually prepared bedside visits by siblings. Even before the current pandemic led to restrictions in visitation all over the world, 24-h-attendence was made possible in about 88% of PICUs considering hospitals in the US, Canada, Brazil and Europe. Unfortunately, in Europe less than half of PICUs reported permitted 24 h presence by family members (19).

Apart from open doors and the theoretical possibility of being present 24 h a day, parents most benefited from having a place to sleep at the hospital and involvement in daily patient care as per their parental role as primary caregiver.

Another aspect are family centered rounds, including parents in case presentations and discussions at bedside after first informing parents of the purpose behind these rounds. Problems perceived by staff such as lack of teaching, inhibition regarding the discussion of difficult topics or prolonged time for rounds receded after adequate education among staff as to the benefits of family centered rounds.

Third, the offer of being present for traumatic events like CPR and for invasive procedures is included in family centered care. As with most other described aspects, education of all professionals involved and open communication with parents is key for success. Once those needs are met, family members overwhelmingly prefer being present and one study could show that parents present during CPR benefited by exhibiting less signs of intrusive thoughts, prolonged symptoms of grief and post traumatic avoidance behavior (82, 83).

One valuable tool is available in pediatric ICU-diaries (84). Adapted from adult intensive care as well, ICU-diaries enable parents to record impressions, information and feelings for later review and age-appropriate sharing with the patient after discharge. It has been shown to be beneficial to both parents and relatives for dealing with their own trauma as well as for patients in filling in gaps in memory (85).

Additionally, ICU-Diaries provided a helpful tool in not only enabling parents and patients to review and understand lived experiences, but also provided support in explaining difficult information to siblings and other relatives (86).

Unfortunately, current restrictions (in space and due to the pandemic) do not allow for 24-h presence of parents or other close relatives at the bedside. However, efforts should go toward lifting of any set visiting hours and allow extended presence of parents with children who are expected to benefit in terms of reduction of sedatives and improvement of psychological wellbeing. It must be taken into account that, for example, the presence of the family is most positively associated with mobilization out of bed, and probably with many other measures as well (17).

For long-term consideration, we propose further modifying and expanding the pediatric ABCDEF-Bundles.

A common denominator within all ABCDEF-Bundles is the topic of communication. Not exclusively regarding children but with a special emphasis within pediatric intensive care, parents and other caregivers are speaking for our patients and need to be included in all aspects of their care and relevant decision making. This necessitates a high level of information and discourse. Parallel to adult patients, communication with the patients themselves is another aspect needing consideration. And within any multiprofessional team such as those in critical care, communication between team members is of utmost importance. In a letter to the editor, Patak et al. (87) wrote "Perhaps communication should be a vital sign," noting the lack of standardized assessment and documentation of patient communication. For further development of pediatric ABCDEF-Bundles we propose following their suggestion and renaming bundle "C" for Communication (87), including necessary education and training protocols for staff (37), standardized systems for information and discussion with parents including informational packets in different languages and reliable access to translator services where needed, implementation and further development of age appropriate communication strategies and tools for intubated or otherwise impaired critically ill children and providing support and infrastructure for calls and video communication with siblings and friends who are unable to visit. Considering the relevant psychological impact any trauma or severe illness has on parents, siblings and other relatives, psychologists should be an integral part of any PICU-team. Professional support for both patients and relatives might help early diagnosis and treatment of associated illness such as depression and anxiety and reduce long-term effects (12). Additionally, crisis-intervention training should be considered for any health care professional within the critical care setting.

The original "C" for choice of sedation will be incorporated into bundle A, being renamed "Analgesia and Sedation."

Concerning this new bundle "C" as well as the established aspect "F," several studies have looked at possibilities of health informational technologies in pediatric intensive care. Based on evidence, that most parents prefer receiving all information concerning their child's health as soon as it is available, rather than summarized at greater intervals, the effect of interactive monitors showing electronic health records for use by parents was evaluated and suggests an improvement in awareness for parents and support in informed decision making (88). In 2016, Brown et al. (89) also found the offer of electronic information tools within the ICU to be welcomed by both patients and relatives for receiving updated medical information for review.

Possibilities within this field seem endless, offering further options for improving individualized support for families, providing general as well as specific information and giving parents and caregivers the opportunity to review given information on their own terms and without the time constraints (real or perceived) often imposed on short updates by medical professionals.

In another bid for expansion of ABCDEF-Bundles in pediatrics, Choong et al. (76) mention "G" for good nutrition and H for humanistic medicine.

Without question, physiological nutrition, and healthy sleep patterns are fundamental needs for children recuperating from severe illness and to prevent further deterioration (90). For a newly developed bundle G we therefore propose to include, again, standardized protocols for daily reevaluation of nutritional needs, determining severity of illness, weighing parenteral against early enteral nutrition, defining caloric needs and identifying patients in need of rehabilitational specialists for assessment and treatment of feeding and swallowing difficulties (91, 92). Next to "Good nutrition" we include "good sleep" and promote early support of a circadian rhythm, moving any possible intervention and diagnostics aside from emergencies into daylight hours and

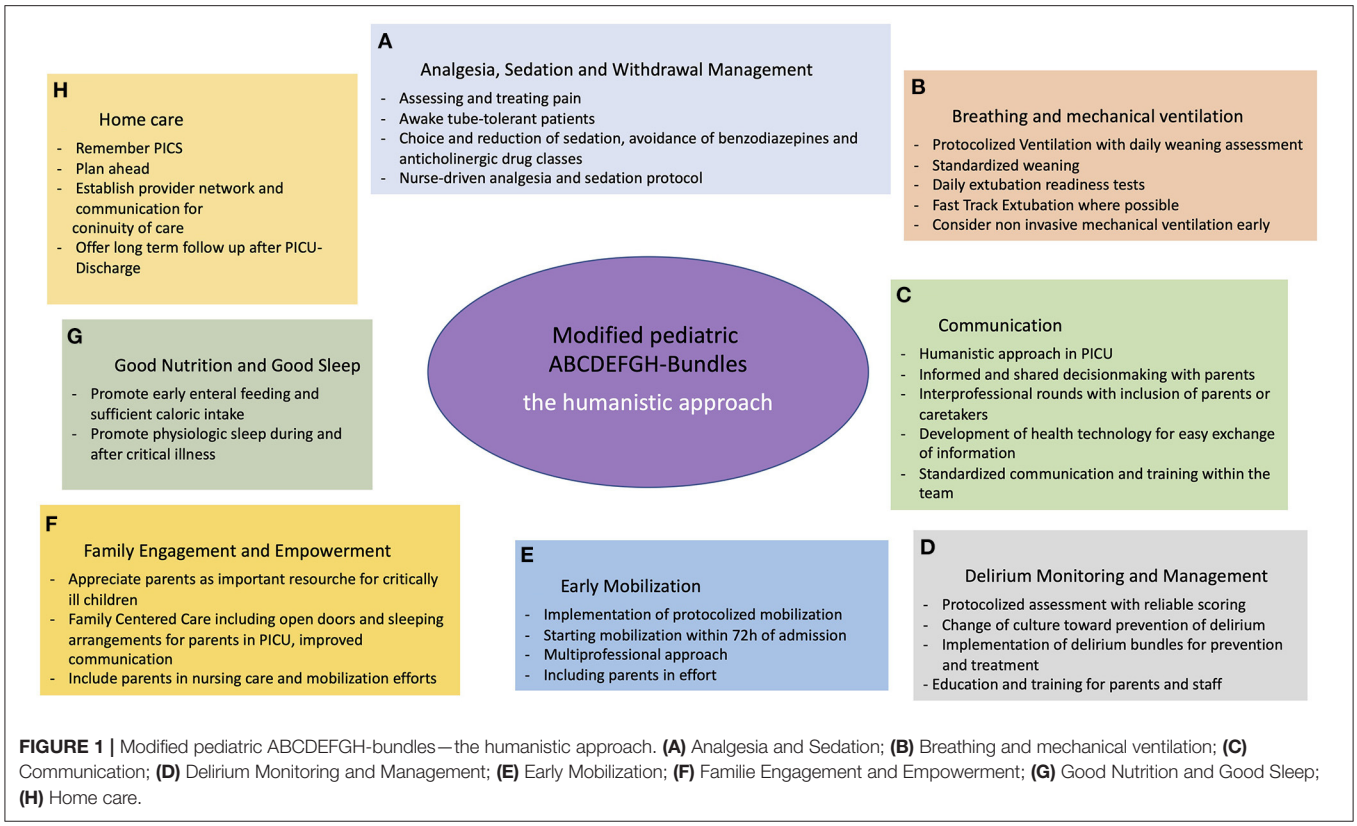

FIGURE 1 | Modified pediatric ABCDEFGH-bundles—the humanistic approach. **(A)** Analgesia and Sedation; **(B)** Breathing and mechanical ventilation; **(C)** Communication; **(D)** Delirium Monitoring and Management; **(E)** Early Mobilization; **(F)** Familie Engagement and Empowerment; **(G)** Good Nutrition and Good Sleep; **(H)** Home care.

providing a calm and dark environment for uninterrupted sleep during nighttime for all children, irrelevant of their depth of sedation (25).

For a newly minted bundle "H", however, we propose focusing on "home care," using a humanistic approach throughout all bundles (**Figure 1**). For very few patients, their illness and treatment ends with discharge from PICU. Instead, more days on other wards within the hospital are often followed by ambulatory treatment and rehabilitation, including home care services, pediatricians and specialists, physiotherapy and many more. Other than during hospital stay, most of these different aspects often have to be coordinated by parents and caregivers themselves, which is made complicated by a scarcity of providers, especially in rural areas.

Long-term problems such as PICS or PTSD are often overlooked in these situations, leaving families without necessary support and treatment.

In order to ease this burden, we propose establishing follow-up services for parents and patients including screening for the development of PICS after discharge and coordinating services for rehabilitation specialists and other long-term health care providers. Comparable with ambitions in improving communication within the PICU-setting, this presents another aspect where health related technology should be developed, providing networking possibility and simplifying communication between providers for improved continuity of care after PICU discharge.

CONCLUSION

While further studies are needed and in progress for the evaluation of long-term benefits of ABCDEF-Bundles in pediatric critical care, there is sufficient evidence for modifying existing ABCDEF-Bundles from adult care for use in children.

For all entities it is paramount to use written protocols which include scoring and daily assessment for early detection of either symptoms of withdrawal, delirium or pain as well as readiness for extubation, early mobility or other opportunities for progress without delay. Standardized interdisciplinary rounds including parents or other caregivers shorten delays in communication and provide parents with valuable information and insight in their children's illness and therefore empower them to actively participate in their improvement.

Key aspect is continuous training of all professionals involved in order to shorten time to diagnosis for both patients and families at risk for PICS and other long-term difficulties. Evidence-based findings should also be established more quickly and more comprehensively in daily routine care, keeping in mind, that successful implementation of only parts of the complete set of bundles already shows benefit for the long-term outcome and expansion of measures can occur gradually and in accordance with individual resources and recommendations from implementation sciences. The complex interaction between the elements and the fast-developing scientific evidence within the separate entities requires any health care provider in pediatric

intensive care medicine to stay up to date and adapt therapies and guidelines accordingly.

AUTHOR CONTRIBUTIONS

JE, FN, and FB wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Neonatal Pain, Opioid, and Anesthetic Exposure; What Remains in the Human Brain After the Wheels of Time?

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Objective: To evaluate possible negative long-term effects of neonatal exposure to pain, opioids and anesthetics in children and adolescents.

Study Design: We studied five unique groups of children recruited from well-documented neonatal cohorts with a history of neonatal exposure to pain, opioids or anesthetics at different points along the continuum from no pain to intense pain and from no opioid exposure to very high opioid exposure in the presence or absence of anesthetics. We evaluated children who underwent major surgery (group 1 and 2), extracorporeal membrane oxygenation (group 3), preterm birth (group 4) and prenatal opioid exposure (group 5) in comparison to healthy controls. Neuropsychological functioning, thermal detection and pain thresholds and high-resolution structural and task-based functional magnetic resonance imaging during pain were assessed. In total 94 cases were included and compared to their own control groups.

Results: Children and adolescents in groups 3 and 5 showed worse neuropsychological functioning after high opioid exposure. A thicker cortex was found in group 1 (pain, opioid and anesthetic exposure) in only the left rostral-middle-frontal-cortex compared to controls. We found no differences in other brain volumes, pain thresholds or brain activity during pain in pain related brain regions between the other groups and their controls.

Conclusions: No major effects of neonatal pain, opioid or anesthetic exposure were observed in humans 8–19 years after exposure in early life, apart from neuropsychological effects in the groups with the highest opioid exposure that warrants further investigation. Studies with larger sample sizes are needed to confirm our findings and test for less pronounced differences between exposed and unexposed children.

Keywords: brain, children, human, neuroimaging, opioids, pain, anesthesia

INTRODUCTION

Not only early exposure to anesthetics, but also pain and opioids are associated with negative outcome at least in animals (1, 2). These consist of cell death in the brain and alterations in pain sensitivity after neonatal pain and degeneration of red neurons, apoptosis in several brain regions, impaired cued fear extinction, and impaired cognitive functioning after neonatal opioid exposure (3–10). While these negative effects occurred in the absence of pain, protective effects of opioid exposure in the presence of pain are observed as well (3, 11, 12).

In humans with major congenital anomalies there is a clinical need for surgery in the neonatal period, resulting in the combination of potential pain, opioid and anesthetic exposure. However, studies on the potential long-term effects of pain, anesthetics and opioids with respect to neurodevelopment in humans are scarce and show contradictory results. Possibly because studies in children are not systematically in design and mainly investigate only very specific groups of patients such as extremely preterm born children and former newborns after thoracotomy (13, 14). To obtain a comprehensive view on the potential individual and combined effect of these factors in human, we studied five unique well-documented groups, which reflect exposure to pain, opioids and anesthetics at different points along the continuum from no pain to intense pain and from no opioid exposure to very high opioid exposure in the presence or absence of anesthetics (**Figure 1**). We hypothesize that children with a history of neonatal pain, opioid and/or anesthetic exposure will experience overall far reaching negative long-term consequences on several domains such as pain sensitivity, brain morphology, brain functioning and neuropsychological performance. We expect the most negative effects in children who received high dosages of opioids in the absence of severe pain, as suggested by animal studies.

MATERIALS AND METHODS

Patients and Methods

Ethics Approval

The study was performed at Erasmus MC in Rotterdam and was approved by the Institutional Review Board at the Erasmus MC (MEC-2010-299). Written informed consent was obtained from the parents and assent was obtained from the participants themselves. Recruitment took place from March 2011 to December 2013.

Patient Population

Cases

Participants were recruited from 5 different cohorts with a history of exposure to neonatal pain, opioids or anesthetics. All selected children were at least 8 years old at time of inclusion. We did not conduct a formal power analysis since brain activation during pain was our main outcome measure and multivariate effect estimates are in general difficult to estimate in fMRI studies. The sample size necessary to obtain adequate power for our fMRI experiment was extracted from two prior studies, which demonstrated differences for pain and brush and cold stimuli with samples containing 8 to 9 children (15, 16). However, due to collecting more groups, with the potential for greater heterogeneity, our goal was to recruit at least 15 participants per group, with each being matched with a control group.

Group 1—Giant Congenital Melanocytic Naevus

Children who required a very painful exchochleation procedure of the skin of up till 30% of their body surface area (BSA) in the first weeks of life due to a GCMN, with extreme pain and high opioid exposure (range perioperative 241-14973 mcg/kg) in combination with exposure to anesthetics during surgery and ICU admission after surgery in our hospital. Twenty-four children between 8 and 18 years of age at the moment of inclusion were eligible and invited for our study. The families of five children declined participation. Two other children had permanent braces and could not participate in the MRI study. The families of these two children chose not to participate solely in the non-MRI tests. Three children were lost to follow up. Thus, 14 GCMN children were included in this study.

Group 2—Major Surgery

The major surgery group consists of children who participated in a double blind RCT as neonate. The original study was conducted between 1995 and 1998 in Rotterdam. Eligible for the present study were 62 children who required major surgery in the first month of life [e.g. abdominal, non-cardiac thoracic (17)] with relatively lower pain intensity compared to group 1 and normal opioid exposure (cumulative dose of 10 mcg/kg/h in the first 24 h) in combination with exposure to anesthetics during surgery. Seven cases had been lost to follow-up, and 23 had a known contra-indication for participation in a neuroimaging and neuropsychological study. Thirty-two children were eligible and invited. Eight families could not be reached by phone and another 14 families declined participation, mostly because the adolescent felt not inclined. The remaining 10 cases were willing to participate and were included in our study.

Group 3—Neonatal Extracorporeal Membrane Oxygenation

For the ECMO group we invited children who as neonates had received venoarterial ECMO treatment in our hospital (18), and received high dosages of opioids for extended periods to avoid accidental ECMO decannulation, generally in the absence of major pain as ECMO cannulation should be considered as minor surgery. Of the 165 children, 44 (27%) had died. Excluded were 15 children who did not join our follow-up program, and 46 children with contra-indications for participation in a MRI study or neuropsychological assessment. The remaining 60 children were invited. Six families were not traceable and 17 declined participation. One child turned out to have permanent braces and was given the opportunity to participate in the non-MRI tests, but the family declined. The remaining 36 children were included in our study.

Abbreviations: BSA, Body surface area; ECMO, Extracorporeal membrane oxygenation; FMRI, Functional Magnetic Resonance Imaging; GCMN, Giant congenital melanocytic naevus; MRI, Magnetic Resonance Imaging; NAS, Neonatal abstinence syndrome; TSA-II, Thermal Sensory Analyzer-II.

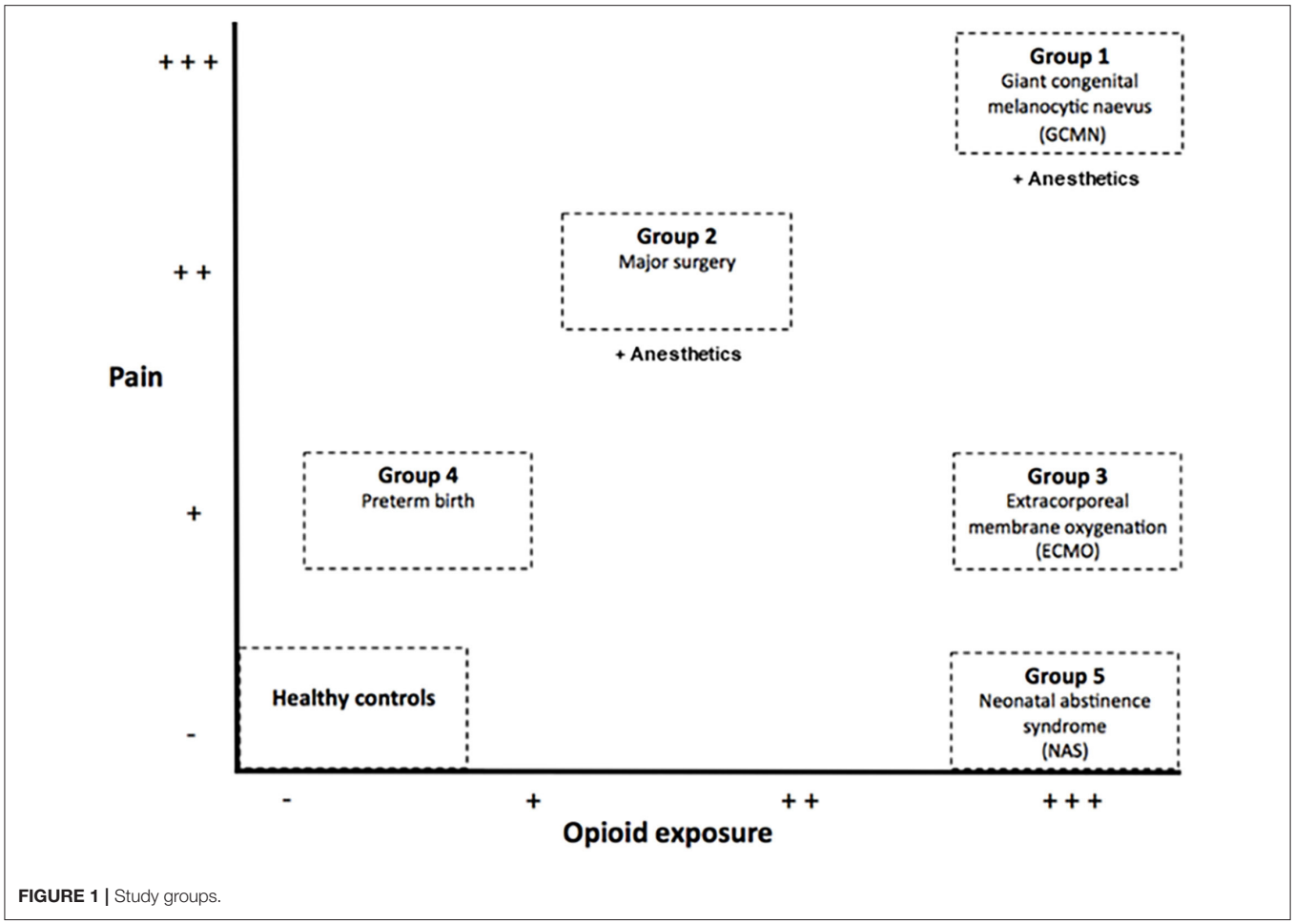

FIGURE 1 | Study groups.

Group 4—Preterm Born Children

The preterm born children were recruited from a cohort of preterm born children who at neonatal age had participated in an RCT comparing continuous infusion of morphine with placebo with repeated short periods of exposure to pain and hardly opioids (19, 20). For this specific cohort no twins or triplets were included. Twenty-two families were invited. One child was lost to follow-up and two families declined. The other 19 were included.

Group 5—Neonatal Abstinence Syndrome (NAS)

For the NAS cohort we selected children form our electronic patient system who were admitted to the Erasmus MC-Sophia Children's Hospital in Rotterdam from October 1993 to May 2005 for treatment of NAS due to prenatal exposure to opioid related substances (morphine, methadone, heroin) taken as drugs of abuse by their mothers. Eighty children were found, but one died, 17 were lost to follow-up and 19 were excluded from this study for several reasons including medical problems, such as severe hearing loss, since these children could not properly participate in the different tests. A letter with relevant information was sent to the remaining 43 cases. Of these children, 17 could not be reached by phone, and 10 cases declined participation. One case was excluded because of previously unknown intellectual disabilities. The remaining 15 cases were included (see also **Supplementary Figure 1**).

Controls

Healthy controls were recruited in two ways. First, we asked all participating families whether they could recommend someone in the age range of 8–18 years. Second, we mailed invitation letters to parents of children attending primary schools in Rotterdam. Each case group was compared to its own controls based on sampling from the total control group. Controls were selected within a comparable age range. Controls were term born children without a history of admission to a (Neonatal) Intensive Care Unit (NICU) and without neonatal opioid exposure or significant pain experience, analgesic or sedative use in the first year of life.

Exclusion Criteria

Candidates were screened for exclusion criteria and contra-indications for participation in an MRI study; brain abnormalities found on previous ultrasounds, CT, or MR scans including any grade of intraventricular hemorrhage

(IVH), periventricular leukomalacia (PVL) and subependymal cysts since brain abnormalities could possibly influence brain functioning during pain or MRI segmentation resulting in unreliable brain measures), diagnosed mental or neurologic disorders, or gross motor or sensory disabilities (such as blindness or deafness) since these children could not properly understand the procedure and brain abnormalities would influence our structural and functional MRI results. Additional exclusion criterion for children from the preterm born cohort was being a twin or triplet and for controls a history of severe early pain or intensive care admission.

Procedure

All children and adolescents were tested using a comparable systematic study design. Cases and controls first underwent a neuropsychological assessment. Subsequently, thermal detection- and pain thresholds were determined. Finally, a structural MRI scan and two task-based functional MRI scans with thermal pain stimuli were obtained.

Neuropsychological Assessment

The NEPSY-II-NL neuropsychological test was conducted in children up till 16 years of age (Pearson, Amsterdam), which is a Dutch translation of the North American NEPSY-II (21). Children between 8 and 12 years of age performed nine subtests including domains of attention and executive functioning, language, memory and learning, sensorimotor functioning, and visuospatial processing. Older participants performed only six of these subtests due to the age limit of the three other tests.

Examination of Detection and Pain Thresholds

To determine detection- and pain thresholds we used the Thermal Sensory Analyzer-II (TSA-II, Medoc Advanced Medical systems, Israel). See the **Supplementary File** for detailed information on the examination of detection and pain thresholds.

Image Acquisition and Functional MRI Block Paradigm

Detailed information on the image acquisition and functional MRI paradigm are given in the **Supplementary File** including the **Supplementary Figure 2**—Block Paradigm.

Structural Imaging Analysis

We used the FreeSurfer image analysis suite version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/) for cortical reconstruction and volumetric segmentation. See the **Supplementary File** for detailed information on the structural imaging analysis.

Functional Imaging Analysis

For functional MRI analyses (fMRI), we used a combination of Analysis of Functional Neuroimages (AFNI, http://afni.nimh.nih.gov/) (22) and FSL's FMRIB's Software Library (FSL 5.0, FMRIB Software Library; FMRIB, Functional Magnetic Resonance Imaging of the Brain; http://www.fmrib.ox.ac.uk/fsl/) (23). See the **Supplementary File** for detailed information on the functional imaging analysis.

Data Analysis

MRI analyses are described in detail in the **Supplementary File**. For the analyses on neuropsychological functioning we used the Mann-Whitney U and ANCOVA tests. For the analyses on detection- and pain thresholds we used Independent samples *T*-test for continuous and Fisher's Exact and χ^2-tests for categorical variables. We corrected for multiple testing using Bonferroni correction. Correlations between morphine exposure in our largest (ECMO) cohort were compared to detection- and pain thresholds, neuropsychological outcome, and brain volumes were determined using Spearmans' rank order correlation coefficient. A *p*-value of 0.05 or less was considered statistically significant.

Each case group was compared to its own controls. We included 5 different heterogeneous clinical case groups with differences in pain and opioid exposure. Because of the heterogeneity between the groups in, for example gestation age, age at testing and underlying disease, we did not want to make assumptions about the relationship between pain, opioid exposure and the underlying neurobiology in the pooled sample. Pooling of the groups is associated with the possible incorrect assumption that opioids and pain at different times during development and in heterogeneous groups will result in similar long-term outcomes.

RESULTS

Study Population

Background characteristics were retrieved from the medical records and are presented in **Table 1** and with more detail in the **Table 2**.

The numbers of children included per group as well as the age and gender distribution are presented in the **Table 3**. Moreover a summary of the results per outcome measure is shown in this **Table 3**.

Neuropsychological Functioning

ECMO-treated children performed statistically significantly worse on the memory task Narrative memory $p = 0.001$ (**Table 4**). Children of the NAS group performed statistically significantly worse on several domains including visiospatial, language, attention and executive functioning tests compared to controls (Geometric Puzzles $p = 0.002$; Response Set (more omission errors) $p = 0.002$, Word Generation $p = 0.002$, and Arrows $p = 0.002$; **Table 4**). Children of the Major Surgery group and the Preterm born children showed no differences compared to controls.

Detection and Pain Thresholds

No differences in pain thresholds were found between the groups compared to their control groups. With respect to detection thresholds the ECMO survivors (group 3) were less sensitive for the detection of cold compared to controls; mean (SD) cases 29.9 (1.4) vs. controls 30.6 (0.8); $P < 0.01$. Children of the GCMN (group 1), major surgery (group 2), preterm born (group 4), and NAS case groups (group 5) showed no statistically differences compared to controls.

TABLE 1 | Background characteristics per group.

(a). Group 1–GCMN ***N* = 14**		
General characteristics		
Gestational age in weeks (median, range)*		40.4 (35.3–41.6)
Birth weight (grams, median, range)*		3,540 (2,500–5,000)
Pharmacological data		
Total use of IV morphine perioperative in mcg/kg (median, range)**		2,766 (241–14,973)
Total use of IV midazolam postoperatively in mg/kg (median, range)***		9.7 (0–58)
(b). Group 2–Major surgery ***N* = 10**		
General characteristics		
Gestational age in weeks (median, range)		38.3 (33.2–41.0)
Birth weight (grams, median, range)		3,178 (2,200–4,230)
Pharmacological data		
Additional morphine administration first 24 h [*n* (%) yes]		3 (30)
Cumulative morphine dose first 24 h (μg kg^{-1} h^{-1}, median, range)		10.0 (10.0–11.2)
(c). Group 3–ECMO ***N* = 36**		
General characteristics		
Gestational age in weeks (median, range)		40 (37–43)
Birth weight in grams (median, range)		3,535 (2,300–4,985)
Pharmacological data		
Maximum morphine exposure prior to ECMO (*n,* %)*	None	2 (6)
	10 mcg/kg/h or less	16 (47)
	11–20 mcg/kg/h	12 (35)
	More than 20 mcg/kg/h	4 (12)
Maximum morphine exposure during ECMO (*n,* %)*	None	3 (9)
	10 mcg/kg/h or less	14 (41)
	11–20 mcg/kg/h	9 (26)
	More than 20 mcg/kg/h	8 (24)
Maximum morphine exposure after ECMO (*n,* %)**	None	4 (11)
	10 mcg/kg/h or less	15 (43)
	11–20 mcg/kg/h	6 (17)
	More than 20 mcg/kg/h	10 (29)
Maximum sedative exposure prior to ECMO (*n,* %)*	None	16 (47)
	0.1 mg/kg/h or less	11 (32)
	0.11–0.2 mg/kg/h	6 (18)
	More than 0.2 mg/kg/h	1 (3)
Maximum sedative exposure during ECMO (*n,* %)***	None	6 (18)
	0.1 mg/kg/h or less	11 (33)
	0.11–0.2 mg/kg/h	9 (27)
	More than 0.2 mg/kg/h	7 (21)
Maximum sedative exposure after ECMO (*n,* %)***	None	1 (3)
	0.1 mg/kg/h or less	12 (36)
	0.11–0.2 mg/kg/h	10 (30)
	More than 0.2 mg/kg/h	10 (30)
Duration of morphine exposure (%)**	<1 week	6 (17)
	1 week−1 month	25 (71)
	More than 1 month	4 (11)

(Continued)

TABLE 1 | Continued

Duration of sedative exposure (%)**	<1 week	7 (20)
	1 week–1 month	23 (66)
	More than 1 month	5 (14)
Methadone treatment in the first year of life for weaning from opioids (% yes)****		5 (14)
(d). Group 4–Preterm born children ***N* = 19**		
General characteristics		
Gestational age in weeks (median, range)		31.1 (26.1–36.3)
Birth weight (grams, median, range)		1,415 (675–2,895)
Pharmacological data		
Morphine administration (% yes)		78.9
Cumulative use of IV morphine in the first 28 days in mcg/kg (median, range)		393.6 (0–4873)
(e). Group 5–NAS *N* = 15		
Birth characteristics		
Gestational age, weeks (median, IQR)		38 (36–41)
Birth weight, in grams (median, IQR)		2,935 (2,400–3,215)
Pharmacological data		
Prenatal exposure to Methadone (*n,* %)		13 (87)
Prenatal exposure to Heroine (*n,* %)		12 (80)
Prenatal opioid exposure in combination with:	Cocaine (*n,* %) Benzodiazepines (*n,* %)	13 (87) 1 (7)
Phenobarbital treatment (*n,* %)		14 (93)

*(a). *Based on n = 8 due to missing data.*
***In 4 children the medical record was incomplete and therefore the actual morphine dose could be higher than reported.*
****In 2 children the medical record was incomplete and therefore the actual midazolam dose could be higher than reported.*
*(b). *The surgical stress score measures the severity of surgical stress in neonates and has a range from 3–22, for more information see van Dijk et al. (17).*
***Based on n = 9 since one child was removed from the original RCT after 6 h postoperatively due to incidental removal of the arterial line.*
*(c). *Based on n = 34 due to missing date.*
***Based on n = 35 due to missing data.*
****Based on n = 33 due to missing data.*
*****Methadone was started at a median age of 30 days (range 20 to 47 days) at a median daily dose of 4 mg (range 2 to 9 mg).*

Structural Imaging Results

In GCMN children (group 1) we found a significantly thicker cortex compared to controls in the left rostral-middle-frontal pole, corrected for age and gender and multiple testing and involved a region with a surface extent of 954.52 mm^2 (**Figure 2**). We found no other statistically significant differences in brain morphology in this or the other groups compared to their controls.

Differences in cortical thickness in the left hemisphere in which GCMN children (group 1) have a statistically significant thicker cortex compared to controls in the rostral-middle-frontal pole (region marked in blue).

Correlations With Morphine Exposure

With respect to morphine exposure in the ECMO cohort and the NEPSY results ($n = 22/26$ depending on the subtest), only the subtest Narrative Memory Recognition was significantly correlated (Spearman's coefficient 0.42, $p = 0.05$). No statistically significant correlations between total morphine exposure ($n = 26$) and detection thresholds (MLI and MLE), pain thresholds, or NRS scores were found. Moreover, no statistically significant correlations between total morphine exposure ($n = 16$) and brain volumes were found, and the positive and negative correlation coefficients indicated weak to moderate associations varying between <0.01 and 0.49.

Functional Imaging Results

A direct comparison of brain activation during pain in group 1 (GCMN) revealed statistically significant increased activation bilaterally in the parietal and occipital lobe in the GCMN children. After correction for gender and age the intensity of the activation was reduced in both groups and no longer significantly different. A direct comparison of statistically significant brain activation during pain in group 2 (major surgery) revealed significantly more brain activation in mainly the lateral occipital cortex in the control group compared to the case group. Due to the small sample size additional correction for age and gender was not conducted. In group 5 (NAS), a direct comparison revealed statistically significantly greater brain activation in one cluster consisting mainly of the frontal

TABLE 2 | Additional background characteristics per group.

(a). Group 1–GCMN ***N* = 14**		
Surgery		
Age at time of surgery in days (median, range)		31 (10–53)
Total body surface area in % (median, range)*		18 (5–30)
Location of the Tierfell Naevus (%)	Back	35.7
	Face or skull	28.6
	Chest and arm(s)	14.3
	Chest and leg(s)	14.3
	Legs	7.1
Postoperative phase		
Age at ICU admission in days (median, range)		31 (10–53)
Duration of ICU stay in days (median, range)		8 (2–36)
Total duration of hospital stay in days (median, range)		18 (7–46)
Postoperative need for mechanical ventilation (% yes)		64.3
Duration of mechanical ventilation in days (median, range)		6.5 (4–11)
(b). Group 2–Major surgery ***N* = 10**		
General characteristics		
Preterm born (*n*)		3
Total score surgical stress* (median, range)		8.5 (6–15)
Age at ICU admission (days, median, range)		1.5 (0–29)
Age during surgery (days, median, range)		3.5 (1–30)
Surgical diagnosis (*n*)	Diaphragmatic hernia	3
	Malrotation	2
	Oesophageal atresia	1
	Malignancy (sacrococcygeal teratoma)	1
	Bladder exstrophy	1
	Perforation of the ductus choledochus	1
	Omphalocele	1
Mechanical ventilation postoperatively (% yes)		70
(c). Group 3–ECMO ***N* = 36**		
General characteristics		
Age at ICU admission in days (median, range)		0 (0–16)
Oxygenation Index* prior to ECMO treatment (median, range)		42 (21–106)
Age at start ECMO treatment in h (median, range)		24 (5–398)
ECMO duration in h (median, range)		125 (53–369)
Duration of mechanical ventilation in days (median, range)		11 (2–70)
Surgery in the first months of life (*n,* %)		6 (17)
Diagnosis (%)	Meconium aspiration syndrome (*n,* %)	23 (64)
	Congenital diaphragmatic hernia (*n,* %)	6 (17)
	Sepsis (*n,* %)	2 (6)
	Persistent pulmonary hypertension of the newborn (*n,* %)	3 (8)
	Pneumonia (*n,* %)	1 (3)
	Other (*n,* %)	1 (3)

(Continued)

TABLE 2 | Continued

(d). Group 4–Preterm born children ***N* = 19**		
General characteristics		
Ethnicity (Western European %)		68.4
Number of painful procedures per day* (median, range)		12 (4–18)
CRIB score (median, range)		4 (0–8)
Age at ICU admission in days (days, median, range)		0 (0–0)
Duration of ICU stay in days (days, median, range)		15 (4–63)
Duration of mechanical ventilation (days, median, range)		4 (2–26)
(e). Group 5–NAS ***N* = 15**		
Birth characteristics		
Prematurely born (less than 37 weeks of gestation) (*n,* %)		4 (27%)
Apgar scores after 1 min (median, IQR)		9 (7–9)
Apgar scores after 5 min (median, IQR)		10 (9–10)
Apgar scores after 10 min (median, IQR)*		10 (10–10)
Born in our Hospital (*n,* %)		15 (100)
Intensive care admission (*n,* %)		3 (20)
Length of stay, in days (median, IQR)		17 (11–22)
NAS		
NAS (Finnegan score ≥8) (*n,* %)		14 (93)
Demographic characteristics		
West-European (*n,* %)		8 (53)
Caregiver	Adopted/foster parents (*n,* %)	13 (87)
	With relatives (grandmother) (*n,* %)	3 (23)
	Biological parents (*n,* %)	2 (13)
Education level of the child	Special primary education (*n,* %)	2 (13)
	Primary education (*n,* %)	4 (27)
	Lower vocational education (*n,* %)	5 (33)
	Intermediate vocational education (*n,* %)	3 (20)
	Higher vocational education (*n,* %)	1 (7)

*(a). *Based on n = 9 due to missing data.*
*(b). *The surgical stress score measures the severity of surgical stress in neonates and has a range from 3–22, for more information see van Dijk et al. (17).*
*(c). *Oxygenation index is a calculation to measure the fraction of inspired oxygen (FiO2) and its usage within the body.*
Based on n = 34 due to missing data.
(d). CRIB: Clinical Risk Index for Babies, IV: intravenous.
**Measured in the first 14 days, presented as mean per subject per day. Based on n = 14 due to missing data.*
(e)IQR, Interquartile range.
**Apgarscore (after 10 min) was not scored for one child.*

pole in the control group compared to the cases, but the significance disappeared after correction for age and gender (**Figure 3** and **Table 5**). We found no statistically significant differences in brain activation during pain between the ECMO group and controls. Because of poor image quality due to movement, no fMRI analyses could be conducted in the Preterm born group.

The axial slices show colored areas of activation during pain in the cases (a), the control group (b) and the direct comparison between both groups (c; cases > controls in group 1 and controls > cases in group 2 and group 5) using a cluster significance threshold of $p < 0.05$.

DISCUSSION

While previous studies focused on one specific cohort such as very preterm born children (24) or conducted a follow-up study among children exposed to very high supratherapeutic amounts of opioids (30 mcg/kg/h) (25), our study covers the continuum from no pain to intense pain and from no opioid exposure to very

TABLE 3 | Overview of background characteristics and statistically significant results per group.

	Group 1 GCMN		Group 2 Surgery		Group 3 ECMO		Group 4 PRETERM		Group 5 5 NAS	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Number of cases	*14*	*42*	*10*	*10*	*36*	*64*	*19*	*22*	*15*	*71*
Mean age at inclusion (SD)	12.3 (2.1)	11.6 (2.4)	15.5 (14.5–17.0)*	15.1 (14.0–17.0)*	11.1 (2.4)	11.1 (1.7)	10.2 (0.4)	10.4 (0.8)	14.2 (3.2)	11.7 (2.5)
% boys	64.3	52.4	80.0	60.0	47.2	43.0	68.2	68.4	26.7	42.3
Neuropsych. functioning	***Not conducted*****		**NS**		ECMO group worse on memory test		**NS**		NAS groups worse on several domains	
Results NEPSY					Lower total score on narrative memory; $p = 0.001$ $N = 28$ vs. $N = 56$				Worse performance on response set, word generation, arrows and geometric puzzles; $p = 0.002$ $N = 12$ vs. $N = 68$	
Detection/pain thresholds	**NS**		**NS**		ECMO group less sensitive for cold detection		**NS**		**NS**	
Results TSA-II					Mean cold detection (SD) EMCO 29.9 (1.4) vs. 30.6 (0.8) in controls using MLI; p<0.01 $N = 36$ vs. $N = 62$					
Structural MRI	Thicker cortex left rostral middle frontal pole in GCMN		**NS**		**NS**		**NS**		**NS**	
Results T1 MRI	Thicker cortex left rostral middle frontal pole of 954.52 mm^2, additionally corrected for age and gender $N = 13$ vs. $N = 30$									
Functional MRI	More parietal and occipital brain activation in GCMN		Less occipital brain activation in surgery group		**NS**		***Not conducted***		Less frontal brain activation in NAS group	
Results fMRI	Increased activation bilaterally in the parietal and occipital lobe $N = 10$ vs. $N = 25$		Less activation in the lateral occipital cortex $N = 10$ vs. $N = 9$						Less activation in one cluster consisting of the frontal pole $N = 9$ vs. $N = 48$	

**Data presented in median (range).*

***Due to the relatively wide age range and small sample size in this group.*

NS means no statistically significant differences between experimental cohort group and controls (after correction for multiple testing).

GCMN, giant congenital melanocytic naevus; ECMO, extracorporeal membrane oxygenation; MLI, Method of Limits; NAS, neonatal abstinence syndrome.

TABLE 4 | Neuropsychological outcome.

NEPSY-II Subtests		Group 3–ECMO			Group 5–NAS			
		ECMO *N* = 36	Controls *N* = 64	*P*-value*	NAS *N* = 12	Controls *N* = 68	*P*-value*	*P*-value**
Attention and executive functioning								
Auditory Attention median (IQR)	Commission *errors*	0 (0–0)	0 (0–0)	0.71	0 (0–2)	0 (0–0)	0.17	0.43
	Omission *errors*	0 (0–1)	0 (0–1)	0.45	0 (0–4)	0 (0–1)	0.46	0.06
	Inhibitory *errors*	0 (0–0)	0 (0–0)	0.09	0 (0–0)	0 (0–0)	0.30	0.49
Response set median (IQR)	Commission *errors*	1 (1–3)	2 (0–4)	0.82	2 (0–5)	2 (0–4)	0.40	0.18
	Omission *errors*	3 (1–6)	3 (2–5)	0.79	4 (2–6)	3 (1–5)	0.18	**0.002**
	Inhibitory *errors*	0 (0–1)	0 (0–1)	0.92	0 (0–2)	0 (0–1)	0.74	0.24
Language								
Word Generation total score, median (IQR)		32 (25–40)	35 (27–40)	0.22	30 (25–35)	35 (27–41)	0.15	**0.002**
Memory and learning								
Memory for Faces total score, median (IQR)		12 (11–13)§	12 (10–13)	0.54	12 (10–13)	12 (10–13)	0.84	0.94
Memory for Faces Delayed total score, median (IQR)		12 (10–14)	12 (10–14)	0.99	13 (9–13)	12 (10–14)	0.75	0.29
Narrative Memory§§ total score, median (IQR)	Free recall	18 (14–24)	24 (20–26)	**0.001**				
	Free and cued recall	22 (19–25)	26 (22–29)	**0.001**	25 (20–29)	26 (22–29)	0.74	0.54
	Recognition	14 (14–15)	15 (15–16)	**0.001**	15 (14–15)	15 (15–16)	0.26	0.31
Sensorimotor functioning								
Visuomotor Precision§§ *total errors*, median (IQR)		7 (1–13)	10 (4–22)	**0.05** ***	15 (5–46)	10 (4–22)	0.52	0.41
Visuospatial processing								
Arrows total score, median (IQR)		28 (26–32)	28 (26–30)	0.53	26 (20–32)	28 (26–31)	0.12	**0.002**
Geometric Puzzles total score, median (IQR)		30 (27–33)	30 (27–34)	0.58	27 (25–31)	30 (28–34)	**0.02**	**0.002**
Route Finding§§ total score, median (IQR)		9 (8–10)	9 (8–10)	0.81	8 (7–8)	9 (8–10)	**0.02**	0.33

**P-values were derived from Mann-Whitney U-test.*

***P-values were derived from ANCOVA tests adjusted for gender and age (additional analyses because of wider age range).*

****Not significant after correction for multiple testing.*

§n = 35 due to missing data in one subject.

§§ECMO n = 28 vs. n = 56 since 8 subjects in both groups conducted six subtests of the NEPSY-II (since they were older than 12 years of age), NAS; n = 6 vs. n = 56 since 6 cases and 12 controls conducted six subtests of the NEPSY-II (since they were older than 12 years of age).

The minimum and maximum scores of these subtests are: Auditory Attention commission errors: 0–180, omission errors: 0–30, inhibitory errors 0–35, Response set commission errors: 0–180, omission errors: 0–36, inhibitory errors: 0–37, Word generation: 0–no maximum, Memory for faces: 0–16, Memory for faces delayed: 0–16, Narrative memory free and cued recall: 0–34, recognition: 0–16, Visuomotor precision: 0–382, Arrows: 0–38, Geometric puzzles: 0–40, and Route finding: 0–10 points.

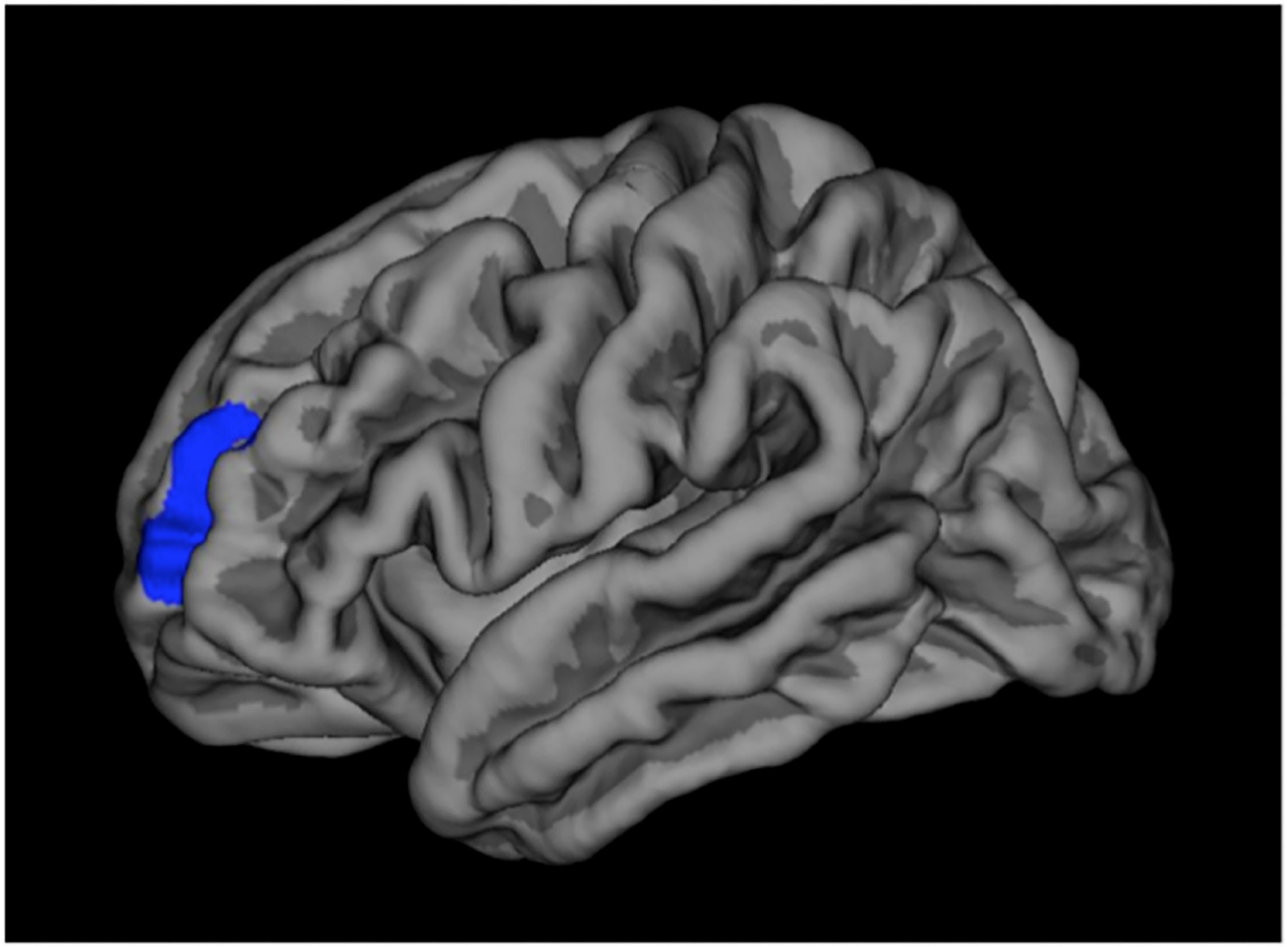

FIGURE 2 | Cortical thickness.

high opioid exposure in the presence or absence of anesthetics in five unique groups with a wide age range from children to young adults. We found no major long-term effects (between 8 to 19 years after exposure) on pain sensitivity, brain functioning during pain and brain morphology. Nevertheless, the memory performance of ECMO survivors and the neuropsychological performance of children exposed to opioids *in utero* were worse compared to controls.

Previous studies in animals suggest neurotoxic effects of early exposure to pain, opioids and anesthetics separately from each other (3–9, 26–34), while opioids were found neuroprotective if administrated in the presence of pain (3, 11, 12). Interestingly, studies in humans show contradictory results (1). Possibly since children are exposed to a combination of pain, opioids and anesthetics. In order to unravel the potential negative long-term effects of those three elements we studied the continuum from no pain to intense pain and from no opioid exposure to very high opioid exposure in the presence or absence of anesthetics in five unique study groups.

In the group of children with GCMN (group 1), extensive tissue damage (median 18% BSA) and associated intense pain in combination with very high exposure to opioids and exposure to anesthetics was associated with more parietal and occipital brain activation during pain compared to healthy controls. Less extensive tissue damage in the group children that required major non-cardiac thoracic or abdominal surgery and received usual amounts of opioids (10.0–11.2 mcg/kg/h in the first 24 postoperative h) combined with exposure to anesthetics (group 2) showed less occipital brain activation during pain compared to healthy controls. It is interesting that the differences in brain activation during pain between group 1 and 2 and their controls were not specifically located in the pain centers of the brain, but rather in sensory regions. Since primary cortical areas typically develop earlier than secondary or tertiary brain regions (35), it is possible that early exposure to pain, opioids and anesthetics resulted in activity-dependent neuronal changes in the primary and secondary sensorimotor cortical regions. We were surprised to find more brain activation in group 1 (GCMN) and less in group 2 (major surgery) in the same occipital brain region. A possible explanation could be that mean postnatal age differed between these groups during our follow-up program, but also during the moment of surgery early in life (**Table 2**).

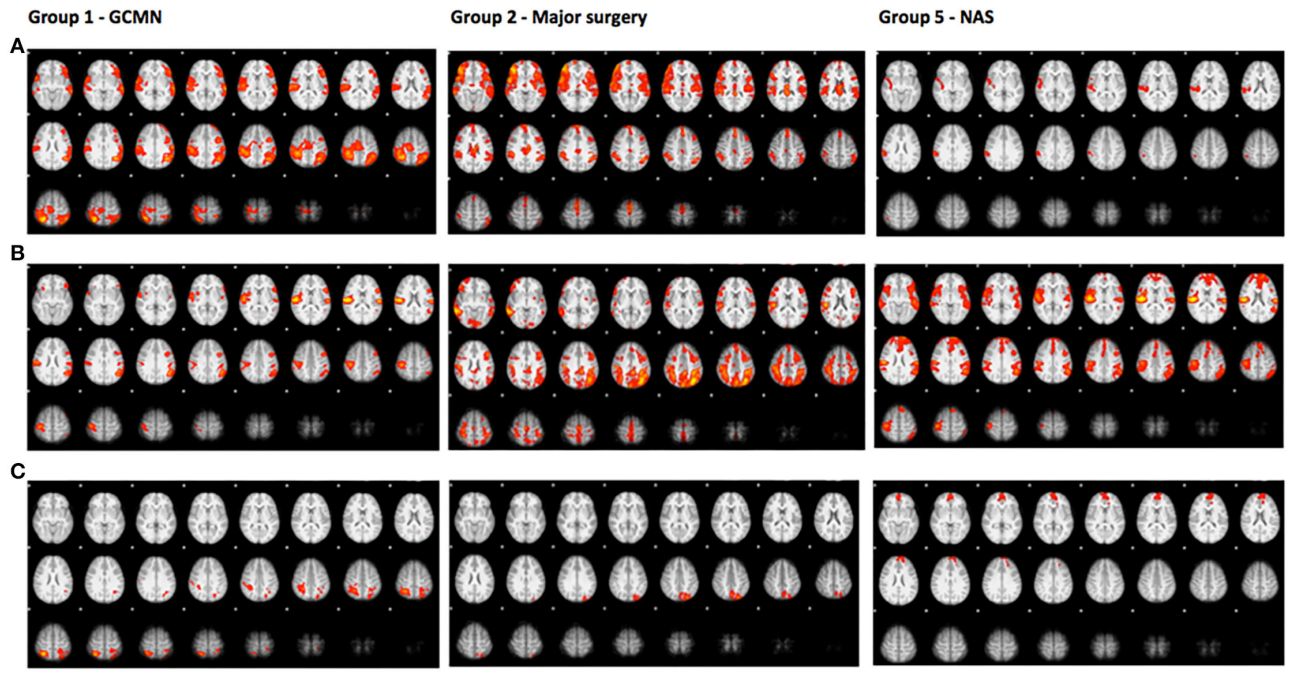

FIGURE 3 | Brain activation during pain.

Another potential explanation could be that children in group 1 experienced more breakthrough pain due to the extensive tissue damage as reflected by the high need for opioids. This difference in neonatal pain and opioid exposure could have caused the difference between groups since it is known that the effects of opioids are different when given in the absence or presence of pain, at least in rodents (3, 11, 12). Unfortunately, we only have detailed information regarding opioid exposure in the first 24 h in group 2. However, we expect the postoperative course in group 1 as more painful than group in 2 which associated higher opioid exposure in group 1. With regard to the effects of anesthetic exposure, our results are in line with the findings of the GAS study indicating that general anesthesia with sevoflurane does not alter neurodevelopmental outcome in children (36, 37).

Prolonged continuous opioid exposure in the absence of major pain, as seen in ECMO-treated newborns (group 3), induced no alterations in brain morphology. We did find hyposensitivity for cold detection, although prolonged use of opioids even in the most critically ill newborns did not result in an altered response of the central nervous system–at least as evaluated by fMRI. No statistically significant correlations between total morphine exposure and detection and pain thresholds, NRS scores, or brain volumes were found. ECMO survivors performed statistically significantly worse on specific memory subtests compared to healthy controls. When a subtest result indicates statistically significant worse functioning, the worse functioning is likely associated with clinically significant difficulties in daily life and does warrant further investigation. The findings for the ECMO group were indeed in line with our own experience at the ECMO survivors' outpatient follow-up clinic (38). The worse functioning is important from a neurodevelopmental point of view and probably unrelated to pain and opioids, although one memory subtest was significantly correlated to morphine exposure. A common neurodevelopmental pathway seems to exist across various types of neonatal critical illness, in which early hippocampal alterations result in long-term memory deficits (39). Moreover, vasoactive medication during neonatal life seems to be associated with verbal and visiospatial memory later in life, suggesting an effect of early cerebral hypoperfusion (40).

Our cohort of preterm born children exposed to low dosages of opioids in the absence of tissue damage and substantial pain (group 4) has been comprehensively studied in two other follow-up studies in our department (41, 42). In line with these two previous studies, in the present study we did not find major negative effects of prematurity, procedural pain and routine preemptive morphine administration on neuropsychological functioning. Moreover, we did not find an influence of morphine consumption on pain sensitivity, in contrast to a study by Buskila et al. in 60 preterm born children compared to 60 controls at age 12–18 years, which, however, did not report the amount of neonatal morphine exposure (43). The contrast between both studies might perhaps be explained by a higher morphine exposure in the study of Buskila et al. We found no statistically significant differences in brain volumes between preterm born children and healthy controls, indicating no major clinically relevant influence of pain and opioid exposure on brain morphology. This is in contradiction to previous studies in

TABLE 5 | Areas of activation during pain.

Cluster size (voxels)	*P*-value	MNI coordinates local maxima (mm)			*Z*-value	Anatomical area
		X	*Y*	*Z*		
Group 1–GCMN						
Mean activation cases						
16,872	<0.0001	30	−54	56	5.22	Superior parietal lobule (R)
		34	−52	62	4.94	
		38	−42	44	4.69	
		36	−64	58	4.90	Lateral occipital cortex (R)
		42	−58	56	4.61	
		58	10	−14	4.69	Temporal pole (R)
10,579	<0.0001	−40	−58	30	4.69	Angular gyrus (L)
		−48	−56	56	4.47	
		−34	−60	42	4.66	Lateral occipital cortex (L)
		−62	−16	30	4.54	Postcentral gyrus (L)
		−70	−30	4	4.46	Superior temporal gyrus (L)
		−66	−30	4	4.43	
5,355	<0.0001	−36	22	−30	3.95	Temporal pole (L)
		−52	16	−12	3.74	
		−44	6	40	3.85	Middle frontal gyrus (L)
		−52	32	0	3.79	Inferior frontal gyrus (L)
		−54	22	10	3.75	
		−46	18	10	3.70	
Mean activation controls						
6,129	<0.0001	52	−16	16	5.48	Central opercular cortex (R)
		64	−16	16	5.08	
		52	−6	10	4.58	
		44	−30	52	4.36	Postcentral gyrus (R)
		56	22	−16	4.25	Temporal pole (R)
		36	6	10	3.79	Insular cortex (R)
3,580	0.002	−58	−22	18	4.62	Central opercular cortex (L)
		−52	−48	28	4.57	Submarinal gyrus (L)
		−52	−48	36	4.23	
		−46	−58	32	4.40	Angular gyrus (L)
		−64	−54	28	3.57	
		−62	−60	38	3.44	Lateral occipital cortex (L)
2,942	0.005	−50	26	−24	3.86	Temporal pole (L)
		−46	22	−28	3.70	
		−38	10	36	3.85	Middle frontal gyrus (L)
		−50	12	50	3.83	
		−54	14	46	3.81	
		−52	18	14	3.83	Inferior frontal gyrus (L)
Direct comparison (mean cases > mean controls)						
2,807	0.006	36	−64	58	4.84	Lateral occipital cortex (R)
		26	−60	68	3.87	
		20	−64	68	3.71	
		30	−54	56	4.57	Superior parietal lobule (R)
		32	−54	62	4.35	
		26	−48	44	4.04	
2,073	0.026	−30	−72	60	3.82	Lateral occipital cortex (L)
		−28	−68	58	3.72	
		−26	−72	50	3.66	

(Continued)

TABLE 5 | Continued

Cluster size (voxels)	*P*-value	MNI coordinates local maxima (mm)			*Z*-value	Anatomical area
		X	*Y*	*Z*		
		−36	−72	56	3.54	
		−38	−48	64	3.42	Superior parietal lobule (L)
		−36	−46	68	3.40	
Group 2–Major surgery						
Mean activation cases						
21,434	<0.0001	−10	−8	24	3.92	Midline, cingulate gyrus
		−46	−52	38	3.89	Angular gyrus (L)
		−46	−50	32	3.76	
		−38	−82	−44	3.74	Cerebellum (L)
		−50	−22	−14	3.70	Middle temporal gyrus (L)
		−52	12	−12	3.63	Temporal POLE (L)
20,233	<0.0001	52	42	0	4.50	Frontal pole (R)
		40	38	−4	4.44	
		52	46	−4	4.41	
		50	40	−10	4.22	
		48	52	8	4.12	
		66	8	−2	4.13	Superior temporal gyrus (R)
Mean activation controls						
42,699	<0.0001	−36	−70	42	4.53	Lateral occipital cortex (L)
		−32	−76	38	4.25	
		66	−44	−6	4.28	Middle temporal gyrus (R)
		54	−46	−6	4.21	
		58	−48	−4	4.17	
		−48	−50	36	4.16	Supramarginal gyrus (L)
Direct comparison (mean controls > mean cases)						
1,747	0.030	−28	−80	42	3.67	Lateral occipital cortex (L)
		−22	−70	58	3.06	
		−46	−82	32	3.05	
		−36	−82	46	2.98	
		−26	−86	30	2.92	
		−2	−72	44	3.40	Precuneus cortex (L)
Group 5–NAS						
Mean activation cases						
2,767	0.013	66	−32	28	3.63	Supramarginal gyrus (R)
		60	−38	26	3.48	
		38	−6	−12	3.42	Insula (R)
		38	−14	−6	3.16	
		40	−26	18	3.40	Parietal operculum cortex (R)
		38	−16	−10	3.18	Planum polare (R)
Mean activation controls						
14,473	<0.0001	−60	−24	18	5.12	Parietal operculum cortex (L)
		−52	−48	30	4.57	Supramarginal gyrus (L)
		−52	30	−18	4.52	Frontal pole (L)
		−56	−24	−14	4.49	Middle temporal gyrus (L)
		−50	26	−22	4.38	Temporal pole (L)
		−60	−58	40	4.36	Lateral occipital cortex (L)
12,820	<0.0001	46	−18	14	6.00	Central opercular cortex (R)
		66	−16	14	4.94	
		36	6	10	4.25	

(Continued)

TABLE 5 | Continued

Cluster size (voxels)	*P*-value	MNI coordinates local maxima (mm)			*Z*-value	Anatomical area
		X	*Y*	*Z*		
		50	24	−20	4.76	Temporal pole (R)
		54	22	−18	4.74	
		70	−34	−4	4.42	Middle temporal gyrus (R)
7,226	<0.0001	−2	70	26	4.79	Frontal pole (L)
		−20	66	22	4.67	
		−2	66	30	4.62	
		−2	62	38	4.08	
		20	74	16	4.20	Frontal pole (R) Frontal pole (R)
		2	74	14	4.06	
Direct comparison (mean controls > mean cases)						
2,604	0.017	4	60	−4	3.80	Frontal pole (R)
		6	66	2	3.42	
		2	68	30	3.24	
		−6	64	28	3.52	Frontal pole (L)
		−8	68	22	3.37	
		−8	54	6	3.22	Paracingulate gyrus (L)

Areas of activation during pain (46°C vs. baseline) with cluster size, Z-values of the local maximum, Montreal Neurological Institute (MNI) coordinates, and the anatomical area of the local maximum (Harvard-Oxford Cortical Structural Atlas).
R, Right; L, Left.

preterm born morphine-exposed children that found differences in head circumference, cortical thickness, brain microstructure, and brain functioning at term-equivalent age, and in childhood (13, 16, 44–46). A possible explanation for differences between studies is that any reductions in brain volume at term-equivalent age had disappeared over time due to the inherent plasticity of the brain. Additionally, the children in our cohort had received low doses of opioids, while other cohorts were exposed to higher dosages (25).

Since animal studies describe different outcomes of opioid exposure when given in the absence or presence of pain, we added a unique group of individuals exposed to synthetic opioids *in utero* (group 5). We did not find differences between this group and healthy controls with respect to pain sensitivity or brain morphology. However, we found worse neuropsychological functioning, in line with cognitive, memory and behavioral problems in rodents after exposure to opioids in the absence of pain (7–9). This is also in line with negative behavioral and cognitive outcome in humans after opioid exposure *in utero* (47). We also found less frontal brain activity in this group during pain. The frontal brain region is associated with attention and executive functioning. Taken together, high exposure to opioids in the absence of pain appears to have the most negative effects, especially on neuropsychological functioning (ECMO group and *in utero* exposed group). However, in these particular circumstances several factors in both groups may also have contributed to worse neuropsychological outcomes, such as the illness severity in group 3 and genetic and psychosocial factors and polydrug abuse of mothers of the children in group 5. Moreover, most of the children in group 5 (93%) were exposed to phenobarbital after birth to treat the neonatal abstinence syndrome. This exposure could have influenced our results since phenobarbital is a drug with potential neurotoxic properties and has been associated with long-term behavioral problems in rats (48).

Animal studies hamper from a methodological disadvantage since the painful stimuli are not similar to those in humans, therefore animal studies using stimuli mimicking the human situation are needed (49). Moreover, experimental animals often receive supratherapeutic high dosages of drugs and mostly for prolonged periods of time and in the absence of pain (50, 51). Furthermore, the manifestation of peak synaptogenesis may occur at different periods among species, and the window of vulnerability between animals and humans may be different (52).

Our study does provide a proof-of-principle to assess the feasibility of evaluating possible long-term neurodevelopmental effects of early exposure of pain, opioids, and anesthesia. The neurodevelopmental effects can be evaluated through the examination of neuropsychological functioning, thermal detection and pain thresholds and high-resolution structural and task-based functional magnetic resonance imaging during pain. Our comprehensive follow-up study should not be considered as definitive proof due to specific limitations. Notably, while we conducted several important and feasible subtests, we did not focus on other potential long-term effects such as differences in quality of life or behavior. Our study can serve as a springboard for future studies evaluating this important topic including other relevant outcomes such as quality of life and behavior as well. Moreover, although we evaluated five unique groups of children recruited from well-documented neonatal cohorts in a systematic

way, our sample size per subgroup was relatively low. Some subgroups were underpowered and too small to draw firm conclusions on outcome. Besides, the sample size did not allow to correct for possible confounders other than age and gender. Confounders such as social economic status, nutrition, level of parental education, comorbidity or exposure to other drugs than opioids or anesthetic agents could have played a role in our findings. Since controls were recruited by asking all participating families whether they could recommend a child who would be willing to participate, selection bias is a possibility. However, we tried to overcome this by additional random recruitment from schools. Moreover, possible selection bias has occurred because children with the most severe neurological and cognitive outcomes did not participate. While most data were prospectively collected during neonatal life, some variables such as illness severity scores and length of anesthesia were not routinely collected at that time. However, the included children had all been exposed to early severe pain, opioid-related substances or anesthetics.

In conclusion, we show no major effects that remain in the human brain after neonatal pain, opioid or anesthetic exposure some 8–19 years later. We conclude that besides specific neuropsychological effects in humans that warrant further investigation, we did not detect major clinical relevant effects with respect to thermal and pain sensitivity, brain functioning during pain or brain morphology. However, future studies with larger sample sizes are needed to confirm our findings or to detect less pronounced effects of neonatal pain, opioid or anesthetic exposure. We believe that pain treatment is extremely important and that the use of low dosages opioids for procedural pain or intense pain because of major tissue damage seem not harm the brain in humans dramatically later in life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at the Erasmus MC (MEC-2010-299). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GB: literature search, recruitment, data collection, data analysis, data interpretation, writing up the first draft version of the manuscript, and approval of the final manuscript as submitted. DT: study design, data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript as submitted. JG and AL: data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript as submitted. HE: assistance in the structural imaging analyses, data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript as submitted. TW: study design, supervision of MRI data collection and analyses, data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript as submitted. MD: study design, supervision of TSA and NEPSY analyses, data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript as submitted. All authors contributed to the article 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.2022.825725/full#supplementary-material

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Italian Version of the Cornell Assessment of Pediatric Delirium: Evaluation of the Scale Reliability and Ability to Detect Delirium Compared to Pediatric Intensive Care Unit Physicians Clinical Evaluation

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Background: Delirium is an acute brain dysfunction associated with increased length of hospitalization, mortality, and high healthcare costs especially in patients admitted to the pediatric intensive care unit (PICU). The Cornell Assessment of Pediatric Delirium (CAPD) is a screening tool for evaluating delirium in pediatric patients. This tool has already been used and validated in other languages but not in Italian.

Objectives: To test the reliability of the Italian version of the CAPD to screen PICU patients for delirium and to assess the agreement between CAPD score and PICU physician clinical evaluation of delirium.

Methods: Prospective double-blinded observational cohort study of patients admitted to a tertiary academic center PICU for at least 48 h from January 2020 to August 2021. We evaluated intra- and inter-rater agreement using the Intraclass Correlation Coefficient (ICC). The ability of the scale to detect delirium was evaluated by comparing the nurses' CAPD assessments with the clinical evaluation of a PICU physician with expertise in analgosedation using the area under the ROC curve (AUC).

Measurements and Main Results: Seventy patients were included in the study. The prevalence of pediatric delirium was 54% (38/70) when reported by a positive CAPD score and 21% (15/70) when diagnosed by the PICU physician. The CAPD showed high agreement levels both for the intra-rater (ICC 1 0.98, 95% CI: 0.97–0.99) and the inter-rater (ICC 2 0.93, 95% CI: 0.89–0.96) assessments. In patients with suspected

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delirium according to the CAPD scale, the observed sensitivity and specificity of the scale were 0.93 (95% CI: 0.68–1.00) and 0.56 (95% CI: 0.42–0.70), respectively. The AUC observed was 0.75 (95% CI: 0.66–0.8490).

Conclusion: The Italian version of the CAPD seems a reliable tool for the identification of patients at high risk of developing delirium in pediatric critical care settings. Compared to the clinical evaluation of the PICU physician, the use of the CAPD scale avoids a possible underestimation of delirium in the pediatric population.

Keywords: Cornell Assessment of Pediatric Delirium, CAPD, pediatric delirium, pediatric intensive care unit, PICU

INTRODUCTION

Delirium is a common and severe neuropsychiatric complication in critically ill patients defined by the Diagnostic and Statistical Manual of Mental Disorder V (DSM-V) as a disturbance of attention and awareness which develops over a short period of time from a patient's baseline (1, 2). It may appear as hyperactive, hypoactive, and mixed subtypes. There is a large literature describing the incidence, duration, risk factors, subtypes, and outcomes of delirium in the adult population (3–5); however, the lack of use of a common diagnostic tool, the few prospective studies contributed the difficulty of interpreting the impact of the delirium on pediatric population (6, 7). Pediatric delirium has recently received increasing attention for the negative effects on critically ill children admitted to pediatric intensive care units (PICUs), among which a significantly increased length of hospitalization, mortality and high healthcare costs (8). According to a recent study, delirium incidence rates in the pediatric population are estimated to reach up to 57% of patients admitted to PICUs (9). Delirium in children can be difficult to recognize because its symptoms can fluctuate over hours and days and may be confused with those of other medical conditions (8, 10). The Cornell Assessment of Pediatric Delirium (CAPD) is a screening tool for the assessment of delirium in pediatric patients admitted to the PICU which demonstrated a good performance in children of all ages for the accurate and timely identification of delirium in this high-risk population. A recent position statement by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) recommended the use of CAPD as an instrument to assess pediatric delirium in critically ill infants and children (grade A of recommendation) (11) and its use has been implemented as a standard of care in a growing number of European centers. This tool has been translated and/or previously tested for reliability in different countries such as Japan, Portugal, Denmark, and Spain (9, 12–14). The CAPD was previously translated into Italian to guarantee linguistic equivalence to the original version (15), but its use in clinical practice has yet to be evaluated.

Therefore, the primary aim of this study was to analyze the reliability of the CAPD tool and the performance of each item of the scale. The secondary aim was to compare the CAPD results with the clinical assessment of delirium performed by PICU physicians.

MATERIALS AND METHODS

Design and Setting

The study was set up as a single-center prospective double-blinded observational cohort data collection of patients admitted to the 10-bed PICU of the academic teaching University Hospital of Padova from January 2020 to August 2021. This is a mixed PICU which admits critically ill children with medical, surgical (both general and cardiac surgery), and traumatic diseases. This study was approved by the Ethics Committee of the University Hospital of Padova (CODE CESC 4792/AO/19 and CODE URC AOP1605, 10 October 2019).

Study Population

The study enrolled pediatric patients less than 18 years old admitted to the PICU. All patients were included after a caregiver signed the informed consent. The following exclusion criteria were applied: (i) subjects whose parents were unavailable or unwilling to provide their consent; (ii) premature babies with a gestational age less than 37 weeks; (iii) subjects who were paralyzed, deeply sedated, or with a COMFORT Behavior Scale (CBS) score less than 11 (i.e., unarousable to verbal stimulation and therefore they could not be assessed for delirium); (iv) subjects with severe neurological diseases and with a Pediatric Cerebral Performance Category (PCPC) score more than 3 to reduce the risk for any bias during the assessment (16).

The Cornell Assessment for Pediatric Delirium

The CAPD is an adaptation of the Pediatric Anesthesia Emergence Delirium (PAED) (7). The tool consists of eight questions aiming to assess critically ill children who are at risk of developing delirium, and it was designed to detect the symptoms of delirium. All questions correlate with DSM-V diagnostic domains and include psychomotor symptoms as well. Every question has a score from 0 to 4 points and a range from "never" to "always," with a total score ranging from 0 to 32. A CAPD score of 9 or higher was considered as positive for the presence of delirium. The tool is associated with anchor points which indicate the development and behavior of children in different age groups.

Study Procedures

In this study, we continued the CAPD psychometric validation process after the initial translation of the scale by Simeone et al. (15) (see **Supplementary Table 1**).

The assessment of CAPD scores was conducted by two clinical nurses (rater A and rater B) with different working experiences in the PICU (rater A with more than 2 years of experience in PICU, rater B with PICU experience between one and 2 years). The child's bedside assessment was done as early as possible and when the CBS score was adequate.

The two nurses evaluated the patients using both the CBS and the Italian-CAPD:

1. Rater A performed a first and a second evaluation after a time lag of 2 min from the end of the first assessment for the intra-rater agreement;
2. Rater A and rater B performed the evaluations simultaneously in double-blind for the calculation of the inter-rater agreement.

The raters also collected data on the presence of parents, light, noise, and ongoing care activities. Each child was identified anonymously with a sequential three-digit numerical code. The results of the CAPD score were recorded in a paper Data Collection Form. All the files were collected by the nurse in charge of the study and inserted in an electronic database (Excel file) created for this study.

In this study, the final CAPD score was compared to the clinical assessment of delirium performed by two PICU physicians (MD and AA) with specific training in analgosedation who evaluated together and blinded from the nurses the patients while the nursing team was performing the CAPD score. The two physicians involved in the evaluation had more than 10 years of experience in the management of children in PICU and published more than 10 manuscripts on peer review journals on the analgosedation topic. In our setting, it was not possible to compare the CAPD score with a gold standard for delirium assessment, as it would require a child psychiatrist to confirm or reject the diagnosis of pediatric delirium (17). However, pediatric psychiatrists in our country do not have experience in PICU delirium and they are not usually involved in the care of these children. Therefore, the evaluation of delirium performed by PICU physician is considered the best delirium assessment to which we can aspire.

Outcome Measures

The primary outcome measure of the present study was to evaluate the reliability of the CAPD scale defined as follows: (1) assessment of the intra- and inter-rater agreement of the CAPD scores between the two raters; (2) evaluation of the intra- and inter-rater agreement for each of the items of which the CAPD is composed.

The secondary outcome measure was the comparison between the ability of the tool in determining delirium and the pediatric delirium assessment performed by two PICU physicians.

Sample Size

Assessment of the Intra- and Inter-Rater Agreement

The estimation problem refers to the evaluation of the concordance between the measures in terms of the Intraclass Correlation Coefficient (ICC). A moderate agreement between the measures is given by an ICC between 0.7 and 0.84. Different scenarios have been hypothesized for the calculation by varying the ICC from 0.7 to 0.9 following a step of 0.01. The approach used is that of the derivation of the ICC as suggested by Temel and Erdogan (18).

The calculation formula used is the following:

$$n = \frac{8Z^2_{1-\alpha/2}(1-\rho_{plan})^2[1+(k-1)\rho_{plan}]^2}{k(k-1)W_D^2}$$

where, $Z^2_{1-\alpha/2}$ is the percentile of the normal standard associated with an alpha level of 0.05; ρ_{plan} is the ICC hypothesized to size the study; k is the number of measurements considered, in the specific case $k = 2$; W_D is the probability of the type II error in evaluating the estimated ICC as significantly different from zero.

As highlighted in the **Supplementary Figure 1** is represented the accuracy of CAPD in predicting delirium using ROC curves, considering the PICU physician assessment as the best possible evaluation to be compared to. The black curve refers to the score cut-off of 9 while colored one's report results for different score cut-off (from 8 to 15). The AUC for different scores are also reported. The best AUC could be found for the cut-off of 8 and 9 [0.755 (95% CI: 0.688–0.821) and 0.749 (95% CI: 0.656–0.841), respectively].

Assessment of the Sensitivity and Specificity of the Tool

In order to assess the sensitivity and specificity of CAPD tool, the sample size was determined using the area under the curve (AUC) estimation. The procedure is based on the optimization of the sample size determined by defining a specific margin of error d and a confidence level 1-α. Calculation has been performed using the approach proposed by Hajian-Tilaki (19). The formula applied is the following:

$$n = \frac{Z^2_{\alpha/2}V(AUC)}{d^2}$$

In the previous equation (AUC) can be estimated as:

$$V(AUC) = (0.0099 \times e^{-\alpha^2/2}) \times (6\alpha^2 + 16)$$

where $\alpha = \varphi^{-1}(AUC) \times 1.414$ and φ^{-1} is the inverse of the standardized cumulative distribution.

Different simulation scenarios have been defined for the calculation of the sample size by setting: (i) a 95% confidence level 1-α; (ii) an accuracy level d ranging from 0.08 to 0.1; (iii) an AUC value between 0.75 and 0.85, with a 0.01 step. The optimal sample size results for the various scenarios are presented in the **Supplementary Figure 2**. The results show that a sample size of 70 patients ensures a predictive ability of 0.8 with an error in the sample estimates $d = 0.08$.

Overall, a sample size of 70 subjects ensures the identification of both outcomes.

Statistical Analysis

The descriptive analysis of the sample is reported using the median and the interquartile range (I–III quartile) for continuous variables given the non-parametric distribution and absolute numbers and percentages for categorical ones. The presence of statistically significant differences between two groups was assessed using the Wilcoxon–Kruskal–Wallis test for continuous variables and the χ^2 test for categorical ones.

The intra- and inter-rater agreement was evaluated with the ICC [and its 95% confidence interval (CI)]. The sensitivity and specificity of the scale were evaluated by the calculation of the area under the curve (AUC) with the associated 95% CI.

The value of statistical significance considered as possible evidence of a difference between groups, after adjustment of the test values for test multiplicity according to the method by Benjamini and Hochberg, is set as p of 0.05 (20).The analyses were performed using R 4.1.1 (21) with pROC package (22).

RESULTS

Cohort Descriptive Analysis

During the study period, 70 patients were enrolled with a total of 210 observations and corresponding CAPD scores reported. **Table 1** reports the demographic and baseline characteristics of the overall population of patients included and the comparison of patients based on the presence of suspected Delirium (i.e., CAPD score ≥9) according to the first nurse evaluation. Overall, 40 patients (57%) were females, the median age was 7.11 months (IQR 1.98–52.73) and 11 patients (16%) were ex-premature. Forty-one patients (59%) have been evaluated while receiving mechanical ventilation.

Patients with suspected delirium were more often male (58 vs 25%, p = 0.013) and evaluated during the analgosedation weaning process (55 vs 28%, p = 0.036). The median total

TABLE 1 | Characteristics and diagnosis of study subjects based on suspect of delirium (CAPD ≥ 9).

Characteristic	All study population (*N* = 70)	No suspect of delirium (*N* = 32)	Suspect of delirium (*N* = 38)	*p*-value
Gender, % (*n*)				0.013
Female	57% (40)	75% (24)	42% (16)	
Age, months, median (IQR)	7.11 (1.98-52.73)	11.13 (3.33-76.77)	6.13 (1.22-31.30)	0.278
Age, categories, % (*n*)				0.209
0–2 years	64% (45)	56% (18)	71% (27)	
3–5 years	11% (8)	9% (3)	13% (5)	
6–12 years	10% (7)	19% (6)	3% (1)	
13–17 years	14% (10)	16% (5)	13% (5)	
Prematurity, % (*n*)	16% (11)	12% (4)	18% (7)	0.498
PIM III at admission, median (IQR)	2.51 (1.14–5.42)	3.61 (1.20–5.94)	1.96 (1.02–4.60)	0.305
Primary diagnoses, % (*n*)				0.036
Cardiological disease	16% (11)	28% (9)	5% (2)	
Surgical	31% (22)	19% (6)	42% (16)	
Digestive	4% (3)	9% (3)	0% (0)	
Infective/inflammatory	4% (3)	3% (1)	5% (2)	
Neurological pathology	9% (6)	3% (1)	13% (5)	
Respiratory insufficiency	19% (13)	19% (6)	18% (7)	
Shock	6% (4)	3% (1)	8% (3)	
Polytrauma	1% (1)	0% (0)	3% (1)	
Other	10% (7)	16% (5)	5% (2)	
Respiratory support, % (*n*)				0.314
Non-invasive MV	20% (14)	28% (9)	13% (5)	
Invasive MV	59% (41)	47% (15)	68% (26)	
Length of ventilation (hours), median (IQR)	48. (0–138)	0 (0–78)	70 (23–191)	0.010
Use of sedation, % (*n*)				
Midazolam	49% (25)	19% (6)	50% (19)	0.009
Opiates	49% (34)	22% (7)	71% (27)	0.007
Ketamine	13% (9)	0% (0)	24% (9)	0.009
Analgosedation weaning, % (*n*)	43% (30)	28% (9)	55% (21)	0.036
Development of delirium*, % (*n*)	21% (15)	3% (1)	37% (14)	0.007

°*Patients receiving sedation and drugs type at time of CAPD assessment. *Prevalence of delirium according to physicians' evaluations.IQR, interquartile range; PIM III, Pediatric Index of Mortality Score III; MV, mechanical ventilation.*

TABLE 2 | CAPD scoring (overall and single item), intra-(ICC 1) and inter-(ICC 2) rater agreement.

	Rater A (1)	Rater B (1)	Rater A (2)	ICC 1 (95% CI)	*p*-value	ICC 2 (95% CI)	*p*-value
Overall score	10.00 (3.00–20.00)	11.50 (3.00–20.00)	10.50 (3.00–20.00)	0.98 (0.97–0.99)	<0.001	0.93 (0.89–0.96)	<0.001
Item 1 (eye contact)	1.00 (0.00–3.00)	1.00 (0.00–3.00)	1.00 (0.00–2.00)	0.95 (0.92–0.97)	<0.001	0.91 (0.86–0.94)	<0.001
Item 2 (action)	1.00 (0.00–3.00)	1.00 (0.00–3.00)	1.50 (0.00–3.00)	0.95 (0.93–0.97)	<0.001	0.87 (0.80–0.92)	<0.001
Item 3 (awareness)	1.00 (0.00–3.00)	1.00 (0.00–3.00)	1.00 (0.00–3.00)	0.94 (0.90–0.96)	<0.001	0.80 (0.70–0.87)	<0.001
Item 4 (communicate)	1.00 (0.00–3.00)	2.00 (0.00–4.00)	2.00 (0.00–3.00)	0.96 (0.94–0.98)	<0.001	0.85 (0.77–0.90)	<0.001
Item 5 (restless)	2.00 (1.00–2.00)	1.50 (1.00–2.00)	1.00 (1.00–2.75)	0.90 (0.85–0.94)	<0.001	0.85 (0.76–0.90)	<0.001
Item 6 (inconsolable)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	0.93 (0.89–0.96)	<0.001	0.84 (0.75–0.90)	<0.001
Item 7 (underactive)	1.00 (0.00–2.00)	1.00 (0.00–1.75)	0.50 (0.00–2.00)	0.92 (0.87–0.95)	<0.001	0.89 (0.83–0.93)	<0.001
Item 8 (respond)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	0.88 (0.81–0.92)	<0.001	0.70 (0.56–0.80)	<0.001

ICC 1 = Intraclass Correlation Coefficient intra-rater (rater A at time 1 and rater A at time 2); ICC 2, Intraclass Correlation Coefficient inter-rater (rater A and operator B at time 1); CI, confidence interval.

TABLE 3 | Sensitivity, specificity, PPV, and NPV according to different cut-off of the CAPD scale.

Cut-off	Apparent prevalence	PICU physician prevalence	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Original (≥9)	0.54 (0.42–0.66)	0.21 (0.13–0.33)	0.93 (0.68–1.00)	0.56 (0.42–0.70)	0.37 (0.22–0.54)	0.97 (0.84–1.00)
≥8	0.60 (0.48–0.72)	0.21 (0.13–0.33)	1.00 (0.78–1.00)	0.51 (0.37–0.65)	0.36 (0.22–0.52)	1.00 (0.88–1.00)
≥10	0.53 (0.41–0.65)	0.21 (0.13–0.33)	0.87 (0.60–0.98)	0.56 (0.42–0.70)	0.35 (0.20–0.53)	0.94 (0.80–0.99)
≥11	0.49 (0.36–0.61)	0.21 (0.13–0.33)	0.80 (0.52–0.96)	0.60 (0.46–0.73)	0.35 (0.20–0.54)	0.92 (0.78–0.98)
≥12	0.47 (0.35–0.59)	0.21 (0.13–0.33)	0.80 (0.52–0.96)	0.62 (0.48–0.75)	0.36 (0.20–0.55)	0.92 (0.78–0.98)
≥13	0.41 (0.30–0.54)	0.21 (0.13–0.33)	0.73 (0.45–0.92)	0.67 (0.53–0.79)	0.38 (0.21–0.58)	0.90 (0.77–0.97)
≥14	0.39 (0.27–0.51)	0.21 (0.13–0.33)	0.73 (0.45–0.92)	0.71 (0.57–0.82)	0.41 (0.22–0.61)	0.91 (0.78–0.97)
≥15	0.37 (0.26–0.50)	0.21 (0.13–0.33)	0.67 (0.38–0.88)	0.71 (0.57–0.82)	0.38 (0.20–0.59)	0.89 (0.75–0.96)

PPV, positive predictive value; NPV, negative predictive value; CI , confidence interval.

duration of ventilation (considering both invasive and non-invasive mechanical ventilation) was significantly higher in patients with suspected delirium (70 h, IQR 23–191 vs 0 h, IQR 0–78; $p = 0.0010$). Moreover, suspected cases received more often a sedation with midazolam ($p = 0.009$), opiates ($p = 0.007$), and ketamine ($p = 0.009$).

Intra- and Inter-Rater Agreement

Table 2 reports the concordance between the measures using the ICC. Considering the overall CAPD score, both intra-rater assessment (ICC 1 0.98, 95% CI: 0.97–0.99) and inter-rater assessment (ICC 2 0.93, 95% CI: 0.89–0.96) showed high agreement levels. Considering single item scores, only high intra-rater ICC (ICC 1) and moderate-to-high inter-rater ICC (ICC 2) have been observed. For almost all items, an inter-rater ICC 2 between 0.70 and 0.90 have been detected, except for item 1 (eye contact) which was higher (0.91, 95% CI: 0.86–0.94) and for item 3 (awareness) and 8 (respond) where a moderate inter-rater agreement was showed (item 3: ICC 2 0.80, 95% CI: 0.70–0.87 and item 8: 0.70, 95% CI: 0.56–0.80).

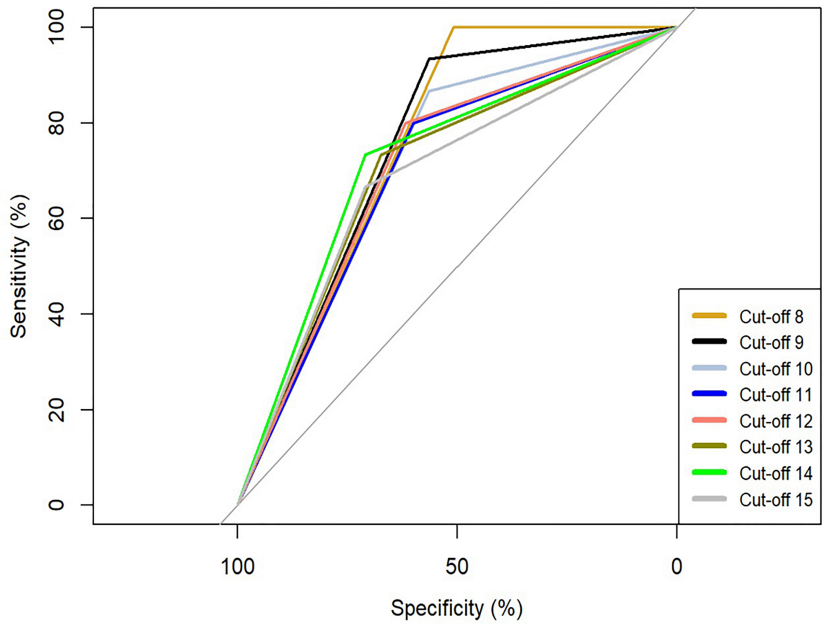
Comparison of the Cornell Assessment of Pediatric Delirium Scores With the Pediatric Intensive Care Unit Physician Assessment

About half of the study cohort has been identified as cases of suspected delirium ($n = 38$, 54%) using the CAPD score, while the prevalence of pediatric delirium in our cohort diagnosed by the clinical assessment was 21% ($n = 15$).

Overall, patients' with delirium not detected by the PICU physician were significantly younger than the rest of the population (median age 4 months, IQR 0.5–10 vs 14 months, IQR 3–119, $p = 0.003$) and received more frequently more than two sedatives than the other patients (46 vs 35%).

Table 3 shows the sensitivity and specificity according to the different cut-off of CAPD scale. Using the original cut-off of 9 of the CAPD score to identify patients with suspected delirium, the observed sensitivity and specificity of the CAPD scale were 0.93 (95% CI: 0.68–1.00) and 0.56 (95% CI: 0.42–0.70). A cut-off value of 8 for the CAPD total score provided a sensitivity of 1.00 (95% CI: 0.78–1.00), a specificity of 0.51 (95% CI: 0.37–0.65), a PPV of 0.36 (95% CI: 0.22–0.52), an NPV of 1.00 (95% CI: 0.88–1.00). Instead at the other extreme, a cut-off of 15 showed a sensitivity of 0.67 (95% CI: 0.38–0.88), a specificity of 0.71 (95% CI: 0.57–0.82), a PPV of 0.38 (95% CI: 0.20–0.59), and lastly a NPV of 0.89 (95% CI: 0.75–0.96). As the CAPD score cut-off increased, emerged a parallel raise of the specificity against sensitivity which was reduced.

In **Figure 1** is represented the accuracy of CAPD in predicting delirium using ROC curves, considering the PICU physician assessment as the best possible evaluation to be compared to. The black curve refers to the score cut-off of 9 while colored one's report results for different score cut-off (from 8 to 15). The AUC for different scores are also reported. The best AUC could be



Cut-off score	AUC (95% CI)	Cut-off score	AUC (95% CI)
8	0.755 (0.688-0.821)	**12**	0.709 (0.586-0.832)
9	0.749 (0.656-0.841)	**13**	0.703 (0.571-0.834)
10	0.715 (0.604-0.826)	**14**	0.721 (0.591-0.852)
11	0.700 (0.577-0.824)	**15**	0.688 (0.550-0.825)

FIGURE 1 | AUC for ROC curves based on different cut-off scores of CAPD tool.

found for the cut-off of 8 and 9 [0.755 (95% CI: 0.688–0.821) and 0.749 (95% CI: 0.656–0.841), respectively].

DISCUSSION

The present study describes the cross-cultural adaptation of the CAPD scale from English to Italian and highlights a good reliability of this tool and a possible underestimation of the delirium prevalence when it is evaluated clinically by PICU physicians. Our results suggest that the Italian version of the CAPD scale shows a moderate to high intra- and inter-rater agreement for all items, as according to the original CAPD study (23).

The overall prevalence of delirium was 54% according to the CAPD score screening and 21% as per the clinical evaluation of the PICU physician. Current literature describes the delirium as a frequent complication of critical illness in childhood, with a point prevalence reported up to 57% (11, 24). The prevalence of delirium as assessed by the two physicians in our population was comparable to the delirium rate reported in the original CAPD validation study (i.e., 20.6%), but lower compared with other studies which included a higher percentage of children with delirium (11, 23–26). The underestimation of the phenomenon observed in our study could be due to the physicians performing the assessment, as they were not experienced psychiatrists, as it happens instead in other European regions. In fact, in our setting, psychiatrists do not have experience in PICU delirium and they are not usually involved in the management of critically ill patients affected by this disease. Despite the large experience and expertise in analgosedation, the two PICU physicians without the support of the CAPD may have misdiagnosed some of the patients leading to a possible underrating of the real delirium prevalence. The CAPD is a tool that does not aim to diagnose delirium, but to guide physicians to recognize the symptoms of delirium and to treat early these patients. Furthermore, patients with suspected delirium who were not detected by the PICU physicians were younger and more sedated than the other patients and their diagnosis could have been dismissed by intensivists performing non-standardized assessments. These patients could be suffering hypoactive delirium which has been previously reported as being the most frequent delirium subtype and more difficult to diagnose (8, 27, 28). This issue underlines the need for a screening program training on delirium and its risk factors within the PICU staff which should involve a multidisciplinary team composed of PICU nurses, physicians, and psychiatrists.

It is interesting to note that we found the highest prevalence of delirium in children requiring ventilation and with a higher need of midazolam, opiates, and ketamine. This finding may mirror a possible higher severity of illness in this sub-group. However, it should be noted that PIM III score has been assessed only at PICU admission but not at the moment of the CAPD evaluation; therefore, despite the similar PIM III values at arrival, we cannot exclude that they were significantly different at the time of the CAPD evaluation.

Intra- and inter-rater agreement analysis shows good results, reporting ICC above 0.70 both overall and for single items. Item 3 (awareness) and item 8 (respond) demonstrated the lowest inter-rater reliability with a moderate intraclass correlation (ICC 0.87 and 0.70, respectively) which was confirmed also with the lowest intra-rater agreement for item 8 (ICC 0.88). Awareness of the surroundings is difficult to determine in critically ill children, while the response time to interaction can be influenced by countless factors. However, these two values are still above the accepted threshold for defining a good agreement between the measures (i.e., $\geq$0.7 ICC). Nevertheless, improving the agreement for these questions may be an area of clinical investigation in future studies. Conversely, in the Japanese study by Hoshino, item 6 (inconsolable) and item 7 (underactive) showed a low inter-rater correlation, 0.67 and 0.69, respectively. This could be due both to the different measure used (Cohen's *k*) and to the use of different exclusion criteria. In fact, we excluded children with severe neurological disorders to reduce further biases at the time of CAPD assessment. However, it is also important to underline that the inter-rater correlation was overall high, despite the different level of working experience of the evaluating nurses, demonstrating a good reliability of the scale.

Considering the CAPD accuracy using the AUC measurement, the Italian version demonstrated an optimal scoring cut-off point of 8, showing an area under the curve of 0.755 (95% CI: 0.688–0.821), while the AUC for the cut-off score of 9 is 0.749 (0.656–0.841). The cut-off value of 9 of the CAPD (usually used to discriminate patients at risk from those not at risk of delirium), showed a good balance between the sensitivity of the scale (which was very high, 93%) and its specificity (56%), maintaining a good false negative screen, in comparison to the other versions previously created both in English and in Japanese (23, 24). However, the cut-off point of 8 shows an even greater sensitivity, but with a further decrease in specificity (100 and 51%, respectively). Overall, CAPD appears to be an excellent screening instrument for assessing the risk of developing delirium, but it cannot be used alone as the only tool for the diagnosis of this disorder.

This study has several limitations that should be acknowledged. First, the abovementioned difference in delirium prevalence detected by the CAPD tool and the clinical evaluation can be explained by the fact that, in our setting, it was not possible to involve a psychiatrist in delirium evaluation and the assessment was performed by the PICU physician without the support of a validated tool. Indeed, the diagnosis of delirium may sometimes be difficult especially for the hypoactive subtype of patients. Furthermore, the study was conducted in a single center, possibly limiting the external validity of our results to other Italian PICUs.

CONCLUSION

The Italian version of the CAPD showed a good intra- and inter-rater reliability and a high sensitivity for the detection of delirium in PICU. CAPD should be used as a screening tool to early identify patients with a high risk of developing delirium in pediatric critical care settings in order to avoid a possible underestimation of delirium in this population. We believe this translated version of the original scale can be applied by healthcare providers in Italy. Further studies would be helpful to confirm the reliability and to explore the validity of this translated version in other Italian PICUs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University Hospital of Padova (CODE CESC 4792/AO/19 and CODE URC AOP1605, 10 October 2019). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. PF, ID'A, MM, and SF performed the material preparation and data collection. PF, MD, and AA wrote the first draft of the manuscript. RC and DG performed the data analysis. All authors commented on previous versions of the manuscript and, read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.894589/full#supplementary-material

Supplementary Figure 1 | Sample size estimated for different ICC values (alpha = 0.05, beta = 0.2).

Supplementary Figure 2 | Sample size for AUC and precision, confidence level 0.95.

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Current Knowledge Regarding Long-Term Consequences of Pediatric Intensive Care: A Staff Survey in Intensive Care Units in German-Speaking Countries

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Background: The Post Intensive Care Syndrome (PICS) describes new impairments of physical, cognitive, social, or mental health after critical illness. In recent years, prevention and therapy concepts have been developed. However, it is unclear whether and to what extent these concepts are known and implemented in hospitals in German-speaking countries.

Methods: We conducted an anonymous online survey in German-speaking pediatric intensive care units on the current state of knowledge about the long-term consequences of intensive care treatment as well as about already established prevention and therapy measures. The request to participate in the survey was sent to the heads of the PICUs of 98 hospitals.

Results: We received 98 responses, 54% of the responses came from nurses, 43% from physicians and 3% from psychologist, all working in intensive care. As a main finding, our survey showed that for only 31% of the respondents PICS has an importance in their daily clinical practice. On average, respondents estimated that about 42% of children receiving intensive care were affected by long-term consequences after intensive care. The existence of a follow-up outpatient clinic was mentioned by 14% of the respondents. Frequent reported barriers to providing follow-up clinics were lack of time and staff. Most frequent mentioned core outcome parameters were normal developmental trajectory (59%) and good quality of life (52%).

Conclusion: Overall, the concept of PICS seems to be underrepresented in German-speaking pediatric intensive care units. It is crucial to expand knowledge on long-term complications after pediatric critical care and to strive for further research through follow-up programs and therewith ultimately improve long-term outcomes.

Keywords: PICS, PICUs, critical care, long-term outcome, sequelae

INTRODUCTION

Over the last decades, there has been a significant reduction in mortality among critically ill patients. At the same time, however, the proportion of patients discharged from intensive care with therapy and disease associated long-term consequences has increased (1). The health consequences of intensive care treatment for adult patients were summarized in 2010 at a conference of the *Society of Critical Care Medicine* in physical, cognitive and mental impairments. The term "*Post Intensive Care Syndrome*" (PICS) was coined to describe this symptom complex resulting from intensive care treatment (2). This also includes frequently reported physical consequences of intensive care treatments such as *critical illness myopathy* and *polyneuropathy*, which occur together in 30–50% of cases (3) and are summarized under the term "*intensive care unit acquired weakness*." Since long-term consequences after intensive care treatment have also been demonstrated in children (4–7), the clinical picture is gaining attention in the field of pediatric intensive care medicine and is referred to as "*pediatric PICS*" (PICS-p). A concept developed by Manning et al. (8) includes four spheres that are essentially affected and relevant to health: functional impairments, cognitive impairments, losses in emotional experience, and disturbances in social life. In addition to the more frequently discussed functional impairments, pediatric patients also suffer from other long-term consequences such as post-traumatic stress disorder (PTSD), anxiety disorders, developmental deficits, and cognitive impairments (9, 10). The above-mentioned limitations are often accompanied by reductions in health-related quality of life and participation (9, 11, 12). The pathophysiology is multifactorial, due to the different modalities of intensive care treatment and partly unexplained. Particularly in childhood, the individual situation with regard to underlying diseases, but also developmental status and social environment, plays a major role in determining the course of the disease (8, 13). Since intensive care treatment often affects the family environment, which in turn has an influence on the recovery of the patients, research has been turned to affected families in recent years and the term "*PICS family*" (PICS-f) was introduced (14, 15). Due to the critical illness and sometimes long-term care of their child, families can not only reach their economic limits, but also family cohesion as well as the psychological and physical health of individual family members often suffer (16).

It remains unknown whether and to what extent PICS-p and PICS-f are known and implemented in hospitals in German-speaking countries, probably being representative for Central European countries. With a survey of pediatric intensive care units (PICUs) in German-speaking countries, we assessed the current state of knowledge about long-term consequences of intensive care treatment. The data collected will subsequently be used to expand the general body of knowledge and assess the need for further research. Our goal is to raise awareness of pediatric PICS, display its' underrepresentation, and ultimately push the development of follow-up programs.

MATERIALS AND METHODS

For data collection, we conducted an anonymous online survey in German-speaking PICUs (Germany, Austria, Swiss). For this purpose, a catalog of 27 questions was designed with the help of the survey platform LimeSurvey.[1] the questionnaire was drafted after a thorough review of the current literature. The questionnaire was reviewed by independent pediatric intensive care physicians for clarity of questions, appropriateness of responses, and ease of participation. The questionnaire contained demographic, nominal, cardinal, and open-ended questions. The translated version of the questionnaire is available as **Supplementary Material**. In addition to the characteristics of the respective intensive care units and the professional status of the respondents, individual levels of knowledge about the clinical picture, perceptions of the current situation on the units as well as obstacles regarding prevention and therapy of PICS-p and PICS-f were assessed. The weighting of individual risk factors and long-term consequences from the respondents' point of view was surveyed in order to obtain an idea of the current situation in the respective PICUs. Respondents were asked to select risk factors and outcome measures from a list and add others as appropriate. At the beginning of the questionnaire, a short definition of terms (PICS-p; PICS-f) was given.

The request to participate in the survey was sent by e-mail to the heads of the PICUs of 98 hospitals (physicians) in June of 2021: 87 hospitals in Germany, 4 hospitals in Austria, and 7 hospitals in Switzerland. Contacts were obtained through the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI). The contact list was completed by internet research on additional hospitals providing PICUs. The authors assume that the 98 PICUs contacted represent the central European PICU landscape. The heads of the intensive care units could forward the survey-link also to physicians, nursing colleagues, and psychotherapists working at the PICU. A reminder to participate was sent after 6 weeks. All responses received by October 2021 were considered. To ensure the anonymity of the survey, it was not possible to allocate the answers to the respective clinics. Only fully completed questionnaires were included in the analysis and evaluated descriptively. The survey identified the subgroups PICS-experienced and PICS-inexperienced. In order to examine these subgroups with regard to their categorial answers concerning risk factors and outcomes, the statistical calculation was carried out using the Chi-square test. PICS-inexperienced respondents were not excluded from questions on presumed risk factors or long-term outcomes. All statistical analysis were conducted using R statistical computing, version 4.0.3, 2020-10-10 for Mac Os X (Copyright (C) 2020 The R Foundation for Statistical Computing, Vienna, Austria). The study protocol and survey was approved by the Institutional Research Ethics Committee of the Technical University Dresden, Germany. Reporting of the survey was done according to the consensus guidelines for reporting survey studies (CROSS) (17).

[1] https://www.limesurvey.org/

TABLE 1 | Responder characteristics (N = 98).

	n	%
PICU type		
Pure pediatric	69	29.6
Mixed neonatal- pediatric PICU	29	70.4
Work experience		
1–5 years	16	16.3
5–10 years	21	21.4
>10 years	61	62.2
Hospital type		
University	72	73.5
Other tertiary-care hospital	16	16.3
None of both	10	10.2
PICS experienced		
Yes	30	31
No	68	69

RESULTS

Of 142 responses, 44 were excluded due to incompleteness. A total of 98 questionnaires were included in the analysis. An analysis of unit characteristics revealed that participating respondents came from at least 46 different units. The characteristics of the respondents can be found in **Table 1**.

Twenty five percent of the respondents stated that they not yet had any contact with the concept of PICS, 31% stated that PICS had a significance in their daily clinical practice. We did not exclude respondents who stated to have no experience with the concept of PICS from further questions as we believe that most clinicians are aware of the potential consequences of intensive care. The question referred to their perceptions, and we wanted to get a picture of the respondents' suspected long-term problems.

On average, respondents estimated that about 42% of children receiving intensive care were affected by PICS-p and 45% of families by PICS-f. Among the respondents' perceptions PTSD (56%), sleep disturbances (48%), feeding problems (42%), cognitive impairment (34%), and muscular weakness (20%) were the most common long-term consequences of intensive care treatment. 31% of the respondents stated that in the absence of follow-up, it was difficult to determine long-term consequences. A large proportion of respondents (43%) perceived most long-term consequences on a psychological level (**Figure 1**). **Figure 2** presents the most important measures to prevent PICS from the respondents' point of view.

The most important risk factors were found to be length of stay (56%), delirium and disorientation (53%), number of invasive procedures (28%), lack of family involvement (27%), and severity of illness (24%). The length of stay (55%) and lack of involvement in the child's care (37%) were also most frequently named as risk factors for family PICS. In addition, the tension between the remaining family at home and the child in the ICU (33%) and an insufficient transfer of information to the family (32%) were frequently identified as risk factors. There was no significant ($p < 0.05$) difference between the perceived risk factors and long-term outcomes stated by PICS-experienced and PICS-inexperienced respondents.

Fifty one percent of the respondents stated that a social history was taken on admission to the ward, 32% stated that the physical condition before admission was assessed in a standardized way. Forty percent of the respondents stated that their PICU did not collect information on social as well as physical, mental, and cognitive conditions prior to admission. Three percent of respondents reported regular and 5% irregular PICS assessments

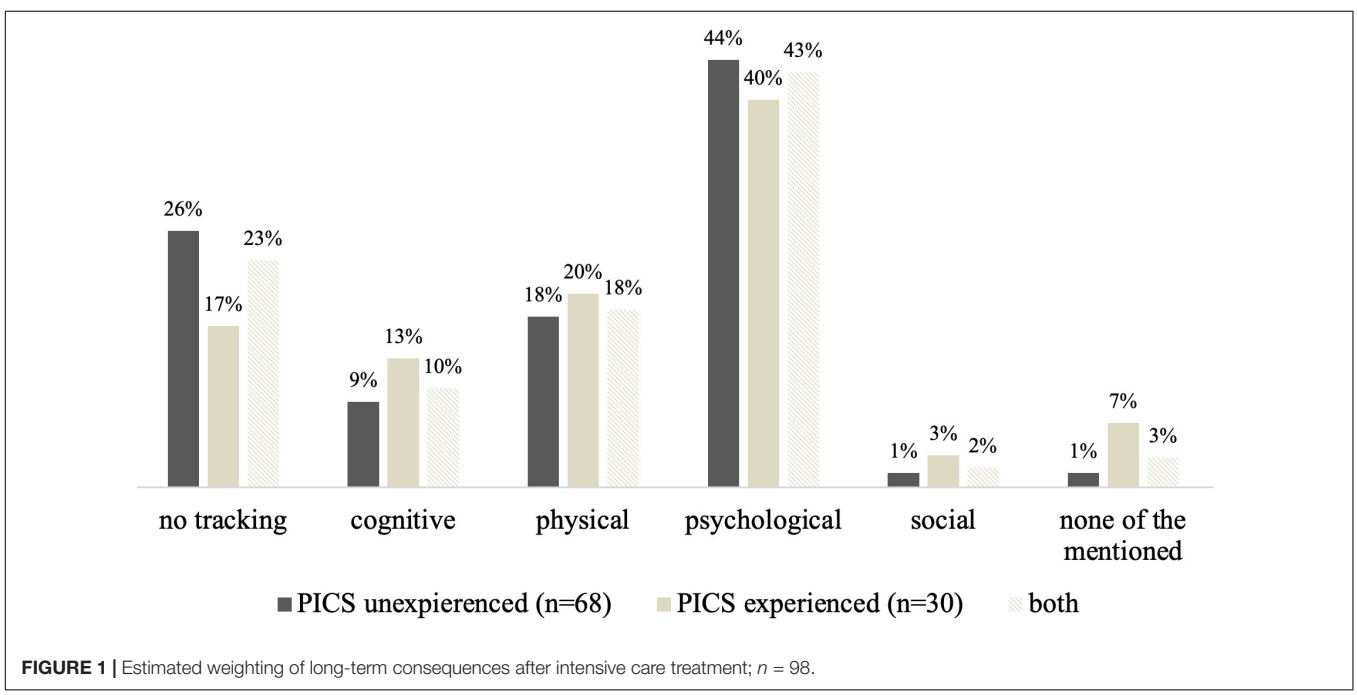

FIGURE 1 | Estimated weighting of long-term consequences after intensive care treatment; n = 98.

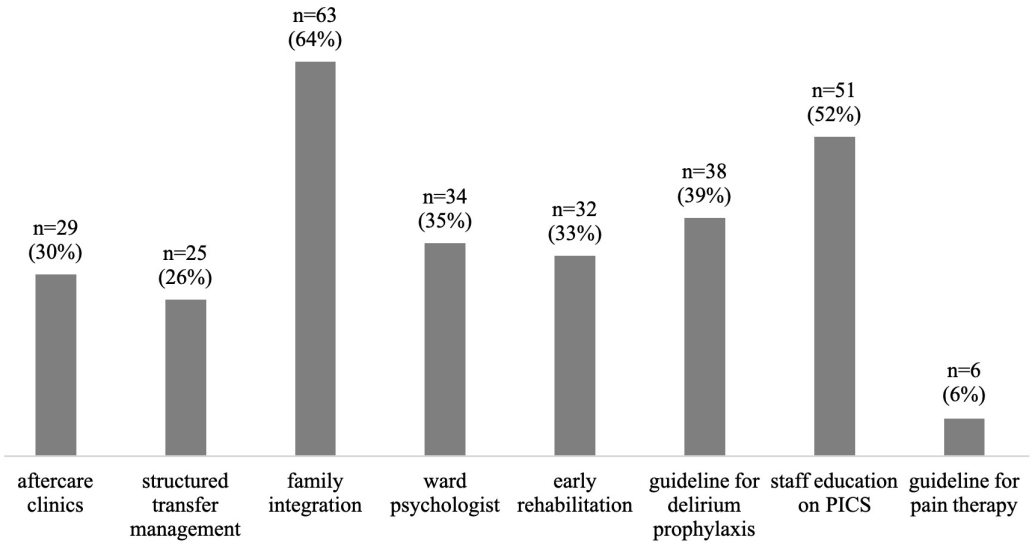

FIGURE 2 | Suitable measures (in terms of effort/benefit) to prevent PICS; *n* = 98 (multiple choice).

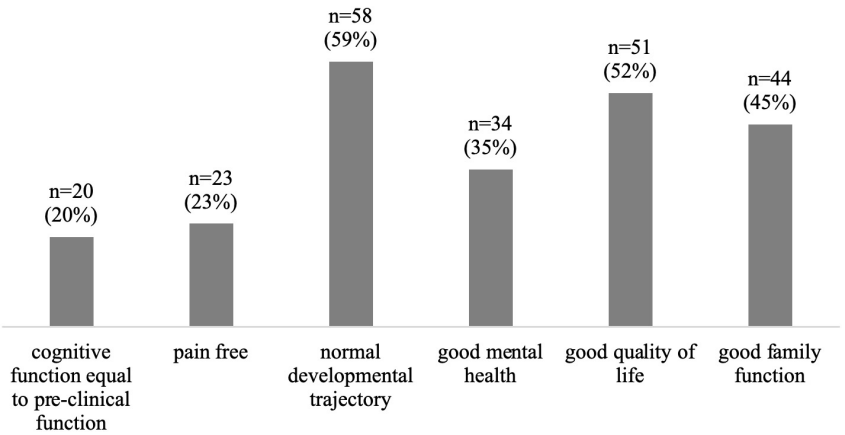

FIGURE 3 | Most frequent selected significant outcome parameters after PICU treatment; *n* = 98 (multiple choice).

at their unit. Forty two percent of the respondents stated that a standardized physical status assessment was carried out before discharge, 40% stated that the need for social support was assessed. Regular assessment of the need for further psychological support was mentioned by 36%.

Seventy percent of the respondents stated that their ward had a guideline on pain therapy, 66% had a sedation guideline, 56% had a nutrition guideline, and 42% had a guideline on delirium prophylaxis. Eight percent stated to have a guideline on family-oriented treatment and 5% stated to have an implemented guideline for increasing patient comfort. Lack of staff (66%), lack of time (64%), and lack of routine (40%) were named as the most important barriers to the regular implementation of early mobilization, 20% of the responders stated to have a guideline for early mobilization in place.

The existence of a follow-up outpatient clinic was mentioned by 14% of the respondents. A proportion of 54% of respondents said they had no follow-up program at all in their clinic. The most frequent obstacles to the implementation and regular supervision of follow-up programs were a lack of personnel (54%), a lack of awareness of its necessity (46%), and the unclear allocation of tasks between the outpatient and inpatient sectors (41%).

Normal age-appropriate development (59%), high quality of life (52%), normal family function (45%), and mental health (35%) were named as the most important parameters for measuring a therapeutic success after discharge (**Figure 3**).

DISCUSSION

The aim of this study was to assess the clinicians' awareness and knowledge on long-term consequences of pediatric intensive care therapy in childhood. A quarter of the respondents had no previous contact with the term "*Post Intensive Care Syndrome,*"

only 31% stated that PICS played a role in their daily routine. According to almost half of the respondents, the biggest barrier to the implementation of post-intensive care programs was the lack of awareness of their necessity. The occurrence of PICS-p, on the other hand, was estimated at a mean of 42%. This suggests that there is a discrepancy between the occurrence of long-term impairments and their perception and treatment. What has been shown for adults (2) has also been observed in children after critical care; 6 months after discharge 72% suffer from sleep disorders and 38% from chronic fatigue. In 75% of pediatric patients negative consequences for the health-related quality of life are observed; the PTSD rate is given at about 30% (4, 12, 18–20). About one third of the respondents stated that they lacked knowledge from follow-up to be able to make statements about long-term consequences. However, it is precisely the follow-up and research of late effects that seems to be necessary in order to develop therapy concepts and to avert negative courses (21). Knowledge about risk groups makes targeted prevention and therapy possible, not least in order to be able to use the already scarce resources sensibly (22, 23). Lack of personnel and time were named by the interviewees as the most significant hurdles for PICS prevention and therapy.

In order to assess the individual long-term course, it is not only necessary to provide follow-up care, but also to record the initial condition before intensive care treatment. Many patients already have an impairing underlying disease before their intensive care stay (7, 21, 24). About one third of pediatric patients admitted to a PICU have at least one adverse social determinant (25). Notably, poorer socioeconomic status is correlating with poorer cognitive outcome (26). In our survey, 42% of respondents reported that there was no standardized collection of baseline social, psychological or physical status at their PICU.

Only 14% percent of the respondents reported a follow-up program, this seems low but goes in line with other observations. Williams et al. found in an US focused survey on PICU follow-up programs that 35% of the responding PICUs had a program in place of which only about one quarter was broadly inclusive to a wide range of PICU patients (27). What follow-up after pediatric intensive care should look like in our health system remains unclear. Does the responsibility fall within the scope of professionals within intensive care medicine, who are familiar with the acute illness and therapy and have already gotten to know the patient in their new health condition? Or should an existing outpatient system (pediatrician, outpatient rehabilitation, psychiatrist) deal with it (28)? A feasible option in our health care system could be risk assessment and therapy planning by the staff of intensive care units to enable targeted multidisciplinary outpatient treatment, controlled by pediatricians in ambulatory care (29, 30). To our knowledge, such a system does not yet exist. From our point of view, the development and evaluation of such programs would be important to possibly improve PICS management. To make this possible, patients at-risk must be reliably identified and outcome parameters should be defined. In a Delphi study published in 2020, the following core outcome parameters after critical care were agreed upon: cognitive function, emotional function, communication, general health, painlessness, physical function, survival, and health-related quality of life (31). It should be emphasized that among the respondents of our study, the most frequently selected outcomes tend to be long-term outcomes and that general spheres such as age-appropriate development and good quality of life play an important role. This is in line with previous surveys. In a survey of 85 parents of children receiving intensive care treatment, the respondents indicated important long-term outcomes such as normal appearance and behavior as well as long-term health and lack of developmental problems in addition to short-term outcomes (32). In a survey by Merritt et al. parents and healthcare professionals were both asked about important outcomes. Again, quality of life as well as good function after leaving the hospital were most frequently mentioned by both groups (33). This definition of success of intensive care treatment beyond survival cannot be measured in the short term and in our opinion highlights the need of research in follow-up programs.

A limitation to this study was the impossibility to trace individual survey respondents. Therefore, it is assumable that some respondents work in the same hospital. Thus, we can neither provide a response rate nor can we display the data covering the entire clinical landscape, data on clinical properties can only be considered a tendency. We performed an analysis of the characteristics of the respondents and found that respondents from at least 46 different units participated in the survey. This equals a response rate of at least 47%. We cannot conclude whether this is a representative sample for the German-speaking region. It is possible that there was an over-sampling of PICUs with PICS experience, which would shed an even worse light on the level of knowledge.

Also, the answers reflect the perception of the respondents and not necessarily the practice in the respective PICUs. Because there was a lack of experience with the symptom complex of PICS-p among the respondents, we were not able to provide a sound overview of possible prevention or treatment options. Moreover, the survey has not been validated to assess for PICS management. A next goal with the emergence of new follow-up programs would be to re-survey with a validated questionnaire focusing on risk factors and outcomes as well as program feasibility and barriers. Inherent in the study design is the possibility of the occurrence of response bias. A limited generalizability of our data may be caused by the possibly more frequent survey participation of respondents from hospitals that have already dealt with PICS or have an interest in the topic.

CONCLUSION

The survey outlines a picture of current knowledge regarding *Pediatric Post Intensive Care Syndrome* in pediatric intensive care units. Overall, the concept of PICS-p and PICS-f seems to be underrepresented in German-speaking pediatric intensive care units. In contrast, long-term sequelae were observed in an average of more than 40% of the survivors. It is crucial to expand knowledge on long-term complications after pediatric

critical care and to strive for further research to develop screening tools and treatment options and therewith ultimately improve long-term outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommision der TU—Dresden Fetschstraβe 74 01307 Dresden NR: BO-EK 221042021. Consent was implied by completing the survey.

AUTHOR CONTRIBUTIONS

JE, FN, JM, and FV contributed to the study conception and design and wrote the manuscript. FH created the PICU contact list. FV performed material preparation, data collection, and analysis. All authors read and approved the final manuscript.

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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.2022.886626/full#supplementary-material

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ORIGINAL RESEARCH
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Rescue Paracetamol in Postoperative Pain Management in Extremely Low Birth Weight Neonates Following Abdominal Surgery: A Single Unit Retrospective Study

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Background: Intravenous paracetamol added to morphine reduces postoperative morphine consumption in (near)term neonates. However, there are only sparse data on intravenous paracetamol as multimodal strategy in extremely low birth weight (ELBW) neonates.

Objectives: This study aims to assess the effects of rescue intravenous paracetamol on postoperative pain management (≤48 h postoperatively) in relation to both analgesic efficacy (validated pain assessment, drug consumption, adequate rescue medication) and safety (hypotension and bradycardia). This rescue practice was part of a standardized pain management approach in a single neonatal intensive care unit (NICU).

Methods: A single-center retrospective observational study included 20 ELBW neonates, who underwent major abdominal surgery. The primary endpoints of the postoperative study period were pain intensity, over-sedation, time to first rescue analgesic dose, and the effect of paracetamol on opiate consumption. Secondary endpoints were safety parameters (hypotension, bradycardia). And as tertiary endpoints, the determinants of long-term outcome were evaluated (i.e., duration of mechanical ventilation, intraventricular hemorrhage - IVH, periventricular leukomalacia - PVL, postnatal growth restriction, stage of chronic lung disease – CLD or neurodevelopmental outcome according to Bayley-II Scales of Infant Development at 18–24 months).

Results: All neonates received continuous opioids (sufentanil or morphine) and 13/20 also intravenous paracetamol as rescue pain medication during a 48-h postoperative period. Although opioid consumption was equal in the non-paracetamol and the

paracetamol group over 48 h, the non-paracetamol group was characterized by oversedation (COMFORTneo < 9), a higher incidence of severe hypotension, and younger postnatal age ($p < 0.05$). All long-term outcome findings were similar between both groups.

Conclusions: Our study focused on postoperative pain management in ELBW neonates, and showed that intravenous paracetamol seems to be safe. Prospective validation of dosage regimens of analgesic drugs is needed to achieve efficacy goals.

Keywords: extremely low birth weight neonates, postoperative pain, COMFORTneo score, paracetamol, opioid consumption

INTRODUCTION

In 2016, a multidisciplinary ESPNIC (The European Society of Pediatric and Neonatal Intensive Care) position statement was published guiding professionals in assessing and re-evaluating treatment interventions for pain, distress, inadequate sedation, withdrawal syndrome, and delirium in the pediatric populations for various pain profiles across ages (1, 2). It is widely accepted that neonates can experience pain, and knowledge of the relevance of pain management has increased significantly over the decades (3–5). However, short-term and long-term consequences of pain management approaches remain sparse in extremely low birth weight (ELBW) infants (6–10).

Unfortunately, the treatment of ELBW neonates is still difficult at present, and setting the key endpoints in neonatal analgesic clinical trials is necessary (11, 12). First, validated pain assessment tools are crucial for targeted analgesia. However, out of 65 scores, only 37% were validated for premature neonates, and only one score (the Pain Assessment Tool) for postoperative pain in extremely premature neonates (13). Second, age-appropriate drugs and dose adjustments of analgesic drugs used to adequately treat pain are also important while a still high percentage of analgesic drugs is used in an unlicensed or off-label manner in the intensive care unit (NICU) settings (14). For postoperative pain, in neonates aged between 36 weeks gestational age (GA) and infants <1-year-old, an intermittent intravenous paracetamol dose of 10 mg/kg per 6 h resulted in a significant reduction in opioid use and exposure following non-cardiac major surgery (15).

This is, even more, the case in the specific setting of pain management in ELBW for necrotizing enterocolitis or abdominal surgery, as recently observed by ten Barge et al. (16). In their dataset on 79 preterm cases with necrotizing enterocolitis, the authors concluded that the majority experienced pain, and in some cases, this pain persisted for several hours. Based on a similar concept of using data collected during clinical care within one neonatal intensive care unit (NICU), we performed a comparative analysis and audit of postoperative pain management in ELBW neonates after abdominal surgery.

Consequently, this study aimed to evaluate the unit protocol for postoperative pain management (≤48 h) to achieve postoperative analgesic efficacy goals (e.g., validated pain scores) after major abdominal surgery in ELBW infants. This standardized local approach included the use of single-dose paracetamol as a rescue drug. We hereby documented drug utilization, effective drug dosing (pain scores within the target zone, with emphasis on rescue intravenous paracetamol) as well as safety parameters (e.g., hypotension and/or bradycardia) related to the use of analgesics and sedatives in ELBW neonates.

Abbreviations: BW, birth weight; BSID, Bayley Scales of Infant Development-BSID-II-mental (MDI) and psychomotor (PDI) developmental index; CLD, chronic lung disease; COMFORTneo, COMFORTneo scale; ELBW, extremely low birth weight; GA, gestational age; IVH, intraventricular hemorrhage; LD, loading dose; MD, maintenance dose; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; Non-P group, non-paracetamol rescue group; NRS, numeric rating scale; P group, paracetamol rescue group; PD, pharmacodynamics; PK, pharmacokinetics; PMA, postmenstrual age; PNA, postnatal age; PVL, periventricular leukomalacia; RD, rescue dose; SIP, spontaneous intestinal perforation.

METHODS

Setting and Study Population

The retrospective single unit study included ELBW neonates admitted to the Level III NICU of General University Hospital, 1st Faculty of Medicine of the Charles University in Prague, Czech Republic, who underwent acute major abdominal surgery between January 2014 and December 2019. An institutional review board (IRB) approval for publication of the study was obtained (No. 117 248/21 S-IV). The use of anonymous data for scientific purposes is part of general informed consent, which parents signed during admission to the hospital.

Inclusion criteria were birth weight (BW) <1,000 g and gestational age (GA) ≤28 weeks; abdominal surgery [e.g., laparotomy due to necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), bowel obstruction or volvulus] by postmenstrual age (PMA) ≤36 weeks.

Exclusion criteria were the refusal of an informed consent form. One of the operated patients was excluded for infaust prognosis (pan intestinal NEC) and decision of care termination at the time of surgery. Furthermore, we did not enroll the same patients undergoing the second planned operation (stoma closure), because the planned operations and the first days of postoperative care took place in another center.

Enrolled neonates were stratified into two groups according to paracetamol administration as rescue analgesic therapy: a paracetamol (P) group, $n = 13$; and a non-paracetamol (non-P)

group, $n = 7$. In all cases, a treatment period until 48 h post-surgery was assessed.

Data Collection

Demographic characteristics were collected: weeks of gestational age (GA), postmenstrual age (PMA) at surgery, birth weight (BW) and the actual body weight at surgery (g), gender (female/male), Apgar score, and diagnosis (indication for surgery).

The primary endpoints parameters were pain intensity, over-sedation, time to first rescue analgesic dose, and the effect of paracetamol on opiate consumption. Safety parameters (bradycardia <80/min; hypotension defined as a mean blood pressure of $<10^{th}$ percentile-a short episode without treatment or an episode treated with catecholamines) were the secondary endpoints of the study.

As long-term outcome parameters (tertiary endpoints) were evaluated mechanical ventilation duration, length of hospital stay, grade of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), stage of chronic lung disease (CLD); postnatal growth restriction (body weight and height $<10^{th}$ centile according to Fenton growth chart) and breastfeeding on hospital discharge; and long-term neurodevelopmental outcomes evaluated by Bayley Scales of Infant Development-BSID-II-mental (MDI) and psychomotor (PDI) developmental index-standardized in infants (cut-off values for the definition of moderate-severe neurodevelopmental delay impairment of MDI and PDI < 70).

Pain Assessment

Based on the pre-existing unit protocol for pain management, nurses assessed each neonate while resting using a COMFORTneo score at least four times per day. Additionally, the nurses monitored episodes of "obvious pain" (yes/no). The obvious pain score is a locally adapted and internally validated score that simplifies a subjective evaluation system such as the Numeric Rating Scale (NRS) for moderate and severe pain (NRS $\geq$ 4). Obvious pain assessment is a part of the nurses' daily documentation evaluated at least once every 3–6 h. COMFORTneo is a validated pain score even for very premature neonates, consisting of 6 behavioral items (alertness, calmness/agitation; crying/breathing reaction in ventilated patients; movements; muscle tone; and facial tension) (17). In our unit protocol, a target score range of 9–14 was used. A score of 14 is the cut-off value at which some non-pharmacological interventions were used to reduce discomfort (e.g., positioning, non-nutritive sucking) before increasing medication. The COMFORTneo scores below 9 in sedated neonates suggest over-sedation.

Medication Utilization

Analgesic drug dosages were based on standardized international guidelines (5, 18–20). All enrolled patients were treated with opioids (morphine or sufentanil) preoperatively because of severe abdominal disease. Moreover, opioids were given also as part of a combined general anesthesia protocol. Operative drug doses were not included in the analysis. In the postoperative period, along with continuous opioids titrated to the desired postoperative effects, paracetamol and other analgesic drugs (opioids boluses, ketamine, propofol) were administered as rescue medications.

The indication for the rescue paracetamol administration was either one event with a COMFORTneo > 14 or one observation of obvious pain, or both.

Paracetamol

Paracetamol (Paracetamol Kabi inj, 10 mg/1 mL, Fresenius Kabi s. r. o., Prague, Czech Republic) was administrated intravenously (dose 7.5 mg/kg as a single dose or every 6–8 h over 15 min). The loading dose of paracetamol was not administered at that period.

Opioids

Morphine (Morphin Biotika 1 % inj., 10 000 μg/mL, BB Pharma a. s., Prague, Czech Republic) given an initial bolus (10–40 μg/kg/ over 10 min) followed by a continuous intravenous infusion (2.5–10 μg/kg/h, a maximum dose of 20 μg/kg/h in ventilated neonates).

Sufentanil (Sufentanil Torrex 5 μg/mL inj., Chiesi Pharmaceuticals GmbH, Vienna, Austria), an initial bolus of 0.2 μg/kg administered for 10 min intravenously followed by a continuous infusion of 0.05-0.2 μg/kg/h. Sufentanil average daily dose was converted to morphine equivalents (IV sufentanil 0.1 mg = IV morphine 100 mg) (21, 22).

Other Drugs

Ketamine (Calypsol inj 50 mg/mL inj., Gedeon Richter Plc., Budapest, Hungary), given in a single dose (2–3 mg/kg).

Propofol (Propofol MCT/LCT Fresenius 10 mg/mL inj., Fresenius Kabi Deutschland GmbH, Hamburg, Germany), given in a single dose (2 mg/kg).

Statistical Analysis

Basic features were summarized by descriptive statistics such as median, interquartile range (IQR), or range of variables. Mann–Whitney (U-test) or Fisher's exact test was used to comparing patients exposed to paracetamol (P-group) to those without paracetamol (non-P group) exposure. The results are reported in the form of the median (IQR).

RESULTS

Study Population

Of the 1,277 NICU admissions during the study period 2014-2019 about 417 patients were ELBW neonates (birth weight < 1,000 g). Forty eight suffered from NEC (Modified Bell Criteria, stage ≥II), and 8 neonates were diagnosed with SIP (pneumoperitoneum on X-ray). Surgical treatment was indicated in 17 patients with NEC, 4 patients with SIP, and 1 patient with volvulus.

The characteristics of the studied population are shown in **Table 1**. Twenty ELBW neonates (11 females and 9 males), who underwent laparotomy between 2014 and 2019 were enrolled in the study. The median (IQR) birth weight was 667 (558–749) g, and the median (IQR) gestational age (GA) was 24 weeks and 5 days (24^{+1} - 25^{+2}). A statistically significant difference between the P and non-P groups was found in median PMA at the time of

TABLE 1 | Study population and outcome parameters.

Parameter	All patients ($n = 20$)	P group ($n = 13$)	Non-P group ($n = 7$)	*p*-value
Birth weight (g)[e]	667 (558–749)	660 (585–735)	675 (585–735)	0.178
Gender female/male	11/9	8/5	6/1	-
GA (weeks^{+days})[e]	24^{+5} (24^{+1}-25^{+2})	24^{+2} (24^{+0}-25^{+2})	25^{+2} (24^{+4}-25^{+6})	0.121
Apgar 1[e]	3.5 (3–6.25)	5 (3–7)	3 (2.5–3.5)	0.207
Apgar 5[e]	7 (6–8)	7 (6–8)	6 (5.5–7)	0.352
Apgar 10[e]	8 (8–9)	9 (8–9)	8 (7.5–8)	0.160
PMA (weeks^{+days})[e]	27^{+0} (26^{+3}-28^{+4})	28^{+2} (27^{+0}-30^{+0})	26^{+3} (26^{+2}-26^{+6})	**0.034**
Weight at operation (g)	730 (638–850)	745 (670–900)	650 (540–807.5)	0.178
Diagnosis NEC/SIP/bowel obstruction	$n = 15/4/1$	$n = 10/2/1$	$n = 5/2/-$	NA
Length of mechanical ventilation (days)[e]	33 (20–41)	35 (29.3–39.5)	22 (17.3–42.8)	0.383
Length of stay (days)[e]	126.5 (109–134)	126 (110–135.8)	127 (105.3–137.5)	0.202
Bradycardia < 80/min	$n = 2$	$n = 2$	$n = 0$	NA
IVH[e] (grade)	1 (0–2)	1 (0–1)	2 (0–2)	0.237
PVL[e] (grade)	0 (0–0)	0 (0–0)	0 (0–0)	0.201
PDA[e] (severity)	1 (0–1)	1 (0–1)	1 (1–1)	0.295*
Hypotension[e] (severity)	1 (0–2)	1 (0–1)	2 (2–2)	**0.012***
MDI/PDI[e] ($n = 16$)	85 (51–91)/ 79 (50–95)	83.5 (50–90)/ 72.5 (50–94)	87.5 (50–99)/ 85 (67–96)	0.855/ 0.504

P, paracetamol rescue; [e]median (interquartile range), NA, not applicable; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; PDA, persistent ductus arteriosus (0 = none, 1 = spontaneous closure, 2 = pharmacological treatment, 3 = surgery), hypotension (0 = none, 1 = bellow 10th percentile, 2=catecholamines), MDI/PDI mental/psychomotor developmental index according to Bayley II, PMA postmenstrual age, GA, gestational age; statistical testing was provided by U-test or (*) Fisher's exact test. The bold values are statistically significant values ($p < 0.05$).

TABLE 2 | Primary endpoints: COMFORTneo pain assessment in treatment groups within 48 h after surgery.

COMFORTneo scores	All patients (%)	P group (%)	Non-P group (%)	*p-value*
Time proportion in the target range (9–14)[e]	56.5 (47.5–62)	57 (44.7–62.2)	56 (51.5–6.5)	0.905
Time proportion out of the range[e]	43.5 (38–52.5)	43 (37.8–55.3)	44 (38.5–48.5)	0.905
Bellow target (<9)[e]	23.5 (0–39)	11 (0–31.3)	36 (27–43)	**0.027**
Above target (>14)[e]	12 (0–43.5)	33 (0–51.3)	8 (0–12.5)	0.190
	All patients (*n*)	**P group (*n*)**	**Non-P group (*n*)**	
COMFORTneo number of assessments per patient per day[e]	4.9	4.5	4.9	0.936

P, paracetamol rescue; [e]median (interquartile range); all statistical testing was provided by U-test.
The bold values are statistically significant values ($p < 0.05$).

surgery, in the P group at 28 weeks and 2 days (27+0 - 30+0) vs. non-P group at 26 weeks and 3 days (26+2−26+6), thus 29 vs. 8 days of postnatal age, respectively, ($p = 0.034$). The most frequent surgical diagnosis was necrotizing enterocolitis (NEC) in 15 cases, spontaneous intestinal perforation (SIP) was diagnosed in 4 cases, and bowel obstruction in 1 patient, none of the included patients died during the study period.

Primary Endpoints

Pain Assessment

All enrolled patients were scored with a COMFORTneo scale. In addition, the nurses reported "obvious pain," when the discomfort was noted. The nurses performed approximately five COMFORTneo assessments per day on each patient. During the 48-h follow-up period, 57% of the measured COMFORTneo scores were in the target range (9–14), which corresponds to 27 h of adequate pain control in the follow-up period. 23.5% of scores (12 h) corresponded to over-sedation and, conversely, insufficient pain control was reported by 12% of scores (6 h) (**Table 2**).

The non-P group had lower scores than the P group, significantly during the first 24 h after surgery ($p = 0.015$, U-test) (**Supplementary Figure S1**). The score of the non-P group (median 8) signalized over-sedation, while the P group was in the target range (median 13). A score shift was observed on

TABLE 3 | Primary endpoints: medication and pain control in treatment groups for three periods within 48 h after surgery.

Parameter	0–12 h				12–24 h			24–48 h			
	All ($n = 20$)	P group ($n = 13$)	Non-P group ($n = 7$)	*p*-value	All ($n = 20$)	P group	Non-P group	*p*-value	All ($n = 20$)	P group	Non-P group	*p*-value
Total number of drugs per patient[e]	1	2 (max. 4)	1 (max.1)	**0.003**	1.5	2 (max. 4)	1 (max. 1)	**0.017**	2	2 (max. 3)	1 (max. 2)	0.683
Opiate EqCD μg/kg per patient (n=20)[e]	2900 (186–3,950)	3350 (195–4,050)	334 (134–3,475)	0.234	2105 (150–3,685)	2870 (231–3,990)	120 (114–3,188)	0.178	570 (248–6,975)	585 (270–7,488)	376 (204–4,200)	0.476

	0–24 h				24–48 h			
	All ($n = 20$)	P group ($n = 13$)	Non-P group ($n = 7$)	*p*	All ($n = 20$)	P group	Non-P group	*p*-value
COMFORTneo score per patient[e]	9.5 (8–13)	13 (9–13.3)	8 (7–8.8)	**0.015**	12.5 (11–15)	15 (11–15.3)	12 (10.3–12)	0.161
Number of "obvious pain" episodes per patient per day[e]	2 (2.4)	2.5 (2.7)	1 (1.3)	0.221	1.7 (1.9)	2.1 (1.9)	0.9 (1.6)	0.133

P, paracetamol rescue; [e]median (interquartile range), EqCD equivalent cumulative dose od opiates - cumulative dose of morphine and morphine equivalents (μg/kg); all statistical testing was provided by U-test. The bold values are statistically significant values ($p < 0.05$).

the second postoperative day (24–48 h) when the non-P group achieved the target range, and the P group was not under adequate pain control with a median score of 15 (11-15.3). More events of obvious pain were also reported by nurses in the P group, but the difference was not statistically significant, as detailed in **Table 3**. Therefore, the bolus rescue doses (RD) of any analgesics were administered more frequently in the P group ($p < 0.017$, U-test). Intravenous paracetamol RD was indicated if COMFORTneo exceeded 14 ($n = 1$), when obvious pain was observed ($n = 6$), or both ($n = 4$). In 2 patients, paracetamol was added immediately after surgery without documented increased pain score. Accordingly, paracetamol RD was administrated in 10/13 cases although the median (IQR) COMFORTneo score was 12 (9-13.3), i.e. within the target.

The reassessment of the COMFORTneo was performed 5 (4–6) h after the RD because the patients were considered as comfortable and no obvious pain was reported. And the reassessment median score was insignificantly worse 13.9 (11-15) than the previous.

Medication Utilization

During the 48-h treatment period, all patients received continuous opioids, 13 patients (65%) received sufentanil, 12 patients (60%) morphine, 5 patients (25%) both sufentanil and morphine consecutively). Sixteen patients (80%) required an additional bolus analgesic drug to achieve sufficient pain control. The time to the first rescue dose was the median (IQR) 11.5 (3.5–24) h. Of these, 13 (81.3%) received paracetamol, 6 patients (37.5%) had ketamine, 4 patients (25%) received an additional opioid bolus and 1 patient (6.3%) propofol. The average analgesic daily dosage is shown in **Table 4**. The median for equivalent sufentanil and morphine doses (equivalent average daily dose of opiates - EqADD) did not differ between the groups (**Supplementary Figure S2**). The median paracetamol dose was 16 mg/kg/day in the cohort. According to the three postoperative periods (0–12, 12–24, and 24–48 h), the median number of drugs increased (1; 1,5; and 2 drugs, respectively) (**Table 3**).

Secondary and Tertiary Endpoints

Safety parameters such as bradycardia (<80/min) event were observed in 2 patients in the P group (10%), while no severe bradycardia was documented in the non-P group patients. In contrast, events of serious hypotension (treated with catecholamines) were more commonly documented in the non-P group ($p = 0.012$, Fisher's test) (**Table 1**).

The tertiary endpoints are shown also in **Table 1**. All determinants, such as length of mechanical ventilation, length of hospital stay, grades of IVH and PVL, stage of CLD, postnatal growth restriction, or breastfeeding on hospital discharge were not statistically different between groups. The long-term neurodevelopmental outcome according to the Bayley Scales of Infant Development-BSID-II mental (MDI) and psychomotor (PDI) developmental indexes standardized in infants aged 18–24 months has so far been evaluated in 16 (80%) of former ELWB neonates in the cohort. There was no difference between groups in the Bayley MDI and PDI developmental scales.

TABLE 4 | The average daily dose of analgesic drugs within 48 h after surgery.

Parameter	All ($n = 20$)	P group ($n = 13$)	Non-P group ($n = 7$)	*p*-value
Time to first rescue analgesia (h)[e]	11.5 (3.5–24)	8 (3.8–19.8)	31 (10–31.8)	0.350
Paracetamol ADD mg/kg per patient[e] ($n = 13$)	-	16 (7.4–25.4)	-	-
Sufentanil ADD μg/kg per patient[e]	6.1 (3–9.5) ($n = 13/20$)	7.7 (3–9.5) ($n = 9/13$)	4.9 (2–8) (n=4/7)	0.604
Morphine ADD μg/kg per patient[e]	243 (178–316) ($n = 12/20$)	280 (110–382) ($n = 8/13$)	227 (207–246) ($n = 4/7$)	0.683
Opiate EqADD μg/kg per patient[e]	3,085 (359–7,725)	3,105 (473–8,209)	403 (220–5,431)	0.178

P, paracetamol rescue; [e]median (interquartile range); ADD, average daily dose; EqADD, equivalent average daily dose of opiates - average daily dose of morphine and morphine equivalents (μg/kg); all statistical testing was provided by U-test.

DISCUSSION

The main goal of this retrospective study was to generate additional data on the efficacy of paracetamol (effects to reduce postoperative pain) and its safety in ELBW neonates following major abdominal surgery. In this specific setting, and taking the limitations of the small cohort into account, paracetamol rescue medication was associated with less oversedation, suggesting safe postoperative analgesia in this population. Other quality care indicators, such as length of invasive mechanical ventilation or length of hospital stay and long-term outcome according to Bayley II developmental indexes, IVH, PLV, and CLD were similar in both the paracetamol (P) and non-paracetamol (non-P) groups of patients. Additionally, a detailed multimodal analysis focused on identifying deficiencies in pre-existing local postoperative pain management in the neonatal intensive care unit.

According to COMFORTneo, adequate pain control was only partially achieved in patients treated with paracetamol. On the other hand, the non-paracetamol group showed oversedation together along with more severe hypotension. Interestingly, the non-P group was significantly younger at the time of the surgery (median of PNA 8 vs. 29 days, respectively) and more vulnerable as speculated. Based on a local unit protocol, the rescue dose (RD) of intravenous paracetamol was administered to eleven neonates while in two patients, RD was added to analgesic drugs "routinely." The median (IQR) COMFORTneo before the RD of paracetamol was 12 (9–13.3) within the target range but the decision to give the RD of paracetamol was based on the current situation when the neonate was considered as "uncomfortable" based on the standardized treatment protocol. The median (IQR) COMFORTneo after the RD was 13.9 (11–15), but the median (IQR) time to COMFORTneo reassessment was 5 (4–6) h after RD instead of 30–60 min as recommended in the literature because neonates were considered as "comfortable." Moreover, no episode of obvious pain after the giving rescue paracetamol at the time of the COMFORT neo reassessment was reported by nurses. Recently published data on ELBW neonates treated for pain are in line with our results and support the need for improvement of neonatal pain management in ELBW neonates (16).

It seems the use of paracetamol in the "rescue" regimen was not significant in its effects to reduce the dose of opiates or the number of other analgesic boluses administered during the study period. The possible explanations may be (1) lack of consistency of caregivers in reassessing pain scores after interventions, as the daily number of assessments was the same between groups; (2) age-related differences in opiate pharmacokinetics; and (3) possible differences in interindividual disease characteristics and developmental changes in pain perception (23). Krekels et al. presented relevant data on a population pharmacokinetic (PK) model for morphine in (pre)term neonates. In their analysis, a similar difference in rescue medication and likely morphine over-exposure was observed in neonates with PNA $<$ 10 days. By reducing 50–75% of the routine 10 μg/kg/h infusion rate, steady-state concentrations of morphine and its metabolites were achieved. On contrary, in neonates $\geq$10 days of postnatal age (PNA), the infusion rate derived from PK modeling was higher than at the traditional dose (24, 25). Age-related changes in PK (e.g., greater distribution volume, lower clearance, higher free fraction of the drug in neonates) have also been known for synthetic opioids such as sufentanil (18, 26, 27). Drug clearance is generally not only driven by maturation but also by non-maturational covariates (e.g., disease-related differences in distribution and drug elimination) (28).

Opiates have been widely used analgesic agents in neonatal intensive care units in the past few decades despite negative short-term side effects and possible long-term neurobehavioral consequences for premature individuals (29–32). In contrast, the information on paracetamol is still more limited, for example, intravenous paracetamol is effective in reducing opioid consumption in term neonates and infants (15, 33, 34). However, there is limited evidence in ELBW neonates, in whom paracetamol is still off-label, for pain, or to treat patent ductus arteriosus (35). Recent studies show that the introduction of intravenous paracetamol as part of a postoperative pain management protocol along with the education of care providers leads to improved quality of care indicators even in premature infants. (e.g., reduction of analgesic and sedative consumption, shortening of mechanical ventilation, and parenteral nutrition) (36–39). Although these studies did

not mention the usage of a loading dose of paracetamol. In our limited study population, the use of paracetamol to reduce the opioid dose was ineffective. This was probably due to inappropriate dosing and rescue analgesic medication adjustment which are unlikely to reach steady-state paracetamol concentration (40).

This study was performed to evaluate a standardized approach to postoperative pain ($\leq$48 h) to achieve postoperative analgesic efficacy and safety objectives in ELBW neonates and meant as a baseline study for internal prospective validation of postoperative analgesia conducted in this population. The limitations of this study were, for example, the design of a retrospective observational study, the small sample size, and the initial phase of scoring implementation without an adequate reliability score among the caregivers' evidence. Another limiting factor of a designed postoperative follow-up period could be the amount of medication taken before and during surgery and the possible tolerance to opiates, especially in postnatally older patients. However, the median days of continuous opiate use preoperatively and their dosing did not statistically differ between the two study groups.

Therefore, implementing appropriate age-related dosing of opioids co-administered with intravenous paracetamol, including a loading dose, and setting up an educational program to achieve the best consistency and inter-rater reliability of healthcare professionals in pain assessment methods are the main goals of the prospective study. In addition, supporting parental contributions should be part of daily clinical practice. These interventions are the future direction of our project.

CONCLUSION

The introduction of intravenous paracetamol as a rescue medication in ELBW neonates after abdominal surgery was safe analgesia, although it did not reduce opiate consumption in the rescue regimen. Prospective validation is needed to optimize postoperative analgesia according to analgesic efficacy and safety goals in this population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of General University Hospital in Prague (available at https://www.vfn.cz › odbornici › eticka-komise › informace). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HC contributed to conceptualization, data curation, investigation, methodology, and writing—original draft. LB contributed to formal analysis and visualization. BZ contributed to investigation and resources. KA contributed to supervision and writing—original draft. PP contributed to conceptualization, methodology, project administration, supervision, and writing—original draft. All authors contributed to the article 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.2022.895040/full#supplementary-material

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MINI REVIEW
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Implementation Science in Pediatric Critical Care – Sedation and Analgesia Practices as a Case Study

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Sedation and analgesia (SA) management is essential practice in the pediatric intensive care unit (PICU). Over the past decade, there has been significant interest in optimal SA management strategy, due to reports of the adverse effects of SA medications and their relationship to ICU delirium. We reviewed 13 studies examining SA practices in the PICU over the past decade for the purposes of reporting the study design, outcomes of interest, SA protocols used, strategies for implementation, and the patient-centered outcomes. We highlighted the paucity of evidence-base for these practices and also described the existing gaps in the intersection of implementation science (IS) and SA protocols in the PICU. Future studies would benefit from a focus on effective implementation strategies to introduce and sustain evidence-based SA protocols, as well as novel quasi-experimental study designs that will help determine their impact on relevant clinical outcomes, such as the occurrence of ICU delirium. Adoption of the available evidence-based practices into routine care in the PICU remains challenging. Using SA practice as an example, we illustrated the need for a structured approach to the implementation science in pediatric critical care. Key components of the successful adoption of evidence-based best practice include the assessment of the local context, both resources and barriers, followed by a context-specific strategy for implementation and a focus on sustainability and integration of the practice into the permanent workflow.

Keywords: sedation, analgesia, pediatric critical care, implementation science, barriers

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INTRODUCTION

Optimal sedation and analgesia (SA) management are critical components of care in the pediatric intensive care unit (PICU) and an essential piece of the ICU Liberation ABCDEF Bundle (1, 2). Sedative and analgesic medications are utilized in an effort to ensure safety and tolerance of the variety of invasive therapies necessary during care of the critically ill patient. Recent studies demonstrated that the long-term harm from some of these SA medications has highlighted the importance of generating high-quality evidence to guide best practices. The use of benzodiazepines, one of the mainstays of pediatric sedation management, is associated with ICU delirium and worse patient outcomes (3, 4). Overall, safe alternatives to benzodiazepines are limited, and there is a paucity of studies that could guide evidence-based recommendations for SA practices in the PICU. Furthermore, the implementation of evidence-based or consensus-driven SA practices may be impeded due to challenges related to patient heterogeneity, barriers in local culture, weak

evidence of improved patient-related outcomes, and a lack of clear implementation strategies. In this narrative mini-review, we examined 13 studies related to the implementation of SA protocols in PICUs, their study design, implementation strategies, and study outcomes. We then discussed barriers to successful implementation, a few select implementation tools, and proposed future directions for the role of implementation science (IS) in successful adoption of evidence-based SA protocols.

SEDATION AND ANALGESIA REGIMENS IN THE PEDIATRIC INTENSIVE CARE UNIT – A SUMMARY OF RECENT EVIDENCE

Several studies have examined the impact of SA regimens on clinical outcomes in critically ill infants and children over the past decade (**Table 1**) (5–16). Most of these studies were single-center studies conducted in tertiary or quaternary PICUs, i.e., a mix of cardiac, medical, and surgical patients.

A variety of outcomes were considered in these studies. Exposure to SA medications was the most common outcome assessed after the implementation of an SA regimen. Of the 13 studies included in this review, 12 (92%) studies had interventions examining initiation and titration of SA medications and 8 (62%) included a sedation/analgesia weaning protocol. In total, 11 studies (85%) demonstrated a significant reduction in either duration or total dose of opiates, benzodiazepines, or another sedative of interest. Patient-centered benefits were explored in some of the studies with variable results (5, 7, 9–14). Mechanical ventilation duration was a study outcome in 12 (92%) of the 13 studies; it was statistically significantly decreased in 2 (17%) studies, unchanged in 9 (75%), and increased in 1 (8%). The length of stay in the PICU (PICU LOS) was examined in 12 (92%) studies; 3 (50%) studies showed a decrease in PICU LOS and 9 (50%) studies showed no change.

Implementation strategies were described in 11 (85%) studies and predominantly included educational modules, visual aids, and bedside local champions. The majority of implementation strategies center around educational efforts, despite the fact that educational efforts are known to be relatively weak interventions (17). Some studies included the usage of in-person champions for just-in-time decision support, though these were temporary interventions and did not report sustained impact (6–10, 12, 18). Furthermore, although most of the studies describe their implementation strategy, in very few reports, a compliance metric demonstrating the degree of implementation success. This makes interpreting the impact of the SA protocol on the outcome difficult, as "unsuccessful" outcomes may reflect low compliance rather than ineffective intervention. Despite the fact that the majority of the studies did not demonstrate improvements in patient-centered outcomes, none of the studies analyzed the reasons why the implementation was not successful.

Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE), a multicenter unblinded cluster-randomized trial that included 31 PICUs in the United States (18), was the largest study in our review. The RESTORE study intervention consisted of standard pain, sedation and withdrawal score assessments, nurse-implemented goal-directed sedation protocol, and daily extubation readiness assessments. The primary outcome was the duration of mechanical ventilation, measured as ventilator-free days up to 28 days (VFD28). Secondary outcomes included PICU and hospital LOS, sedation-related adverse events, sedative exposure, and occurrence of iatrogenic withdrawal. Compliance with the protocol ranged from 71 to 100% depending on the study site. The primary outcome of VFD28 was not statistically significant between the intervention group and the control group.

The 2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients With Consideration of the ICU Environment and Early Mobility (PANDEM guidelines) reviewed many of these studies (2). However, given the heterogeneity of the data, the only strong recommendations related to sedation management were utilization of the comfort behavior scale (COMFORT-B) score or State Behavioral Scale to assess the level of sedation in mechanically ventilated patients and usage of dexmedetomidine as the primary sedative class specifically in critically ill pediatric post-operative cardiac surgical patients with expected early extubation. Utilization of protocolized sedation is listed as a suggestion with conditional strength and low quality of evidence.

OUTCOMES RELATED TO SEDATION-ANALGESIA PRACTICE

Providers in the PICU must find the balance between providing comfort to critically ill children who underwent invasive interventions while minimizing short- and long-term consequences of the sedative and analgesia medications. In the short term, many sedative agents may cause hypotension, bradycardia, and respiratory depression, which are managed in the PICU as anticipated adverse reactions but may prolong LOS. Furthermore, the consequences of lengthy sedation can include delirium, physical deconditioning, and ICU myopathy, which may not only prolong ICU and overall hospital LOS but also have longer-term impacts on mental health (3, 19, 20). The strong association of benzodiazepines with PICU delirium should prompt future studies of the impact of benzodiazepine-sparing regimens on PICU delirium and is one of the priorities of the PANDEM guideline (2–4). PICU delirium is a significant morbidity and a potentially modifiable factor that may impact the long-term outcomes related to a given SA protocol.

As we have reviewed, existing studies on SA protocols show promise in improving patient outcomes, though there are still gaps to address. Future directions for SA research in the PICU include optimizing study design, a focus on strategic implementation of interventions, efforts to sustain interventions over time, and inclusion of patient-centered outcomes, such as the prevalence of ICU delirium, long-term neurocognitive

TABLE 1 | Summary of recent articles examining SA interventions in pediatric ICUs.

	Authors (year), Setting	Design	Intervention (target phase)	SA regimen (medications)	Implementation	Outcome
1	Deeter et al. (7) Tertiary medical-surgical-cardiac PICU	Retrospective cohort study	Nurse-driven SA protocol (initiation, titration, wean)	1st: morphine, lorazepam 2nd: fentanyl, dilaudid, dexmedetomidine	- 1 h small group training - Daily auditing of compliance - Bedside support for first week	- Reduced duration of midazolam, morphine and lorazepam infusions - Fewer days of MV (not statistically significant)
2	Curley et al. (18) 31 United States PICUs	Unblinded multicenter cluster-randomized clinical trial	SA protocol, ERT, weaning protocol (initiation, titration, wean)	1st: morphine, midazolam 2nd: fentanyl, dexmedetomidine, propofol, clonidine, pentobarbital, ketamine	- Discipline-specific education (slide packages, pocket reminder cards, bedside booklets) - Completion of discipline-specific, scenario-based post-test	- Fewer pressure ulcers - Fewer days of opioid - Exposure to less sedative classes - Greater percentage of days with pain and agitation - No change in MV duration
3	Neunhoeffer et al. (11) Medical-surgical-cardiac PICU	Pre-post implementation study	Nurse-driven SA protocol (initiation, titration, wean)	1st: morphine or fentanyl, midazolam	- Education presentations to nursing - Bedside training with experienced study-nurse - Local nursing champions	- Reduced incidence of withdrawal - Reduced total doses of opioids and benzodiazepines
4	Neunhoeffer et al. (12) Medical-surgical-cardiac PICU	Pre-post implementation study	Nurse-driven SA and withdrawal symptoms-based protocol (initiation, titration, wean)	1st: fentanyl, midazolam 2nd: clonidine, melatonin, chloral hydrate	- Education presentations to nursing - Bedside training with experienced study-nurse - Local champions available daily	- Reduced total daily dose of benzodiazepines - Reduced rate of withdrawal symptoms - No change in PICU LOS, MV duration or total daily dose of opioids
5	Dreyfus et al. (10) Medical-surgical PICU	Pre-post implementation study	Nurse-driven SA protocol (initiation, titration, wean)	1st: sufentanil 2nd: midazolam, ketamine	- 1 h training sessions - Local champions available daily	- Reduced MV duration for surgical patients - Increased COMFORT-B scores per day
6	Gaillard-Le Roux et al. (16) Medical-surgical PICU	Pre-post implementation study	Nurse-driven SA protocol (initiation, titration)	1st: midazolam, morphine or sufentanil 2nd: ketamine, clonidine	- Visual displays of protocol - Staff trainings	- No change in MV duration overall, but appeared decreased in patients older than 12 months - No difference in daily drug dose - Increased comfort assessments
7	Larson and McKeever (15) Tertiary medical-surgical-cardiac PICU	Retrospective chart review	Nurse-driven SA protocol (initiation, titration)	1st: morphine, clonidine 2nd: midazolam Other: fentanyl, dexmedetomidine, propofol	(not described)	- Increase in pain assessments - Reduction in midazolam administration - Increased duration of MV

(Continued)

TABLE 1 | (Continued)

	Authors (year), Setting	Design	Intervention (target phase)	SA regimen (medications)	Implementation	Outcome
8	Amirnovin et al. (9) Tertiary cardiac PICU and acute ward	Pre-post implementation study	Opioid and benzodiazepine protocol (wean)	1st: methadone, hydromorphone, lorazepam	- Educational lectures - Mandatory post-education testing - "Just-in-time" education	- Shorter duration of opioids and benzodiazepines - Decrease in withdrawal occurrence - Reduction in hospital LOS
9	Donnellan et al. (8) Tertiary cardiac PICU	QI PDSA cycles with SPC charts	Comfort-guided SA protocol (initiation, titration, wean)	1st: morphine, dexmedetomidine 2nd: lorazepam	- Bedside review with nurse prior to patient admission	- Decreased opioid infusion rates - Near-eliminated benzodiazepine infusions - No change in MV duration or PICU LOS
10	Sanavia et al. (14) Tertiary PICU	Prospective observational study	SA drug rotation protocol (initiation, titration, wean)	1st: fentanyl, midazolam, clonidine rescue 2nd: ketamine, propofol, metamizole rescue 3rd: remifentanil, midazolam, clonidine rescue 4th: metamizole, dexmedetomidine, morphine rescue	- Training sessions and review sessions for all PICU staff over 15 days	- Lower incidence of withdrawal syndrome - Shorter PICU LOS - Less time of opioid, benzodiazepine and propofol infusion
11	Hanser et al. (5) Tertiary cardiac PICU	Retrospective observational study	Nurse-driven SA protocol (initiation, titration, wean)	1st: morphine, midazolam 2nd: clonidine, melatonin, chloral hydrate	(not described)	- Reduced PICU LOS - Reduced midazolam and morphine exposure - No change in MV duration
12	Yang et al. (6) Quaternary PICU	Pre-post implementation study	SA protocol (initiation, titration)	1st: morphine, dexmedetomidine 2nd: lorazepam or midazolam	- Virtual educational modules with mandatory post-education test - Visual aids, educational lectures, bedside teaching	- Reduced dose and duration of midazolam - No change in PICU LOS or MV duration
13	Shildt et al. (13) Quaternary PICU	Retrospective cohort study	SA protocol (initiation, titration)	1st: morphine or fentanyl, dexmedetomidine 2nd: hydromorphone 3rd: midazolam or lorazepam	- Multidisciplinary training sessions	- Decreased opioid withdrawal and need for methadone - Decreased MV duration - Decreased PICU and hospital LOS

PICU, pediatric intensive care unit; SA, sedation-analgesia; LOS, length of stay; MV, mechanical ventilation; ERT, extubation readiness testing; QI, quality improvement; PDSA, plan-do-study-act; SPC, statistical process control.

function, and behavioral health issues. A study examining long-term neurocognitive outcomes after ICU discharge is currently being designed by the RESTORE cognition study investigators (21). All of these priorities are essential to a meaningful and impactful practice change that becomes ingrained in PICU culture with long-term patient benefits supported by evidence-based medicine. SA protocols are just one piece of the ICU Liberation Bundle and would likely be strengthened if implemented with other practices, such as early mobility, routine extubation readiness assessment, and family engagement.

CHALLENGES WITH IMPLEMENTATION OF SEDATION AND ANALGESIA REGIMENS

Challenges in implementing optimal SA in the PICU include patient heterogeneity (in pathology and weight-based dosing strategies), inability to engage non-verbal patients with non-pharmacologic interventions, concerns about medication effects on long-term neurocognitive outcomes, and the need to balance the depth of sedation with patient safety (such as unplanned extubations or line/tube dislodgment events) (12). Protocolized titration of SA requires reliable and reproducible bedside tools to assess sedation/comfort, analgesia, withdrawal, and delirium. Lack of acceptance for changes to SA regimens might stem from safety concerns with patients at a lighter level of sedation, distrust of newer sedative agents (e.g., dexmedetomidine vs. midazolam), or mobilization of ventilated patients.

The evidence for best SA practices remains scarce with respect to patient-centered outcomes, which may limit provider buy-in, even in the context of increased interest or motivation to change practice. The lack of newer effective drugs with acceptable pediatric safety profiles limits our choice of sedative agents. For example, the use of propofol as a long-term sedative agent is declined in children over the past decade due to concerns for propofol infusion syndrome and increased mortality (22). Midazolam has been associated with an increased risk of ICU delirium and, therefore, potential accrual of long-term morbidity (3, 4, 23). Furthermore, although a number of studies have demonstrated safety in using dexmedetomidine as a primary sedative agent, the adoption of dexmedetomidine as a primary sedative in pediatric critical care is still lagging (6, 24–26). Of the 11 studies reviewed above, only three (27%) utilized dexmedetomidine as a first-line sedative agent (6, 8, 13).

Additionally, most of the interventions in this cohort relied on weak implementation methods, such as educational modules. Several studies recognized the importance of providing bedside clinical decision support (CDS), particularly in the early phase post-implementation, to ensure compliance and sustainability beyond the immediate implementation period (7, 10, 12). However, compliance is rarely measured and only commented upon in three studies (6, 7, 18).

Further barriers in implementation include cultural context barriers, i.e., readiness of the local environment for change, as well as other practical limitations, such as resource requirements, staffing models, lack of PICU or institutional leadership investment, and lack of effective teamwork and collaboration skills (27, 28). These context barriers are rarely assessed or discussed in research studies, yet present significant impediments to successful implementation.

USING IMPLEMENTATION SCIENCE FOR STUDIES EXAMINING THE IMPACT OF BEST PRACTICES IN PEDIATRIC CRITICAL CARE

The studies of SA regimen efficacy in the PICU highlight an important gap in IS in pediatric critical care. IS addresses the effective translation of evidence-based guidelines into bedside practice and is an emerging field of study in critical care (28). Specifically, it includes both the implementation of systemic models and research to understand the performance of the implementation (28).

In pediatric critical care, barriers to effective implementation of new guidelines are multifactorial and span different levels of the healthcare delivery system. A recent study using the integrated Promoting Action on Research Implementation in Health Services (iPARIHS) framework across 58 professionals in 8 United States PICUs utilized structured interviews to examine barriers, facilitators, and processes for change (29). Common themes included complex multiprofessional teams, high-stakes work at near-capacity, and a need for clear evidence as a motivator to integrate change into an already busy workflow. These factors impact the entire change process that includes planning, deciding to adopt change, implementation, facilitator, and sustainability. However, such factors are largely qualitative and difficult to assess in a rigorous quantifiable manner.

FUTURE DIRECTIONS – IMPLEMENTATION SCIENCE METHODOLOGY

In addition to continuing clinical research studies targeted at understanding best SA practices in pediatrics, there should be a parallel effort to specifically examine the adoption and sustenance of the intervention using IS-specific methodology. In addition to the development of an evidence-based intervention, strategically ensuring the successful implementation and sustainment of the intervention is critical to short-term and long-term success. Successful implementation may require effective education, ongoing just-in-time CDS, continuous feedback and evaluation, and strategic planning based on local contextual factors. IS seeks an understanding of why or how an intervention is successful. For example, although the comprehensive ICU Liberation Bundle highlights guidelines related to early mobility, SA practices, and daily extubation readiness assessment for improving patient outcomes, successful implementation has not been consistently demonstrated, and current investigations focus on barriers, such as culture change (19, 27, 28, 30).

Implementation science methodology includes tools, such as implementation mapping, traditional quality

improvement (QI) tools, education, and concept mapping (28, 31). Implementation mapping is a process that identifies determinants of implementation (i.e., barriers and facilitators), which are then "mapped" onto specific strategies to address implementation barriers (28). This is similar to other QI strategies that can be utilized, such as key driver diagrams, stakeholder analysis, cause-and-effect diagrams, and process mapping (32). Furthermore, care delivery in the ICU is a team-based approach. This means that specific strategies in ICU implementation should include promoting team-based and patient-centered care. Patient-centered care should be structured based on guidelines but flexible enough to be tailored to each case depending on just-in-time data input.

A recent review provides an overview of the associated theories, models, and frameworks of IS (33). The authors identified six broad determinants of successful implementation, which are as follows: (1) the implementation object, (2) the user/adopter (e.g., healthcare providers), (3) the end user (e.g., patients), (4) the context, (5) the strategy, and (6) the outcome. Traditional research papers often lack a systematic assessment of the context and strategy. In this case, the context may refer less to the type of clinical environment in which the study is performed and more to the social/cultural factors that affect implementation, representing both potential barriers and unique resources. The context analysis is vital for successful implementation, as the knowledge of available resources and known barriers may allow for the crafting of a more targeted and effective strategy. For example, if a barrier to implementation is due to staffing limitations, the mitigation strategy would be different than if the barrier is due to inherent resistance to change. For the former, leveraging alternative resources (e.g., incentive structures for program participation) may be effective, whereas for the latter, a sequential roll-out with early adopters to demonstrate feasibility and success may be more effective in creating change. In the SA papers reviewed (**Table 1**), none of the studies incorporated a discussion on the assessment of local barriers and resource/barrier-specific strategies for implementation. It is generally assumed that the relevant barrier is a knowledge gap, and therefore, the majority of the center of intervention solely around education. As a comparison, a recent study on implementing blood transfusion recommendations in PICUs incorporated an assessment of potential barriers and then a description of specific barrier-targeting strategies prior to implementation of their intervention (34). Assessment of barriers and resources can be performed with qualitative interviews, structured focus groups, surveys, and stakeholder analyses, which are commonly used tools in quality and process improvement research (29, 32).

Another potentially useful tool for IS is the Dissemination and Implementation (D&I) Models in Health Research and Practice available through the National Institutes of Health (35). The D&I Models Webtool includes a broad framework for project planning: Plan, Select (D&I Models), Combine (D&I Models), Adapt, Use, and Measure. The webtool also includes instructions and examples for creating logic models for planning interventions. Broad categories addressed in the logic model include the dynamic context in which the project is occurring within, the problem being addressed, the evidence behind the intervention, strategies for D&I, short- and long-term outcomes, mediators of the D&I process (e.g., context), and sustainability infrastructure. Again, context and strategy are critical components of this logic model, highlighting the importance of this assessment in IS.

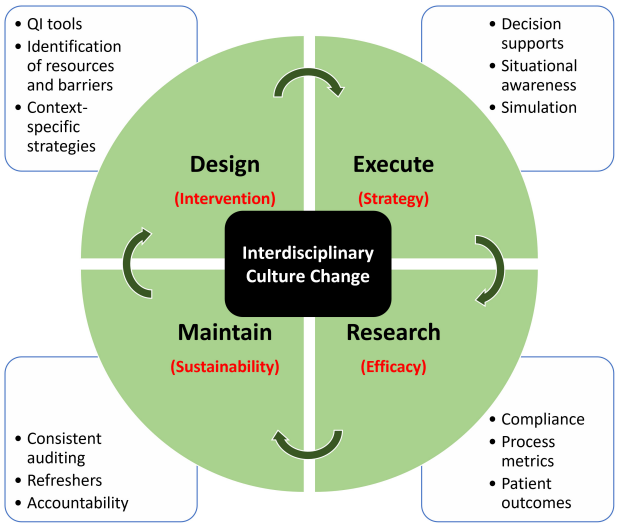

FIGURE 1 | Proposed model of implementation research using a learning healthcare model. Each quadrant domain addresses a specific determinant (in red), which cohesively addresses the largest underlying challenge, which is interdisciplinary culture change. Surrounding each domain describes the tools that can be employed to address that specific component.

Since many protocols and materials rely on team-based approaches, educational material should emphasize the role clarity of team members, as well as identify and employ specific skills and knowledge unique to each team member. This requires an interdisciplinary approach at all stages of implementation, from intervention design to execution to auditing, maintenance, and accountability (36). Common barriers include changing ICU culture, specifically, potential changes in workload, such as needing increased staffing to facilitate early mobility with minimizing sedation, or changes in autonomy when transitioning from physician-driven to nurse-driven sedation plans (28). However, culture change is often difficult to institute and even more difficult to measure. Key components to influence culture change involve buy-in from all levels, such as leadership advocacy, frontline provider champions, and patient and family engagement (28). Furthermore, since IS typically involves the application of evidence-based practices to all patients, large randomized control trials may not be feasible as the study design of choice. However, as evidenced by the strength of recommendations from the PANDEM guidelines, rigorous research methodology is still required for the assessment of meaningful interventions that affect relevant outcomes. Researchers should consider other quasi-experimental research designs, such as the interrupted time series (ITS) design (37). The ITS study design affords the added benefit of visualizing any potential secular trends over time while simultaneously

utilizing segmented regression analysis for rigorous statistical processing. The ITS design is an emerging study design of choice in IS that is more rigorous than simple pre-post implementation studies. There is also potential feasibility in using difference-in-differences analysis with the ITS design that uses a contemporary control group in the analysis of the intervention (37).

CONCLUSION: A PROPOSED FRAMEWORK FOR STUDIES EXAMINING THE IMPACT OF SEDATION AND ANALGESIA REGIMENS

There is heightened interest in employing best practices related to SA regimens in pediatric critical care. There are several studies that have examined the role of evidence-based novel SA regimens in the PICU population, and this area of research has the promise to achieve improvements in patient outcomes. The existing literature on the subject could be significantly enhanced by emphasis on the systematic implementation of the interventions. Research in SA protocol implementation is met with numerous challenges (**Figure 1**). The intervention design requires consideration of medication choice and objective scoring systems. Understanding the efficacy of the intervention requires rigorous research methodology and thoughtful strategies to execute change. Lastly, even with successful implementation, maintaining sustainability has been an additional challenge (38). When healthcare systems build a new process for implementation, metrics examining compliance, process efficiency, and ongoing maintenance of the protocol should be prioritized. Central to this is institutional cultural alignment and a culture of shared responsibility. This describes components of a learning healthcare system that is better equipped for investigating, informing, instituting, and maintaining continual change (39). Taking all of the above into consideration, we recommend an interdisciplinary, data-driven, learning healthcare model to tackle IS and SA issues in pediatric critical care (**Figure 1**). The model incorporates components of Design, Educate, Research, and Maintain to highlight important components in the cycle of implementation. Further attention should be given to study the final step in the care delivery process using IS tools (40). The propagation of the implementation research framework and theory has not yet been systematically adopted in critical care research. However, critical care-specific IS training programs, as well as funding agencies, have recently been created (28). Future studies in SA practices in pediatrics should incorporate attention to methodology and data analytics specific to the IS step of the care delivery process, such as the context assessment of resources and barriers, and context-specific strategy planning. For example, identification of barriers and mapping of specific strategies to address each barrier should be included, and this should take place during the design phase of the implementation cycle. The full potential of basic science, clinical, and translational research can only be realized when we successfully jump the implementation hurdle and close the gap between evidence-based medicine and bedside practices in order to disseminate the best quality of care to all our patients (40).

AUTHOR CONTRIBUTIONS

YY and NM conceived the design of the manuscript. YY performed the review of the studies and prepared the manuscript draft. AG, KM, and NM reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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