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Silver fluoride and caries management

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Silver fluoride and caries management

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Editorial: Silver fluoride and caries management

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Editorial on the Research Topic
Silver fluoride and caries management

If the public was asked to list diseases that have the highest global burden, oral diseases may not be included in the provided answers. According to the WHO (1) in the report on global oral health status, oral diseases represent a global public health problem that necessitates intervention. Since 1990, oral diseases have been the most prevalent worldwide condition. In 2019, 3.5 billion people were affected globally by oral diseases. Moreover, there is an alarming proportion of affected people in middle-income countries where 3 out of 4 residents are affected. Accordingly, oral diseases not only affect the individual's health and well-being but also affect healthcare systems and economies. This can be shown by the US$ 387 billion spent by 194 countries in 2019 as a direct cost for oral diseases in addition to global US$ 323 billion productivity losses resulting from the same conditions.

One of the oral diseases of the highest-burden is untreated dental caries, whether in deciduous or permanent teeth. More than 30% of humanity lives with untreated dental caries. 2 billion people globally have untreated caries in their permanent teeth compared to 514 million children with untreated caries in deciduous teeth making it the sole most frequent chronic childhood disease. The estimated global average prevalence of untreated caries in deciduous and permanent teeth are 43% and 29% respectively. Although these numbers are alarming, it is possible to reduce the global disease burden by self-care or simple measures (1).

The WHO recognized the important link between oral health and overall health, where dental caries and other oral diseases can have significant consequences impacting nutrition, speech, self-esteem, and overall quality of life (2). Accordingly, WHO included a dental section in its Essential Medicines list.

The WHO Essential Medicines List is a curated compilation of the most effective, safe, and cost-effective medicines needed for basic healthcare (3). It provides a guiding framework for countries to prioritize access to essential medicines while ensuring their availability and affordability (4). This list is extremely important because it influences national pharmaceutical policies and procurement decisions, eventually affecting the delivery of healthcare services.

The inclusion of a dental section in the WHO Essential Medicines List highlights the important link between oral health and overall health. In a significant step forward, the World Health Organization has added silver diamine fluoride (SDF) to the dental section of its Essential Medicines List in 2021. This shows the WHO's recognition of its potential to revolutionize the prevention and management of dental caries, especially in resource-constrained settings and vulnerable populations like the elderly and disabled.

According to WHO (5), the newly added medicine, SDF, Ag F (NH3)2 is a clear liquid formulation containing high concentrations (most commonly 38%) of fluoride (approximately 44,800 ppm) and silver (approximately 253,870 ppm silver) (6). It has garnered attention for its remarkable efficacy in preventing and arresting dental caries, showing an 81% success rate for a topical application on primary teeth (7). 80% effectiveness is also confirmed as the general efficacy rate (5). The material costs of recommended bi-annual applications are approximately USD $0.20 per year per person.

The decision of the EML revising committee to add SDF was not only based upon its numerous advantages but also due to the strong 50-year existing evidence about its effectiveness. Studies proved that SDF application decreased the incidence of new dentinal caries significantly when compared to placebo, no received treatment, and fluoride vanish in a 2-year follow-up. SDF was also found to successfully arrest root caries by 90% at 30-month follow-up. Another advantage is that SDF has no reported side effects. However, aesthetically, it stains the treated caries with a dark color. Tooth pain and irritation of the gingiva have rarely occurred and if occurred, they subsided quickly (5).

The importance of SDF extends beyond its role in addressing the global burden of dental caries. For aging populations and individuals with disabilities, SDF offers a minimally invasive, cost and time-effective alternative to traditional restorative treatments. Decades of research have demonstrated its ability to halt the progression of carious lesions, particularly in aging populations or populations with limited access to conventional dental care.

Aging populations often face unique challenges when it comes to maintaining oral health. As people age, they may experience decreased manual dexterity, making it difficult to maintain proper oral hygiene. In addition, many medications commonly prescribed to older adults can cause dry mouth, which could increase the risk of dental caries (8).

Similarly, people with disabilities may face barriers to accessing dental care due to physical limitations (9), transportation difficulties (9), or financial constraints (10). SDF can be easily applied in non-traditional settings, such as nursing homes or community health centers, thus making it more accessible to this population (11). By preventing and arresting dental caries, SDF can help reduce the need for more invasive and expensive dental treatments, which may be especially challenging for people with disabilities.

In this comprehensive discussion, we explore the diverse ramifications of integrating SDF into worldwide oral health strategies, emphasizing its potential to mitigate socioeconomic disparities associated with dental caries. We stress the necessity of proactive measures in fostering oral health equity, advocating for collaborative endeavors and sustained investment in accessible, evidence-based interventions.

Ultimately, this editorial underscores the imperative of addressing the global caries crisis through multifaceted approaches, highlighting SDF as a promising solution to not only prevent and treat tooth decay but also to narrow dental care gaps and advance equity in oral health. Through concerted efforts, we envision a future where dental caries cease to pose a significant threat to global well-being.

Author contributions

CA: Writing – original draft, Writing – review & editing. RD: Writing – original draft, Writing – review & editing. DD: Writing – original draft, Writing – review & editing. LM: Writing – original draft, Writing – review & editing. RB: Project administration, Resources, Supervision, Writing – review & editing.

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Parental acceptance of silver fluoride as a treatment option for carious lesions among South African children with special health care needs

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Providing dental care for children with neurological special health care needs, including Down syndrome, Cerebral palsy and Autism spectrum disorders, is challenging. They often require repeat exposure to sedation or general anaesthesia for routine dental care. 51 parents of children with special needs completed a questionnaire regarding the acceptance of Silver Fluoride as a treatment option.

Background: Silver Diamine Fluoride has become popular as a minimally invasive treatment option for providing oral health care to young or uncooperative children. Silver Fluoride (SF) is a newer development with similar but improved properties. The aim was to determine the acceptance of SDF/SF as treatment option for Children with Special Health Care Needs (CSHCN), including Down Syndrome, Autism Spectrum Disorder and Cerebral Palsy.

Methods: 51 Parents of CSHCN completed a questionnaire on the overall acceptance of SF; aesthetic concerns related to the location of application; the use of SDF as an alternative to general anesthesia; and the composition of SF.

Results: The use of SF on posterior teeth were more acceptable (70.59%) as opposed to its application to anterior teeth (50.98%). Parents generally agreed/strongly agreed to the use of SF to reduce infection and pain (82%); to avoid treatment under GA (26.70%); and to avoid an injection (78%). 64% of parents indicated their agreement in using SF because it has a reduced cost when compared to a conventional restoration. Majority of parents were in agreement to use SF even if it contains Fluoride (84%) and Silver (78%).

Conclusion: The use of SF, as treatment option for caries, was well accepted by South African parents of CSHCN. Shared decision making should be applied when considering SF as treatment option for CSHCN.

KEYWORDS
parental acceptance, silver fluoride, silver diamine fluoride, special care dentistry, caries

Abbreviations
CSHCN, children with special health care needs; SDF, silver diamine fluoride; SF, silver fluoride.

1. Introduction

Within the group of patients with special health care needs are three very common neurological conditions namely Cerebral Paralysis (CP), Down Syndrome (DS) and Autism Spectrum Disorder (ASD). These conditions not only affect the paediatric patients' general health but also their craniofacial development and subsequent oral health (1).

Several studies have highlighted the difficulties of performing dental care on children with a serious mental disability like CP, DS and ASD (1–3). Non-pharmacological behavior management of children with neurological conditions is often challenging as they often struggle with communication and social interaction. Linking with patient cooperation, restoration of cavities requires cooperation, time and moisture control which is often not possible in children with CP, DS and ASD. The Atraumatic Restorative Technique can be considered as a treatment option, however, still requires moderate cooperation to execute and may therefore not be applicable to all patients. As a result, children with CP, DS and ASD often require sedation or general anesthesia to enable routine restorative dentistry procedures to be performed. The risks of exposing children with CP, DS and ASD to repeated sedation and general anesthesia for routine dental treatment is worrying, and hence alternative treatment options are needed.

Silver Diamine Fluoride (SDF) has emerged as one such an alternative arrest dental caries, while being non-invasive and clinically efficient (4). The new generation, ammonia free Silver Fluoride (SF) has the added benefits of less tissue burn and irritation, improved smell, and better stability. Both Silver Diamine Fluoride (Riva Star) and Silver Fluoride (Riva Aqua) is approved for medical use with product registration numbers (D349082/K172047/GMDN code 45232 Class iia).

Parental acceptance of SDF treatments among healthy children has been reported as a limitation, due the resulting unaesthetic black staining when applied to carious lesions (5–7). Limited scientific evidence is available regarding the acceptancy of these techniques among children with special health care needs and their parents.

2. Methods, results and discussion

2.1. Material and methods

The aim of this study was to determine the acceptance of special needs children's parents of SF as a treatment option for carious lesions. The quantitative cross-sectional study was conducted by means of a self-administered questionnaire. The questionnaire included several relevant constructs, namely the overall acceptance; aesthetics concerns by tooth location, and its use as an alternative treatment in order not to admit the children to general anaesthesia for dental treatment.

Parents of children with special health care needs, meeting the inclusion criteria, were invited to participate in this study. The inclusion criteria was parents of patients diagnosed with DS, CP or ASD, in need of dental treatment (at least having one cavity indicated for restoration). Parents were informed about the nature, benefits and risks associated with the study after which written consent for voluntary participation was obtained. After consent was obtained, the parents were educated about SF as alternative to dental restorations by means of an information leaflet, adapted from the British Society of Paediatric Dentistry's patient leaflet for SDF (BSPD) (8). Participants then completed the questionnaire (it was printed in English but a translator was available in Afrikaans and Xhosa when necessary).

A convenience sample of 100 participants, in line with a peer review article published by Bagher et al. (9) was used. From the 100 participants approached, 20 parents declined participation. Questionnaires that were incomplete or had double answers marked were excluded from the study resulting in $n = 51$ questionnaires that were analyzed, indicating a 51% response rate.

2.1.1. Ethical considerations

Ethical clearance was obtained from the Biomedical Research Ethics Committee (BM22/7/9) of the University of the Western Cape. All parents who participated in the questionnaire were not obliged to take SF as a treatment option and could opt for conventional treatment as routinely offered by the hospital. Patients screened for the study that did not meet the inclusion criteria but still required dental treatment received routine care. Parents had the option to opt out from the research at any time with the option to receive conventional restorative treatment or no further treatment. All patients were advised to attend regular follow up visits, regardless of their participation in the study. In terms of the requirements of the Protection of Personal Information Act (Act 4 of 2013), personal information was collected and processed as explained in the information sheet and consent from participants to use this information in the study was obtained on the consent form.

2.2. Results

Fifty-one Questionnaires were available that were correctly completed by the parent/guardian. The participating parents represented 20 (39.21%) children with Autism, 22 (43.13%) with Cerebral Palsy and 9 with Down Syndrome 9 (17.64%). The demographics of the participating parents and their children are summarized in **Table 1**, with the majority of parents being female (80.39% and between the ages of 30–49 years (52.93%). The children of participating parents were mostly male (68.62%) and between the ages of 6–10 years.

The parental acceptance with regards to the use of silver fluoride is reported in **Table 2**. Majority of parents ($n = 38$, 74.5%) agreed/ strongly agreed to the use of SF for their children. The use of SF on posterior teeth was more acceptable ($N = 36$, 70.59%) as opposed to its application to anterior teeth ($N = 26$, 50.98%). Parents generally agreed/ strongly agreed to the use of SF to reduce infection and pain ($N = 42$, 82%); to avoid treatment under GA ($N = 26.70\%$); and to avoid an injection ($N = 40$, 78%). 64% of parents indicated their agreement in using SF because it has a reduced cost when compared to a conventional restoration.

TABLE 1 Demographics of participating parents and their children.

Variable	N (%)
Child age	
0–5 years	13 (24.49)
6–10 years	26 (50.98)
11–15 years	12 (23.52)
>16 years	0 (0)
Male	35 (68.62)
Female	16 (31.37)
Other	0
Parents	
Female	41 (80.39)
<20 years	0 (0)
20–30 years	13 (25.49)
30–40 years	21 (41.17)
>50 years	7 (13.72)
Male	10 (19.61)
<20 years	1 (1.96)
20–30 years	1 (7.96)
30–40 years	6 (11.76)
>50 years	2 (3.92)

Majority of parents were in agreement to use SF even if it contains Fluoride ($N = 43$, 84%) and Silver ($N = 40$, 78%).

The result of the chi-square statistical analysis is reported in Table 3. The Chi-square statistic of 15.7669 is not statistically significant at $p = 0.469343$.

2.3. Discussion

Although SDF if widely researched, the newer Silver Fluoride is not. Most of the comparisons and agreements will be drawn with parental acceptance studies on SDF. However, over time our hypothesis is that acceptance will only improve due to the newer properties of SF.

Bahger et al. (9) reported a 57.8% response rate from a similar questionnaire relating to children aged between 2 and 12 years with a mean ± SD age of 7.27 ± 2.35. These demographics are comparable with our study, at a 51% response rate with majority of the children being between the ages of 6 and 10 (50.98%). Majority of the children (whose parents participated in this study) were diagnosed with ASD and were male. This is in alignment with a higher incidence of ASD being diagnosed in males and the findings of Hu et al. (5) who reported 83% male participants in a SDF acceptance study among children diagnosed with ASD. Moreover, parents' level of acceptance towards SDF increased according to the level of increased difficulty that their child would experience in order to receive treatment (7).

An important factor which influences a parent's decision to accept the use of SDF/ SF in their children's mouth, is whether it is being applied anteriorly or posteriorly due to aesthetic concerns. The acceptance rate for anterior teeth was 50.97% (agree and strongly agree), while for posterior teeth was 70.58% (agree and strongly agree), which concurs with what is reported in the literature. Hu et al. (5) found the parental acceptance rate to increase from 35% for anterior teeth to approximately 67.5% for posterior teeth, while Crystal et al. (7) reported 29.7% and 67.5% respectively. Although no statistically significant difference could be found between the acceptance for use on anterior and posterior teeth in this study, Bahger et al. (9) reported significantly higher acceptance of SDF treatment on their child's primary compared to permanent teeth and posterior compared to anterior in both dentitions ($P < 0.001$).

TABLE 2 Parental acceptance of SF use reported in percentages.

Variable	Definitely disagree N (%)	Disagree N (%)	Neutral N (%)	Agree N (%)	Definitely agree N (%)
Use of SF on front teeth	9 (17.64)	9 (17.64)	7 (13.72)	17 (33.33)	9 (17.64)
Use of SF on back teeth	6 (11.76)	4 (7.84)	5 (9.80)	26 (50.98)	10 (19.60)
Use to reduce infection and pain	3 (5.88)	3 (5.88)	3 (5.88)	25 (49.01)	17 (33.33)
Use to avoid treatment under GA	3 (5.88)	7 (13.73)	4 (7.84)	26 (50.98)	11 (21.57)
Use to avoid injection	2 (3.92)	6 (11.76)	3 (5.88)	27 (52.94)	13 (25.49)
Use for reduced cost compared to filling	4 (7.84)	9 (17.65)	5 (9.80)	26 (50.98)	7 (13.72)
Use even if it contains fluoride	2 (3.92)	2 (3.92)	4 (7.84)	35 (68.62)	8 (15.68)
Use even if it contains silver	2 (3.92)	3 (5.88)	5 (9.80)	34 (66.66)	6 (11.76)
Overall acceptance of use	4 (7.84)	4 (7.84)	5 (9.80)	29 (56.86)	9 (17.65)

TABLE 3 Chi-square analysis of results.

	Results					
	SF front teeth	SF back teeth	Prevent GA	Avoid injection	SF accepted to use	Row totals
Definitely disagree	9 (4.80) [3.68]	6 (4.80) [0.30]	3 (4.80) [0.68]	2 (4.80) [1.63]	4 (4.80) [0.13]	24
Disagree	9 (6.00) [1.50]	4 (6.00) [0.67]	7 (6.00) [0.17]	6 (6.00) [0.00]	4 (6.00) [0.67]	30
Neutral	7 (4.80) [1.01]	5 (4.80) [0.01]	4 (4.80) [0.13]	3 (4.80) [0.68]	5 (4.80) [0.01]	24
Agree	17 (25.00) [2.56]	26 (25.00) [0.04]	26 (25.00) [0.04]	27 (25.00) [0.16]	29 (25.00) [0.64]	125
Definitely agree	9 (10.40) [0.19]	10 (10.40) [0.02]	11 (10.40) [0.03]	13 (10.40) [0.65]	9 (10.40) [0.19]	52
Column totals	51	51	51	51	51	255

However, Crystal et al. (7) further found that the acceptance rate for the use on anterior teeth increased to 60.3% when taking the risk of general anaesthesia into account, which echoes the finding of this study as 72.55% of parents supported the use of SDF to reduce to possibility of general anaesthesia for their child's treatment. Similarly, Hu et al. (5) reported an increase from 60% to 70% when the reality of general anaesthesia was given as a path to facilitate dental treatment and that parents of younger children are more likely to accept SDF as an alternative to GA.

The main ingredients of SDF are fluoride and silver, both of which have been elicited controversy in the past with regards to its safety for use in oral health care. The results from this study indicate that 84.3% of parents did not object to the product containing fluoride or silver (78.42%) for the combined "agree" and "strongly agree" Likert scales. Hu et al. (5) reported that more than 60% of parents would use SDF despite it containing silver and fluoride.

Children with ASD have higher levels of dental fear (5), which poses real contextual difficulties in receiving and delivering optimal dental care. This can delay treatment and increase dental pain, often further complicating the effective treatment pathways. In this study, 82.34% of parents accepted the use of SDF for the possibility of it reducing dental pain, avoiding intra-oral injections (78.43%) and possibly reducing dental costs of restorations (64.7%) as opposed to a minimal approach such as SDF. Both dental pain of pathological origin and giving injections feed dental fear. Crystal et al. (7) reported an increased level of acceptance of SDF as the level of difficulty that their child would experience in order to receive treatment increased, and parents of children with previous uncooperative behavior during dental treatment were significantly more accepting of the use of SDF, regardless of the type (primary or permanent) and location of the teeth (9).

Furthermore, Bagher et al. (9) found no statistically significant difference between the parental acceptance rate of SDF usage with the child's gender, parent's gender, parental education level and family income, which illustrates that the demands of special needs children are more influential on parental decision making (such as pain, anxiety, fear, communication challenges and need for treatment under GA). As such, the overall acceptance of SDF usage in this study was 82.34% (for both "agree" and "strongly agree" scales), which is somewhat higher than was reported by Hu et al. (5), as 60% in Singapore. Given that the dental demands of a developing country such as South Africa would be vastly different from that of a developed country like Singapore, this is not surprising. The burden of disease, caries prevalence and lack of appropriate dental care services for special needs children, makes the benefits of SDF very appealing to families who are struggling to meet the complex dental needs of their children. This not only includes financial constraints, but logistic challenges to find care to promote and maintain their children's oral health without compounding dental fears (i.e., with injections, fillings, extractions, etc.) or having no other options than being referred to GA for extensive treatment plans. It is clear, from this study and international literature, that parental acceptance with the use of SDF, despite its unaesthetic outcome, greatly increases when the benefits are weighed against the risks of not using it, given what the more extensive options are of not arresting active caries early.

3. Conclusion

SF, as treatment option for caries, was well accepted by South African parents of CSHCN and should be offered as a treatment option when indicated. Shared decision making should be applied when considering SF as treatment option for CSHCN.

3.1. Possible benefits of the study to the population

SF application in carious lesions is economic (cost and time effective) and safe not requiring local anaesthesia, sedation or general anaesthesia. The results of this study indicate that majority of parents with CSHCN would accept SF as a treatment option. Dental professionals should therefore consider and present SF as a treatment option for this vulnerable group of children.

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 humans were approved by Biomedical Research Ethics Council at the University of the Western Cape: BM22/7/9. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NP: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. NN: Data curation, Investigation, Methodology, Validation, Writing – review & editing. RM: Investigation, Methodology, Writing – review & editing. CP: Validation, Writing – review & editing. SG: Conceptualization, Writing – review & editing.

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Supplementary material

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ANNEXURE I
Patient information sheet, SF information and consent form.

ANNEXURE II
Questionnaire.

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Penetration of SDF and AgF from the infected dentine towards the unaffected tooth structure

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Background: The use of SEM-EDS line scan analysis to evaluate the movement of ions from dental materials towards the tooth structure and the concept of ion movement is well established. This analysis technique was used to determine the ion movement of two commercially available silver- and fluoride-containing products.

Methods: This study aimed to compare the elemental analysis of primary molar teeth treated with silver diamine fluoride (SDF) and water-based silver fluoride (AgF) and to analyse the penetration of SDF and AgF from the infected dentine towards the healthy dentine. The teeth were cleaned from debris and contaminants off the roots and stored until use. A total of 15 primary molars with large active cavitated lesions, not extending into the pulp (specimens), were divided into three test groups: silver diamine fluoride (SDF) ($n = 5$), water-based silver fluoride (AgF) ($n = 5$), and deionised water (W) ($n = 5$) as the control group. The teeth were sectioned, embedded, and received SEM-EDS line scans. The line scan had a total length of 82.65 µm. The visible end of the infected dentine and the start of the more affected dentine were chosen as the starting point to ensure that the infected caries' line distribution towards the affected dentine's transition area was as standardized as possible. Therefore, the infected dentine length of the scan was 22.80 µm (8 scan points of 2.85 µm apart), and the affected dentine, including the healthy dentine, was 59.8 µm (21 scan points). The SEM-EDS line scan from each specimen determined the average fluoride, iodide, and silver weight percentage for that specimen.

Results: The 15 sample SEM-EDS line scans were used to determine the average ion movement in wt%. The Kruskall–Wallis test and Tukey's HSD test were completed at a $p < 0.05$. SDF and AgF presented no significant fluoride movement in terms of the weight percentage. There was, however, significantly more fluoride movement from infected caries to the healthy dentine with SDF and AgF ($p = 0.0010053$) compared to the control specimens treated with deionised water. There was no significant difference between SDF and AgF for the movement of the iodide ($p = 0.5953$) and silver ($p = 0.3708$) from infected caries to the healthy dentine.

Conclusion: SDF and AgF easily penetrated through infected caries and affected tooth structure to the healthy dentine for the line scan of 82.65 µm. There was no significant difference between SDF and AgF for the movement of ions within the infected dentine nor in the affected/healthy dentine.

KEYWORDS

ion movement, silver diamine fluoride, water based silver fluoride, infected dentine, affected dentine, special care dentistry

1. Introduction

The use of scanning electron microscopy—energy dispersive spectroscopy (SEM-EDS) analysis to evaluate the movement of ions from the glass ionomer restorative cement into the tooth structure and the concept of ion movement is well documented in the literature. These ions and their release into the tooth structure through ion exchange have been established as the mechanism that enables glass ionomer cement to remineralise the demineralised dentine (1). During subsequent research, Gjorgievska et al. (2) indicated that aluminium, fluoride, magnesium, silicon, and strontium were incorporated into the dentine from Fuji IX (GC Corporation, Japan). Although the distance of ion movement was not assessed using SEM-EDS line scans as in this present *in vitro* study, Gjorgievska et al. (2) could conclude that the variation of the ion movement between different teeth would be limited by the dense crystalline nature of the tooth structure (2). This *in vitro* study, therefore, assessed the movement of ions from silver diamine fluoride (SDF) and water-based silver fluoride (AgF) into the healthy dentine through the infected and affected dentine. SDF is known to easily penetrate through 1–1.5 mm dentine discs where the surface was treated with 17% EDTA to open the dentinal tubules (3). Therefore, the depth of penetration and the corresponding weight percentage change will be insightful to the remineralising properties of the SDF and AgF materials. The use of SEM-EDS can be considered to be destructive as the teeth need to be sectioned and prepared. The use of Micro-CT evaluation has shown value in assessing microstructures such as interglobular dentine (4, 5) and is a method that should be considered for incorporation in future research to augment the caries remineralisation assessment of affected and infected dentine, preceding SEM-EDS analysis. Assessing if the AgF where the ammonium was removed as per the previous generation known as SDF becomes clinically relevant to clinicians using AgF in communities where refrigeration is no longer a requirement for AgF.

The hypothesis of this study was that the weight percentage of ion movement from the SDF and AgF towards the healthy dentine structure through the infected and affected dentine would be no different.

2. Materials and methods

This study aimed to compare the ion movement from the infected dentine towards the healthy dentine through elemental analysis of primary molar teeth treated with silver diamine fluoride (SDF) and water-based silver fluoride (AgF).

2.1. Sample size calculation

Based on the fluoride values obtained from Knight et al. (6), the fluoride ion mean of the control group was 4 and that of the test group was 10, with a standard deviation of 3. Assuming a pooled standard deviation of 3 units, the study would require a sample size of 4 teeth per group. The sample size of 5 is, therefore, more than sufficient to achieve a power of 80% and a level of significance of 5% (two-sided) for detecting a true difference in means between the test and the reference groups.

2.2. Specimen collection and SDF/AgF treatment

All teeth used in this study were collected from a pool of teeth that were extracted as part of a comprehensive treatment plan based on the patient's needs and not for the purpose of this study. All patients or parents/legal guardians signed written consent for the treatment plans independently of this research and gave consent for teeth to be used for anonymised research purposes. The teeth used are not traceable to the patients. Specimens were stored appropriately and disposed of according to medical waste guidelines, once testing took place. The study was approved by the University of the Western Cape Research Ethical Committee with approval number: BM22/7/3.

The teeth were cleaned from debris and contaminants from the roots and stored under refrigeration in 1% thymol distilled water until use. When the experiment commenced, teeth were rinsed with double distilled water. A total of 15 primary molars with large active cavitated lesions, not extending into the pulp (specimens), were divided into three test groups: silver diamine fluoride (SDF) ($n = 5$), water-based silver fluoride (AgF) ($n = 5$), and deionised water (W) ($n = 5$) as the control group.

SDF (Riva Star, SDI Limited, Australia) and AgF (Riva Star Aqua, SDI Limited, Australia) were the commercially available products and they were used as per the manufacturer's instructions. The control group was represented with deionised water. The treated teeth were stored in 80% humidity at 37°C for 2 weeks before SEM-EDS assessment. This method allowed for the removal of the confounding factor of excessive moisture that could carry ions deeper than the natural remineralisation progression of the ions into the tooth structure.

2.3. SEM-EDS analysis of the sectioned teeth

The teeth that were sectioned and embedded in clear acrylic resin received an SEM-EDS line scan from the infected tooth structure toward the healthy dentine structure to assess the ion elemental transition in weight percentage concentration (wt%). This SEM-EDS line scan was repeated five times per sample and the average of the corresponding µm positions was used to calculate the average elemental wt% within groups. Each SEM-EDS line scan was 50 µm apart from the adjacent scanning lines. All five specimens from each group were critical-point dried in a desiccator, invested in clear acrylic, polished, and sputter-coated with carbon prior to SEM-EDS analysis. The SEM-EDS line scan from each specimen determined the average fluoride, iodide, and silver weight percentage for that specimen at each point on the line scan. The scanning electron microscopy unit (Hitachi S-4800 FEG Scanning Electron Microscope, Hitachi Ltd, Tokyo, Japan) was used to examine the surface morphology of the specimens to perform the line scan. The line scan had a total length of 82.65 µm. The visible end of the infected dentine to the affected dentine was chosen as the starting point to ensure that the infected caries' line distribution towards the affected dentine's transition area was as standardized as possible. Therefore, the infected dentine length of the scan was 22.80 µm (8 scan points of 2.85 µm apart) and that of the affected dentine, including the healthy dentine, was 59.8 µm (21 scan points) (**Figure 1**). Images were obtained at FOV: 944 µm, Mode: 15 kV—Map, Detector: BSD Full. The measurements of the scan points were 2.85 µm apart and wt% percentage concentration for the ion elements present.

2.4. Baseline elements

The baseline fluoride, silver, and iodide weight percentage concentration (wt%) in the healthy dentine was assessed with SEM-EDS 4 mm away from the infected tooth structure for the teeth used in this *in vitro* investigation and was chosen to be 1.4% per weight. The fluoride results obtained from the line scan did not receive any data correction and were used as analysed per line scan point. There was no iodide nor silver present in these sections of the teeth.

3. Results

The sample ($n = 5$) SEM-EDS line scans were used to determine the average ion movement in wt%. The Kruskall–Wallis test determined there was a difference among the groups.

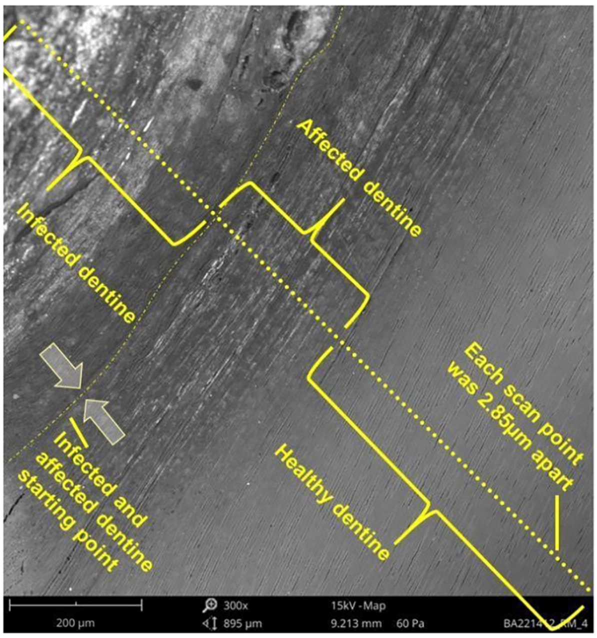

FIGURE 1
Illustration of the sectioned tooth as seen under the SEM.

Tukey's HSD test determined where the significant difference was between groups at a $p < 0.05$. SDF and AgF presented significantly more fluoride movement from infected caries to the healthy dentine, with SDF and AgF showing significantly more ($p = 0.0010053$) movement compared to the control specimen treated with deionised water (**Figure 2**). There was no significant difference between SDF (Riva Star) and AgF (Riva Star Aqua) for the movement of the fluoride ($p = 0.8999$), iodide ($p = 0.5953$) (**Figure 3**), and silver ($p = 0.3708$) (**Figure 4**) from infected caries to the healthy dentine.

There were no significances found between AgF (Riva Star Aqua) and SDF (Riva Star) with regard to the wt% present in the affected and healthy dentine cumulatively for fluoride wt% (**Figure 5**), silver wt%, and iodide ($p < 0.05$).

4. Discussion

The hypothesis that the ion movement from the AgF (Riva Star Aqua) and SDF (Riva Star) towards the healthy dentine structure through the infected and affected dentine would be no different was accepted.

When a carious tooth is restored with a glass ionomer cement it is well established that the carious teeth develop an inter-diffusion zone with a width of 1–2 µm (7). The ion movement from Fuji IX (GC Corporation, Japan) and Riva Self Cure (SDI Limited, Australia) glass ionomer restorative cement was also assessed by Knight et al. (6). Their investigation illustrated the movement of ions into the tooth up to 75 µm for Fuji IX and Riva Self Cure, but their graphs illustrated a sharp decline of ion wt% after 20 µm (6).

The use of 38% SDF encourages the remineralisation of carious lesions when looking at depth, mineral density, and remineralisation (8). SDF, when exposed to demineralised dentine, increases the mineral organic content and increases the size of the hydroxyapatite crystals in the treated dentine (9). This contributes to the improvement of the mechanical properties of the remineralised dentine thus preventing further demineralisation. This was also demonstrated by Iijima and Onuma (10), who reported that the addition of fluoride into the lattice of remnant crystals changed and decreased the solubility of the apatite. This is further supported by Zhi et al. (11), who found that topical application of silver and fluoride ions increases the mineral density of demineralised dentine lesions. This *in vitro* study confirmed this conclusion and was able to quantify the weight percentage for the various ions. The use of a remineralisation product, especially on special care patients, that is nearly odourless, has no tissue irritation, and has a physiological pH like Riva Star Aqua could be considered favourable properties. The mineralisation and arrestation of dental caries is the primary function of SDF and AgF products and this role must be optimal. This *in vitro* analysis compared ion movement in weight percentage concentration (wt%) of Riva Star (SDF) to establish if the physical material properties would hinder the mineralisation effect of the Riva Star Aqua (AgF).

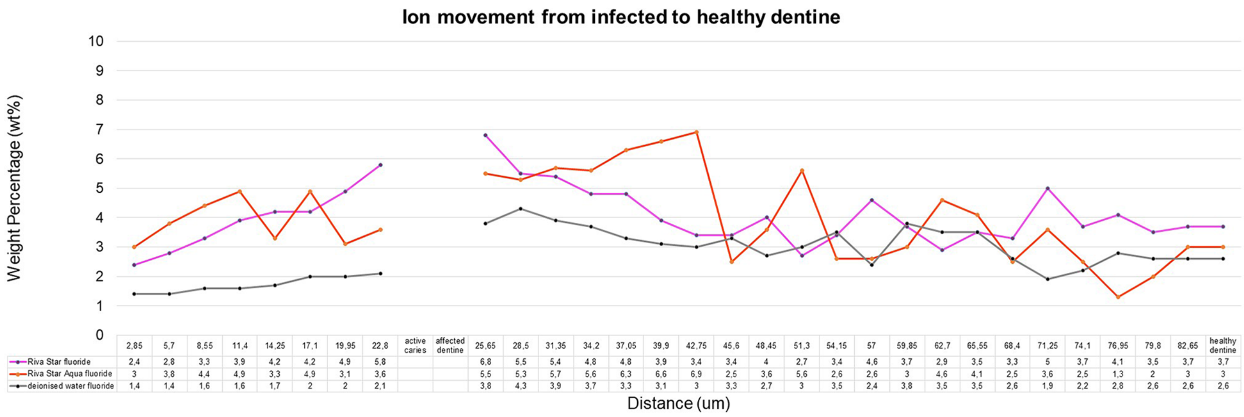

FIGURE 2
Fluoride ion movement in wt%.

It would be expected that the composition of SDF (Riva Star) and AgF (Riva Star Aqua) would play a role in the ion wt% potential of the material that is available to move through the infected and affected dentine into the healthy tooth structure. Although there were no significant differences ($p > 0.05$) between the wt% concentrations of SDF (Riva Star) and AgF (Riva Star Aqua) in the infected tooth structure, affected dentine, healthy dentine nor in the line scan as a whole, there were interesting wt % concentrations that correlate well with the formulation of the Riva Star and Riva Star Aqua product content. The safety data sheets presented by Riva Star and Riva Star Aqua have similar weight concentration percentages of fluoride (5%) and silver (25%) (12). The SEM-EDS detection of calcium-fluoride mineral content is lower for infected dentine and increase progressively towards the unaffected and healthy dentine. It has been documented that Riva Star forms a calcium fluoride precipitation on the surface of the carious lesion as protein-based globules (13), so the higher fluoride wt% of Riva Star Aqua on the surface (**Figure 2**) due to the neutral pH could be investigated further with confocal microscopy to visualize what exact mechanism results in the higher fluoride wt%. It seemed that the wt% for Riva Star Aqua started lower than Riva Star in the infected tooth structure but the line scan wt% increased through the affected tooth structure towards the affected dentine for iodide (**Figure 3**) and silver (**Figure 4**), with Riva Star still achieving the highest wt % of fluoride at the start of the affected dentine compared to Riva Star Aqua. The use of ammonia in Riva Star is postulated, based on microstructural tooth research of ammonia adsorption (14), to result in a greater collagen expansion and binding compared to water alone (15). Adding nitric acid assists with the collagen expansion and stabilisation of the components to achieve a stable shelf life without refrigeration. The storage advantage of Riva Star Aqua (AgF) not needing to be refrigerated like other SDF products is ideal for clinical and outreach events within urban and rural settings. This ability to be used in rural areas where electricity or continuous refrigeration is limited speaks to the United Nations' sustainable development goals of good health and well-being as communities, which otherwise would not have been able to receive this new formulation of AgF, can be reached. Besides speaking to the UN's goal, it also

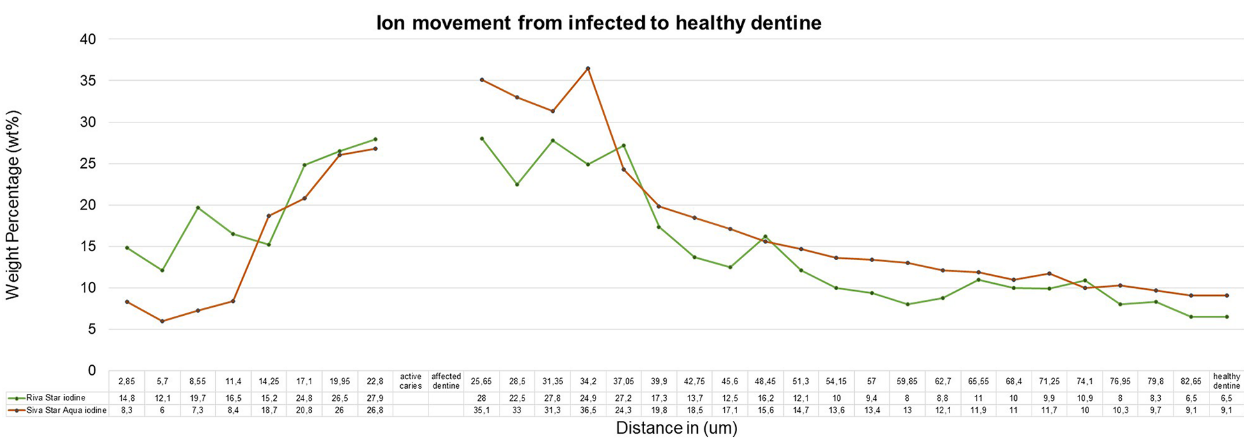

FIGURE 3
Iodine ion movement in wt%.

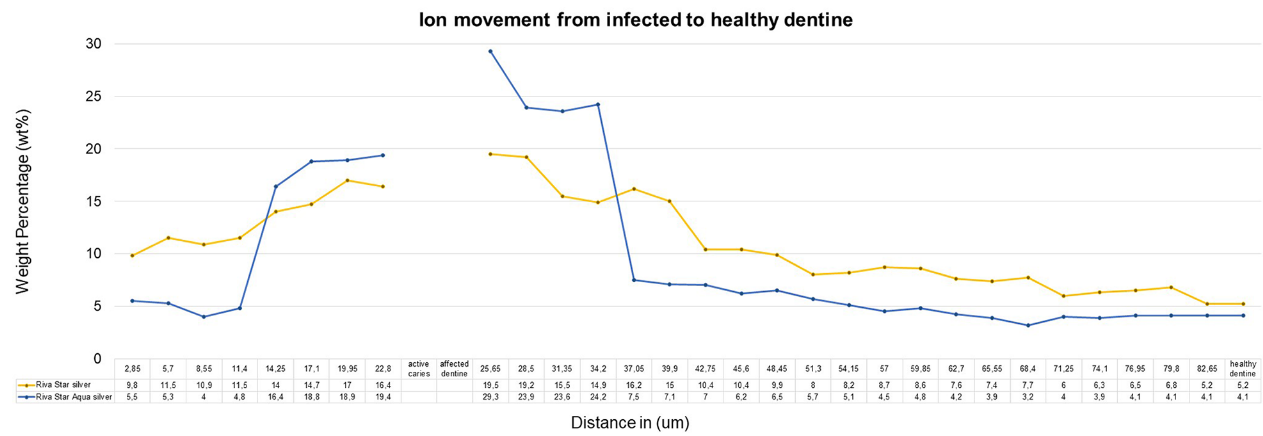

FIGURE 4
Silver ion movement in wt%.

highlights the efforts of manufacturers in creating and delivering innovation to the curative and preventative dentistry sphere. The literature from a 6-month follow-up clinical study (16) supported the findings that Riva Star Aqua and Riva Star are effective in arresting the advancement of caries. Riva Star Aqua is an ideal addition to the armamentarium of the clinician for wider population caries treatment methodologies. Additionally, teeth treated with Riva Star Aqua have shown on a hydroxyapatite microcellular surface an antibiofilm effect on the microbial biofilm (17).

The penetration of the two products through the infected and affected dentine towards the healthy dentine through the affected caries is also an important consideration. The cumulative mean fluoride weight percentage for Riva Star and Riva Star Aqua was similar (Figure 5). As the line scan analysis of the wt% continued towards the arrested caries area, it was noted that the point scan of 25.65 µm into the infected dentine seemed to be the "tipping point" for where the mineral structure became denser towards the affected dentine. The affected dentine also had the initial part closest to the infected dentine where cariogenic bacteria penetrated and was also mineralised by the various SDF products. The interdiffusion zone of Riva Star Aqua has been shown to be an effective product against *S. mutans* when assessed with other SDF products (18). The Riva Star Aqua had a non-significant higher wt% for silver (Figure 4) and iodide (Figure 3) in the various aspects of the line scan compared to Riva Star, which had a slightly higher fluoride wt% (Figure 2). This could be explained by the aqua

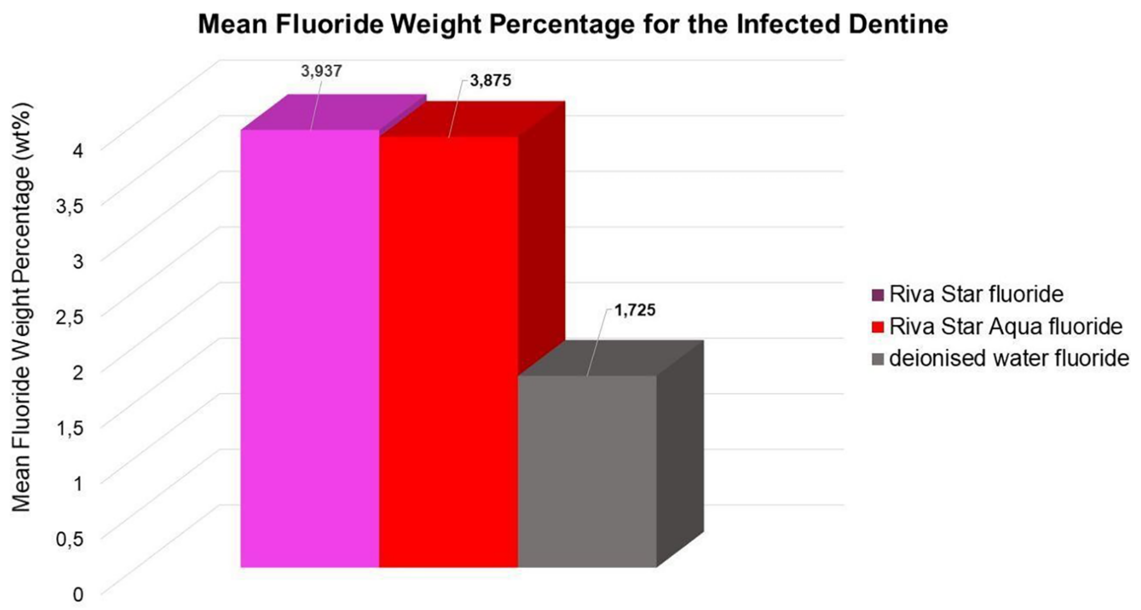

FIGURE 5
Mean fluoride weight percentage in the infected dentine.

component of Riva Star Aqua, which drove the wt% through the infected dentine into the affected tooth structure, whereas the evaporation of the solvent could have possibly delayed the initial penetration of the ions through infected caries for the Riva Star, explaining the much higher wt% of iodide (14.83 wt %) and silver (9.8 wt%) at the first line scan point in the infected dentine. Whereas Riva Star Aqua had 8.3 wt% and 5.5 wt% of iodide and silver, respectively, and could penetrate deeper due to the aqueous content and potential lack of solvent evaporation upon application.

From the literature and reports using various techniques, the silver concentration of Riva Star Aqua was estimated to be 266,477 ppm (26.65% of the content) and the fluoride concentration was estimated to be 42,429 ppm (18) compared to the fluoride concentration of Riva Star at 3,922 ppm (3). The different techniques provide different ppm values for fluoride, and further research should be completed to have the available fluoride values determined with the same methodologies, as it was out of the scope of this research. The Safety Data Sheet documents of the products indicated the same fluoride wt% for Riva Star and Riva Star Aqua. The ion movement in the various parts of the teeth was also found to be similar (**Figures 2**, **5**). Riva Star and Riva Star Aqua at contact with the infected dentine indicated the silver wt% in the infected dentine was 9.8 wt% and 5.5 wt%, respectively, indicating that the silver phosphate layer (19) formed by Riva Star also served as a reservoir and allowed deeper penetration of the silver and iodine. This also explains the lower fluoride wt% close to the caries surface of Riva Star-treated teeth, as the first container of Riva Star contains the fluoride where the initial deeper penetration was supported by the second bottle in the system. The line scan progression towards the affected dentine indicated an increase in the wt% and at the last infected dentine reading Riva Star illustrated a 16.4 wt% and Riva Star Aqua showed 19.4 wt%. The first line scan point in the affected dentine showed the following: Riva Star 19.5 wt% and Riva Star Aqua 29.3 wt%. Riva Star Aqua would, therefore, also offer resistance to future cariogenic attacks, since silver has been cited to react and bind to hydroxyapatite (20). As the line scan progressed from the affected dentine to the healthy dentine, Riva Star (5.2 wt%) had a consistently higher silver concentration than Riva Star Aqua (4.1 wt%).

For both silver and iodide, the 34.2–37.05 µm measurement from the infected dentine presented Riva Star Aqua with a higher wt% at 34.2 µm with 36.5 wt% iodide and 24.2 wt% silver compared to Riva Star with 24.9 wt% iodide (**Figure 3**) and 14.9 wt% silver (**Figure 4**). The crossover of the iodide concentration was at multiple line scan points between Riva Star and Riva Star Aqua.

When Riva Star and Riva Star Aqua came into contact with the infected dentine of the tooth samples, the iodide wt% in the infected dentine was 27.9 wt% and 26.6 wt%, respectively. The line scan progression towards the affected dentine indicated an increase in the wt% and at the last infected dentine reading the Riva Star illustrated a 26 wt% and the Riva Star Aqua registered a much higher reading at 35.1 wt%. The first line scan point in the affected dentine was Riva Star (22.5 wt%), with Riva Star Aqua having once again a much higher wt% (33 wt%). As the line scan progressed from the affected dentine to the healthy dentine, Riva Star (8.5 wt%) had a consistently lower iodide concentration than Riva Star Aqua (9.1 wt%) (**Figure 3**).

After 14 days of the infected dentine lesion, the control group presented with 1.4 wt% fluoride and this increased to 2.1 wt% at the perceived end of the infected dentine. From the affected dentine, 3.8 wt% fluoride was present and stabilized at 2.6 wt%. Riva Star (2.4 wt%) and Riva Star Aqua (2.0 wt%) were similar at the start of the line scan of the infected dentine of the tooth structure. Both Riva Star and Riva Star Aqua presented a significantly higher fluoride concentration in the infected dentine lesion compared to the control. This was to be expected as caries would reduce the wt% of the fluoride and other ions usually present in dentine. At the perceived border of the infected dentine and the transition into affected dentine, the wt% in the infected dentine for Riva Star was 5.8 wt% and 3.6 wt% for Riva Star Aqua. The start of the affected dentine showed an increase: 6.8 wt% for Riva Star and 5.5 wt% for Riva Star Aqua. At both interfaces the wt% between the two products were not statistically significant. Both Riva Star and Riva Star Aqua illustrated a fluoride wt% penetration for the entire length of the line scan to the 82.65 µm healthy dentine at 3.7 wt% and 3 wt%, respectively. Therefore, the combination of ion movement well through the infected dentine towards the healthy dentine from Riva Star and Riva Star Aqua provides the building blocks for maintaining remineralisation of the affected dentine collagen (20) (**Figure 2**).

5. Conclusion

There was no significant difference between SDF (Riva Star) and AgF (Riva Star Aqua) for the movement through the AgF and SDF groups of infected caries nor the wt% in the affected/healthy dentine. Limitations to this study are the degree of demineralisation of the infected and affected dentine between teeth, this is also why the calcium wt% was not discussed. The SDF and AgF in the *in vitro* setting had no artificial saliva exposure, so the calcium wt% changes that would take place in such a scenario were not a confounding factor. This cannot be standardised, but the wt% of fluoride in the teeth could be measured in order to determine the ion movement. Additionally, the visibly infected caries towards the affected caries area were determined to be the transition point, as seen by the line scan wt % values. The use of micro-CT evaluation of the carious lesion before and after treatment of the tooth is a valuable methodology to add to future research.

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 humans were approved by Biomedical and Ethics Committee of the University of the Western Cape. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. NP: Conceptualization, Funding acquisition, Project administration, Writing – review & editing. NN: Writing – original draft, Writing – review & editing.

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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.

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Characterization of chemical reactions of silver diammine fluoride and hydroxyapatite under remineralization conditions

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Introduction: Silver Diammine Fluoride (SDF) is a clinically used topical agent to arrest dental caries. However, the kinetics of its chemical interactions with hydroxyapatite (HA), the principal inorganic component of dental enamel, are not known. The aim was to characterize the step-wise chemical interactions between SDF and HA powder during the clinically important process of remineralization.
Methods: Two grams of HA powder were immersed in 10 ml acetic acid pH = 4.0 for 2 h to mimic carious demineralization. The powder was then washed and dried for 24 h and mixed with 1.5 ml SDF (Riva Star) for 1 min. The treated powder was then air-dried for 3 min, and 0.2 g was removed and stored in individual tubes each containing 10 ml remineralizing solution. Powder was taken from each tube at various times of exposure to remineralization solution (0 min, 10 min, 2 h, 4 h, 8 h, 24 h, and 10 days), and characterized using Magic Angle Spinning-Nuclear Magnetic Resonance (MAS-NMR) spectroscopy.
Results and discussion: ^{19}F MAS-NMR spectra showed that calcium fluoride (CaF_2) started to form almost immediately after HA was in contact with SDF. After 24 h, the peak shifted to −104.5 ppm suggesting that fluoride substituted hydroxyapatite (FSHA) was formed with time at the expense of CaF_2. The ^{31}P MAS-NMR spectra showed a single peak at 2.7 ppm at all time points showing that the only phosphate species present was crystalline apatite. The ^{35}Cl MAS-NMR spectra showed formation of silver chloride (AgCl) at 24 h. It was observed that after the scan, the whitish HA powder changed to black color. In conclusion, this time sequence study showed that under remineralization conditions, SDF initially reacted with HA to form CaF_2 which is then transformed to FSHA over time. In the presence of chloride, AgCl is formed which is subsequently photo-reduced to black metallic silver.

KEYWORDS
remineralization, MAS-NMR, cariostatic, SDF, silver chloride, fluoride-substituted hydroxyapatite

Introduction

Dental caries is a multifactorial process leading to a net mineral loss of dental hard tissues. It is a dynamic process which depends on the interaction of protective and pathologic factors in saliva and plaque biofilm (1). As reported in the global survey (2), 2.3 billion people suffer from dental caries of permanent teeth and more than 530 million children suffer from caries of primary teeth. In the UK, dental caries is the most common preventable disease and despite the prevention procedures provided by dentists in UK, the prevalence of experience of dental decay in 5-year-old children in England (d3mft) was 23.4%.

In the oral environment, the caries process is an alternating cycle of demineralization, the loss of tooth mineral tissue (principally calcium hydroxyapatite) via reactions with organic acids at lower pHs, and remineralization the redeposition of mineral from local calcium and phosphate ions at higher pHs (3) leading to net loss of mineral from the tooth, resulting in cavitation (1). If demineralization exceeds remineralization, then tissue loss occurs, whereas, if remineralization exceeds demineralization, then tissue replacement occurs, which is the aim of non-surgical clinical intervention such as SDF. Saliva is a unique biologic fluid with a complex composition. Saliva acts as a buffering agent, and plays an important role in the demineralization and remineralization in the oral cavity. Salivary calcium, phosphorous and hydroxyl ions are at a dynamic equilibrium with apatite mineral in enamel (4). During remineralization, the calcium and phosphate ions combine with the fluoride ions to rebuild a new surface layer on the subsurface demineralized lesion (1).

Non-restorative caries control (NRCC) treatment with silver diammine fluoride (SDF) is becoming a popular management strategy (5, 6). In the UK (for example), during the COVID pandemic, SDF was used as an intervention to arrest/remineralize cavitated carious lesions in primary teeth for pre-cooperative children due to the long general anesthetic waiting list (7). Clinical trials showed that SDF is an effective cariostatic agent, and safe to be used in children (6–14). However, SDF has the disadvantages of staining teeth black, unpleasant taste, gingival burn, and tattooing, which deters dentists to use it routinely due to low parental acceptance (15).

Solid state Nuclear Magnetic Resonance (NMR) spectroscopy is used to characterize compounds formed in chemical interactions and has been used in inorganic mineralized tissue dental research to identify various components (16, 17). For example, ^{19}F Magic angle spinning (MAS)-NMR can identify all existing fluorine compounds in crystalline, amorphous, or adsorbed forms, within enamel mineral (18–20).

It is known that fluoride (F) interacts with the hydroxyapatite (HA) in enamel or dentine to form fluorapatite (FA) which provides cariostatic protection (e.g., 19, 21–23). Further, other studies have investigated the compounds formed when high concentration F products such as SDF (44,800 ppm F) interact with dental hard tissues (19, 24, 25). However, these previous studies did not investigate the intermediate phases in a time sequential manner, or used the detailed capability and sensitivity of ^{19}F MAS-NMR. Hence, the aim of this current study was to investigate the chemical interactions between SDF and HA powder, and characterize the products, under standard *in vitro* remineralizing conditions at a sequence of time points within 24 h (known to be the time period over which the calcium is used up) and finally at 10 days using ^{19}F, ^{31}P and ^{35}Cl MAS-NMR spectroscopies in order to understand the complex chemistry during the remineralization processes.

Materials and methods

To mimic exposure of dental hard tissue mineral to cariogenic acidic conditions, 2 g of HA powder (4.14 µm particle size, P3R SD, Captal HA, Plasma Biotal, UK) were immersed in 10 ml of demineralizing solution (0.1 mol/L acetic acid buffered to pH = 4.0 using potassium hydroxide) in a centrifuge tube and placed in a shaking-incubator at 37˚C for 2 h (26, 27). After centrifugation for 3 min, the powder was collected, washed, and dried on filter paper for 24 h in an incubator at 37°C. The demineralized HA powder was then mixed with 1.5 ml of 38% SDF (Riva Star, SDI, Australia, LOT 1213678) solution for 1 min, using cement spatula and made into a paste and then air-dried for 3 min, following the British Society of Paediatric Dentists (BSPD) clinical protocol for SDF application. The SDF treated demineralized HA powder was divided equally into 10 samples of 0.2 g each and stored in darkened centrifuge tubes to prevent light interaction with SDF. In 7 of the tubes, 10 ml of remineralization solution [2.0 mmol/L $CaCl_2$,1.2 mmol/L KH_2PO_4, 150 mmol/L NaCl and buffered to pH = 7.0 using potassium hydroxide; as described by Siddiqui et al. (28)] were added. These tubes were placed in a shaking incubator at 37°C for different time intervals (t = 0 min, 10 min, 2 h, 4 h, 8 h, 24 h, and 10 days). At the end of each time point, the powder was collected from one of the tubes, washed, dried and analyzed using MAS-NMR spectroscopies.

MAS-NMR spectroscopy

^{19}F, ^{31}P and ^{35}Cl MAS-NMR spectra were collected using a 600 MHz, 14.1 T, Avance NEO spectrometer (Bruker, Germany) using the parameters listed in Table 1. The ^{35}Cl MAS-NMR spectra were referenced to 0 ppm of the signal in solid NaCl purchased commercially (29, 30). The spectra were processed and analyzed using the TopSpin software package (Bruker, version 4.0.8).

Results

Figure 1 shows the time series of ^{19}F MAS-NMR spectra of HA powder treated with SDF and immersed in remineralization solution. The initial (t = 0 min) spectrum shows a dominant sharp peak at −115.8 ppm which is demonstrative of loosely

TABLE 1 Parameters used for MAS-NMR.

Parameters for MAS-NMR	^{19}F	^{31}P	^{35}Cl
Resonance frequency (MHz)	564.8	242.9	58.8
Spinning frequency (KHz)	22	12	12
Signal of reference adjusted chemical shift/ppm	−120	0	0
Number of scans	128	32	512
Size of rotor	2.5mm	4mm	4mm
Reference material	1 mol/l aq NaF	85% aq H_3PO	Solid NaCl

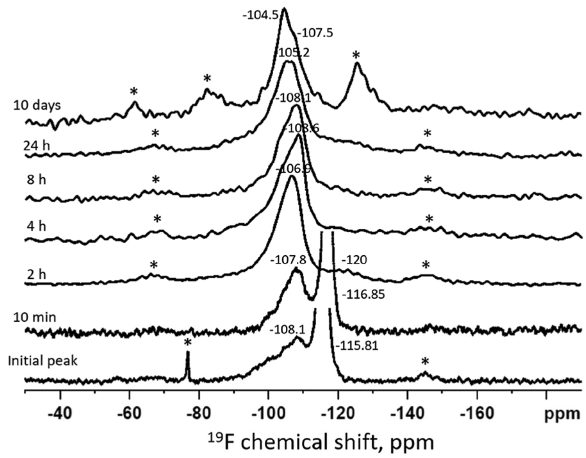

FIGURE 1
Time series of ^{19}F MAS-NMR spectra of HA powder treated with SDF and immersed in remineralization solution. The duration of immersion is indicated next to each spectrum. The asterisks show the spinning side bands. The initial spectrum shows a peak position at −116 ppm indicating presence of free fluoride and the broad peak at −108 ppm suggesting the presence of a mixture of CaF_2 and FSHA. With passage of time, the peak shifted from −108 ppm to −104.5 ppm indicating that more FSHA were formed at the expense of CaF_2.

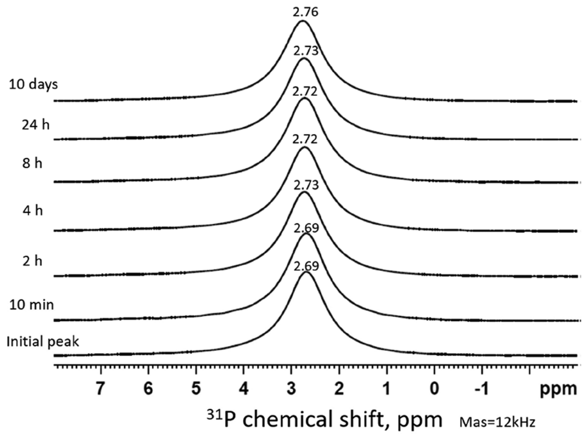

FIGURE 2
Time series of ^{31}P MAS-NMR spectra of HA powder treated with SDF and immersed in remineralization solution. The duration of immersion is indicated next to each spectrum. The peak position (2.7 ppm) represents the HA pattern which remains the same throughout the time sequence.

bound fluoride adsorbed on the surface (31). This sharp signal was also present in the $t = 10$ min sample, though with the center shifted to −116.9 ppm. Also, the broad minor peak centered at −108.1 ppm shows instantaneous reactionary products. Similarly, at $t = 10$ min, a very small and broad peak was visible at −107.8 ppm indicating the formation of calcium fluoride (CaF_2) (18). At $t = 2$ h, the sharp peak around −116 ppm was replaced by a broad peak at −107 ppm confirming formation of CaF_2 (18). At $t = 4$ h, CaF_2 formation continued as indicated by the broader peak at −108 ppm. At $t = 24$ h this peak position shifted to −105.2 ppm, indicating the formation of fluoride substituted hydroxyapatite (FSHA) (18), which is a mineral in which some (but not all) of the hydroxyl (-OH) groups in HA are substituted by F. At $t = 10$ days, the broad peak remained but shifted to −104.4 ppm, confirming the formation of FSHA. In addition to this signal, the spectra at $t = 24$ h and $t = 10$ day also showed a peak at −108 ppm.

Figure 2 shows the time series of ^{31}P MAS-NMR spectra of the demineralized HA powder treated with SDF, collected after immersion in remineralization solution. From $t = 0$ to t = 24 h, there was only one single sharp peak around 2.7 ppm, suggesting the crystalline structure of the HA did not change during their exposure to remineralization solution. No other phosphate phases were detected.

Figure 3 shows a ^{35}Cl MAS-NMR spectrum of the demineralized HA powder treated with SDF after immersion in remineralization solution for 24 h. The spectrum showed the reference peak at 0 ppm for NaCl. The sharp peak at 36.5 ppm shows presence of silver chloride (AgCl).

After the NMR scan, when the powder was retrieved, the whitish color changed to black as shown in Figure 4.

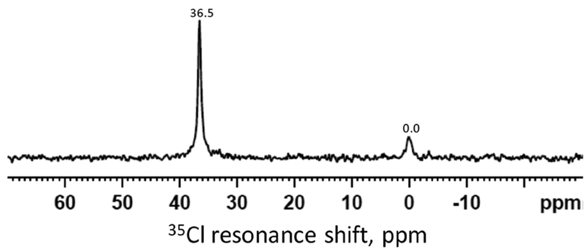

FIGURE 3
^{35}Cl MAS-NMR spectrum of the demineralized HA powder treated with SDF and immersed in the remineralization solution for 24 h. The peak at 0 ppm is the reference peak for NaCl. The peak at 36.5 ppm indicates the presence of AgCl.

FIGURE 4
Powder retrieved after NMR scan and exposed to light. The white powder turned to black indicating metallic silver was formed.

Discussion

The ^{19}F MAS-NMR results (Figure 1) shows CaF_2 was dominantly formed at an early stage ($t < 2$ h). This could be due to the very high F concentration (44,800 ppm) in SDF. When SDF dissolved in the remineralizing solution, the free F^- ions could react rapidly with the Ca^{2+} ions in the solution to form insoluble CaF_2 (20, 32, 33). However, as the signal at −108 ppm was broad and covered a wide range of values with down to −100 ppm, contemporaneous formation (albeit a small amount) of FSHA (between −102 and −107 ppm) at this initial state cannot be excluded. Furthermore, the asymmetrical peaks at −106 to −104 ppm at later time points indicated the overlap of FSHA and CaF_2. However, no fully fluoride substituted fluorapatite (FA) peak was observed. Investigating the chemical shift of the current spectra, the maximum substitution was up to 20% (18). From the trend of the chemical shift, FSHA was formed over time at the expense of CaF_2. In the oral environment, the SDF may interact saliva with high calcium rapidly to form insoluble CaF_2, which acts as a reservoir for FSHA formation, providing protection against acidic attack, though not as effective as fully substituted FA (34–36).

The ^{31}P spectra (Figure 2) show the presence of HA in all time points, mainly from the HA powder. It is surprising that no other phosphate products such as silver phosphate (Ag_3PO_4) was detected, as reported in previous literature (26, 37). This is due to the presence of NaCl in the remineralizing solution, causing the formation of AgCl instead (Figure 3). As the content of Ag^+ was small compared to the NaCl concentration, all the Ag ions were used up before they could combine with the phosphate ions. In previous studies, the demineralizing solutions did not contain NaCl, hence, Ag_3PO_4 was formed (26).

In the present experiment, the powders removed from the tubes were white as they were kept away from light. The black color (Figure 4) after NMR scan was likely due to the photo-reduction of AgCl to metallic silver. Clinically, SDF is topically applied using an applicator brush onto carious tooth surfaces which turn black in minutes, mainly on dentine and less so on enamel. As oral environment saliva contains chloride ions, it is likely AgCl particles are formed, which is a whitish insoluble powder. If the AgCl particles are deposited on the smooth enamel surface, they will be washed away. However, if they are deposited and accumulate in rough exposed dentinal tubules, they cannot be washed away quickly. The AgCl is then photo-reduced to black metallic silver which causes the discoloration in dentine. As these insoluble Ag particles block the dentine tubules, they may act as pulpal barrier, thus reducing dental pain and have anti-bacterial effect to reduce caries progression (38–40).

Conclusions

This study characterized the products formed as a reaction between HA and SDF under remineralizing conditions. It was found that initially CaF_2 was formed, which subsequently changed to FSHA over a 24 h period. AgCl was formed rapidly which could be photo-reduced to metallic silver.

Data availability statement

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

Author contributions

MK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. SS: Supervision, Writing – review & editing, Conceptualization. NK: Formal Analysis, Investigation, Methodology, Supervision, Writing – review & editing. PA: Conceptualization, Methodology, Supervision, Writing – review & editing. FW: Conceptualization, Methodology, Supervision, Writing – review & editing, Writing – original draft.

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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.

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A pilot study on the global practice of informed consent in paediatric dentistry

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Background: Conducting oral treatment early in the disease course, is encouraged for better health outcomes. Obtaining informed consent is an essential part of medical practice, protecting the legal rights of patients and guiding the ethical practice of medicine. In practice, consent means different things in different contexts. Silver Diamine Fluoride (SDF) and Silver Fluoride (SF) is becoming popular and cost effective methods to manage carious lesions, however, cause black discolouration of lesions treated. Obtaining informed consent and assent is crucial for any dental treatment—and has specific relevance with SDF/ SF treatments.

Methods: The aim of this paper is to describe informed consent regulations for dental care in a selection of countries, focusing on children and patients with special health care needs. An online survey was shared with a convenience sample of dental professionals from 13 countries. The information was explored and the processes of consent were compared.

Results: Findings suggest that there are variations in terms of informed consent for medical practice. In Tanzania, South Africa, India, Kenya, Malaysia and Brazil age is the determining factor for competence and the ability to give self-consent. In other countries, other factors are considered alongside age. For example, in Singapore, the United Kingdom, and the United States the principle of Gillick Competence is applied. Many countries' laws and regulations do not specify when a dentist may overrule general consent to act in the "best interest" of the patient.

Conclusion: It is recommended that it is clarified globally when a dentist may act in the "best interest" of the patient, and that guidance is produced to indicate what constitutes a dental emergency. The insights gathered provide insights on international practice of obtaining informed consent and to identify areas for change, to more efficient and ethical treatment for children and patients with special needs. A larger follow up study is recommended to include more or all countries.

KEYWORDS

informed consent, child consent, self-consent, ethical practice, medical consent, paediatric dentistry

1 Introduction

Oral diseases pose a major health burden, affecting over 3.5 billion people globally (1). According to the Global Burden of Disease survey 2017, untreated dental caries in permanent teeth is the most common health condition, whilst over 530 million children suffer from dental caries of primary teeth annually (2). If left untreated, dental caries can lead to pain, tooth loss and infection, affecting quality of life and productivity. As such, conducting treatment early in the disease course is encouraged.

In addition to dental caries, children also suffer from traumatic dental injuries, which are very common in the first ten years of life. These injuries are more common particularly in school-going children who may be involved in sports activities. These injuries may include not only laceration of chin and lips but also fractures of facial bones and teeth that require children to be taken to a dentist for further management and treatment (3).

Obtaining informed consent before treatment, delivered to a patient is an essential part of contemporary medical practice, protecting the legal rights of patients and guiding the ethical practice of medicine (4). Informed consent is when a person gives permission before they receive treatment or an examination after receiving all pertinent information about the procedure. In practice however, consent means different things in different contexts, largely determined by whether consent is being obtained for legal, ethical or administrative purposes.

Globally, persons who can provide consent varies. Typically, whether or not a patient can provide consent themselves is determined by each patient's comprehension of the treatment proposed (5). Younger children, Patients with Special Health Care Needs (PSHCN) or those who are incapacitated, and are unable to fully understand the treatment process or purpose, require consent for care provided by legal parents, guardians or an acting caregiver. In such situations, assent for treatment by children or PSHCN is promoted. Assent pertains to actively involving the patient in making and taking decisions about their own body and health (6).

The aim of this article is to describe informed consent regulations for dental care in a selection of countries, focussing on children and PSHCN. This paper's view of consent aims to provide insights on international practice of obtaining informed consent for paediatric dentistry and to identify areas for change, to more efficient and ethical treatment of children and PSHCN populations.

2 Methods

The cross-sectional study was conducted, in 2021/22, by means of a self-administered questionnaire, by representatives from different countries. The selection of countries was based on personal contacts and past research collaborations. The questionnaire asked each representative to provide information on the policies, guidelines and practice of informed consent and assent in the respective countries/areas. A convenience sample of 13 countries/jurisdictions across the globe were used. The data collected through the questionnaire. The principle researchers collated the data from the questionnaires and and cross-checked the data with the laws and regulations referenced. Once all data were combined, tabled and organized, all authors contributed to the discussion to bring context of the different countries' laws and regulations.

3 Results

3.1 Different measures of competency enable self-consent

Globally, parent or legal guardian are required to give informed consent to "minors" for medical/dental treatment. Age is the main determinant of being a minor in most countries. Table 1 summarizes the legal ages for obtaining consent for dental treatment for children and exceptions to the "age-rule". Of the countries included in this evaluation, Tanzania, South Africa, India, Kenya, Malaysia and Brazil fully rely on age as determining factor for competence and the ability to give self-consent: In contrast, Pakistan and Singapore do not have a standard age for self-consent to medical/dental treatment and instead, only require verbal consent from parents/guardians or family members for treatment (23, 26).

In other countries, there are varying exceptions and multiple factors that are taken into consideration to apply the "age-rule" for consent. In Singapore, the United Kingdom, and the United States the principle of Gillick Competence is applied. Gillick Competence is used to identify children aged under 16 who have the legal competence to consent to medical treatment. Competency is conferred if the child can demonstrate sufficient maturity and intelligence to fully understand the proposed treatment and its implications, including an understanding of the risks and any possible alternative course of action (38).

TABLE 1 Summary of the legal requirements for consent and the age of self-consent for dental treatment.

	Age of giving self-consent	Exceptions to enable giving self-consent as a minor	Act/law/policy stipulating specific age for self-consent	Summary of consent allowed during an emergency situation	Assent legally required?
Brazil (7–9)	>18 years	None	No 2-SEI/2017-CGSAJ/DAPES/SAS/MS, together with Children and Teenager Statute, and The Brazilian Dental Ethical Conduct (Resolution CFO—118/2012) in the article 11°	– Medical professionals are forbidden from performing any medical procedure without previous explanation and consent of the patient or his/her legal representative, except in cases of imminent threat to life	No
China (10)	≥18 years	<8 years has no civil capacity and 8–17 years restricted civil capacity	Civil Code of People's Republic of China Chapter 2 and Chapter 6	– Dentists may provide treatment with the approval by the person-in-charge of the hospital	No
India (11–15)	>18 years	12–18 years can consent for examination but not procedures	Majority Act, Guardian and Wards Act, and Indian Contract Act	– "Loco parentis" person in charge: example: Principle of the school. – No consent needed in medical emergency/ life endangerment	No
Kenya (16, 17)	>18 years	None	Kenyan Children Act No 8 of 2001	– Reasonable steps to obtain consent – Clinician – Court of law – Next of kin – Not necessary in emergency that could result in death or irreversible damage	No
Malaysia (18, 19)	>18 years	None	The Laws of Malaysia Act 21: Age of Majority Act 1971 and Malaysian Medical Council guideline: Consent for treatment of patients by registered medical practitioners	– Court of law – "Protector" when child is in protective custody – When parent or legal guardian is unavailable, Primary and secondary physician co-sign during life endangerment – Dental practitioner may act for the best interest of the patient, in consultation with parents or legal guardian	No
Maryland state USA (20)	>18 years	Gillick Competency[a]	People's Law Library of Maryland	– Minor has the same capacity as an adult	No
Netherlands (21)	>16	Gillick Competency[a]	Wet Geneeskundige BehandelOvereenkomst	– Dentists may act to create a non-acute situation.	Verbally Assent
Nigeria (22, 39)	≥18 years	Married woman and head of households can give consent regardless of their age.	Section 29 (4) of the 1999 Constitution of the Federal Republic of Nigeria	– Dentist to avoid death or serious harm – Police – Nigerian Supreme Court	Yes
Pakistan (23–25)	None set for routine dental procedures. Self-consent is required only major surgical procedures ≥ 18 years	Gillick competence[a]	Majority Act, 1975	– Physician – Consultation with family members	No
Singapore (26–29)	>21 years	Gillick competence[a]	No statute law, however "*…presumption in law and medical practice is that all adults have capacity to consent or refuse treatment, unless proven otherwise…*"	– Doctor/dentist acting in "best interest" – Some healthcare institutions may necessitate a "double clinician consent", where a registrar-level and a consultant-level doctor/ dentist will discuss and concur on a shared best-interest decision. This is not required legally, but an organisational policy.	No

(*Continued*)

TABLE 1 Continued

	Age of giving self-consent	Exceptions to enable giving self-consent as a minor	Act/law/policy stipulating specific age for self-consent	Summary of consent allowed during an emergency situation	Assent legally required?
South Africa (6)	≥12 years	With sufficient maturity Need accompanied parental consent for surgical procedures <16 years	Children's Act No 38 of 2005	– Court appointed Social worker – Clinical manager/Superintendent of hospital	Yes
Tanzania (30)	>18 years	None	The Law of the Child Act, No.21 of 2009	– Government authorities – Doctor/Dentist – Police	Yes
United Kingdom (31, 32)	≥16 years	Gillick Competency[a]	The Children Act 1995 The Children Act 1995 (England, Wales, Scotland) The Children Order 1995 (Northern Ireland)	– Any adult with parental responsibility. – Practitioner in the "best interest of a child"	No
Vietnam (33–37)	>18 years	15–18 years may perform civil transactions (this may be argued as dental treatment)	None	– Legal representative or representative appointed by court – Head of medical facility – Dentist/medical practitioner	No

[a]Gillick Competency: is used to identify children aged under 16 who have the legal competence to consent to medical treatment. Competency is conferred if the child can demonstrate sufficient maturity and intelligence to fully understand the proposed treatment and its implications, including an understanding of the risks and any possible alternative course of action (38).

The Netherlands also have an age range (12–16 years) wherein both the parent and the child should give consent with two exceptions: (1) if not treating the child will give a serious disadvantage; (2) If the treatment is the well-considered wish of the child. In Nigeria, the social status of the child's family can influence the decision to give self-consent (21). If a child, regardless of their age, is married, they are considered as an emancipated minor, which means that they can give consent. Likewise, if a child becomes the head of a household, for example as a result of both parents dying, then again, they are considered capable of providing consent for medical treatment.

In Vietnam, for those who are from 15 to 18 years old, the civil act capacity determines the ability of the individual to provide consent. The civil act capacity of an individual is his or her capability to establish and perform civil rights and obligations. Per article 21 of the Civil Code, those who are above six years of age also have civil act capacity. However, in a similar vein to the Gillick Competency test, if the patient is incapable of "recognizing or controlling his/her acts due to mental disease or other ailments", the court may revoke or restrict their civil act capacity (article 22 and 23). In such a case, a legal representative will give consent to medical/dental treatments on their behalf (35).

Like Vietnam, India applies age as a determinant of competence, however comprehension of treatment is also considered, whereby an incompetent patient is one "who is a minor" or a person of unsound mind or a patient who is unable to weigh, understand or retain the relevant information about his or her medical treatment; unable to make an informed decision because of impairment of or a disturbance in the functioning of the mind or brain: or a person who is unable to communicate the informed decision regarding medical treatment through speech, sign or language or any other mode (40).

3.2 Parents/legal guardian refusing consent

When patients are not deemed capable of providing consent themselves, it is requested that a parent or legal guardian consent on their behalf. However, in some situations, one or two of the parents or guardians may refuse to provide consent for treatment. In this situation, there are different procedures in place depending on the context.

In India, "when the parents/guardian refuses their child to undergo the diagnostic procedure/treatment after a complete and comprehensive information has been provided, the parents should be informed in a discreet professional manner of consequences of refusal, failing that the physician can be held liable in the court of law. The conflict of "best interest standards" for treatment of the child vs. "rational parent standard" for the attitude of parents is matter of never ending debate" (11). In Malaysia, when one parent consents and the other refuses, counselling of the parents to reach an agreement on what is in the child's best interest is conducted. A decision can be made on a case-by-case basis in the best interest of the patient by the medical practitioners when the patient is in a situation of helplessness and the decision is the most appropriate and fair to that child under the circumstances. If the child is under the temporary custody, the protector or police officer may authorise treatment without obtaining consent from the parent/guardian in certain circumstances.

In Tanzania, Section 4 (2) of the Law of the Child Act insists that the best interest of a child should be the primary consideration in all actions pertaining to the child. Also Section 9 (1) of the same Act provides for the right to life, dignity, respect, leisure, liberty and health for children and parents, guardians and relatives are responsible to ensure the enjoyment of those rights.

Again Section 13 (1) of the same Act prohibits degrading treatments to children, and institutions like local government authorities and police are vested with legal duties under the said Act to ensure children's safety (30). Similarly, in *Singapore*, the healthcare provider is expected to uphold the "best interest" of the patient or child, in line with the Mental Capacity Act, regardless of who holds the ultimate authority in healthcare decision making (29). Should a decision, or non-decision (willful neglect or acts of omission), lead to potential harm of the child, this would constitute a child protection concern and other actors are brought in to resolve the conflict. Initially this is sought from a single or multiple agencies, such as a school. If resolution is not sought, then the Child Protection Service (CPS) is brought in (40).

In the United Kingdom, as in Singapore, another actor is brought in if the young person themselves, or the individual with parental responsibility refuses to give consent to medical treatment for the young person or child. In most countries participating in this study, the Court of Protection is brought in and can overrule the decision if it is deemed to be in the best interest of the young person or child, such as, if refusing the treatment may result in the death or permanent injury.

3.3 Country specific ethical dilemmas

There are several country-specific issues related to consent that add to the complexities of securing informed consent for dental treatments.

In India, most dentists are unaware of all the necessary aspects of the consent process (41, 42). This could be explained by the lack of guidance in how to obtain consent, in the Dental Council of India's Code of Ethics (43). In a similar vein, according to a recent study in Pakistan, it was found that 93% of parents are not aware that they need to obtain a copy of a signed informed consent document for their record (23). This reflects the lack of knowledge within the country related to informed consent and rights.

In Nigeria, an ethical dilemma dentist's face is the request to extract the maxillary central primary incisors when they erupt ahead of the lower central incisors. This is because of the widespread belief that a child who erupts the maxillary central primary incisors ahead of the lower has supernatural abilities that makes the child able to pronounce curses. Parents therefore, request dentists to remove these teeth otherwise they hide the child out of sight from guests until the lower teeth fully erupts or get "quacks" to do the extraction. The presence of natal/neonatal teeth gives similar concerns to the parents. Also, a diastema is regarded as a sign of beauty and patients sometimes visit the dentist to create an artificial diastemas (44). Dentists are faced with ethical challenges when the size of the requested diastema is large with increased risk for exposure of dentine and its attendant complications.

In Singapore, healthcare decision making can be affected by the source of financing. Singapore's healthcare utilises a mixed financing system (45). Particularly for dental services, where limited subsidies are available, procedures that are arguably elective, such as orofacial reconstruction or orthodontic cases, may be costly. For example, a child may wish to retain a primary molar by pulpotomy and stainless steel crown, while the parents may deem this too expensive and opt instead for an extraction. As such, treatment decision can become intertwined with willingness-to-pay (46). Patients also face this dilemma in Nigeria.

In Vietnam, an ethical dilemmas often arises when family members of the child disagree on an emergency treatment. Due to the Law on Medical Examination and Treatment, physicians are legally prevented from delivering care, unless the patients' family comes to a consensus (47). However, there is a new draft of the Law on Medical Examination and Treatment, submitted to the National Assembly in March 2021, which proposed that a doctor or dentist provide treatment to a child, even if the parents object to giving consent for treatment on behalf of the child (48).

If the Gillick Competency test is met, then the child is deemed capable of providing consent to treatment (38). In countries applying Gillick competency, ethical dilemmas arise when children who are considered Gillick competent choose different treatment options than the parents. If a Gillick competent child gives consent this may not be overruled by the parents if the practitioner feels the treatment is appropriate.

Beyond the country specific issues related to obtaining informed consent highlighted above, there are also cultural or religious practices that, due to their risk of harm to patients, they raise ethical concerns and have specific consent related considerations. In Pakistan, the religious beliefs can be problematic as some believe a negative medical outcome is God's Will, and as a result they would prefer to accept their child's fate and pray, rather than to provide consent for treatment (49). In Tanzania, due to religious or cultural beliefs, some parents enucleate the tooth buds of as a way of reduction the risk for infections and illnesses (in Swahili- Dawa ya Jino Kung'oa), contrary to the recommendation of dentists or dental professional boards. Consent is often not sought from the parent nor assent from the child (in case of lower incisor extraction). Similar practices are also seen in several other East African countries such as Kenya (50). In South Africa, dentists are sometimes faced with the ethical dilemma of children, over the legal age of consent (12 years), requesting their four maxillary incisors to be extracted with the parents' approval, as it is believed that it will make the individual more "attractive and romantic" and will therefore ensure a better life partner (51).

4 Discussion

Dentists, as professional health care providers, are required to provide care based on sound ethical principles. Ethics is defined as "the moral principles or virtues that govern the character and conduct of an individual or a group" (52). Ethics therefore refers to our actions and how we relate to one another as human beings. It includes our intentions and the consequences, even when one's actions don't always result in the intended outcome. In more simple terms we can translate ethics as: do unto others as you would have them do unto you. However, acting ethical is most often more complex than definitions or principles and the challenges faced in clinical situations. Although ethical principles and guidelines are available to guide dental practitioners—these principles are subject to different individual interpretations. Nonetheless, ethics forms the core of all decision making, patient relationships, hence being an ethical professional and is a lifelong process through consistent ethical behaviour.

The ethical principle "Autonomy" refers to "Patients have the right to determine what should be done to their bodies" (52) and the parents or legal guardians have the right to decide what happens to their children's bodies. In simple terms autonomy can be described as informed consent: "permission granted in full knowledge of the possible consequences, typically that which is given by a patient to a doctor for treatment with knowledge of the possible risks and benefits" (53). The process must be explained to the patient requiring any treatment/clinical intervention, and involving that patient in decision making; and even if that involvement is limited, it is critical in meeting the legal, ethical and administrative requirements of informed consent. However, enabling true informed consent can be challenging and requires flexibility, especially where young children and PSCHNs are concerned.

Although all countries included in this study have governing, rules and regulations regarding consent and the age of consent, the final decision making falls to the dentist. "Regardless of the parent's request, the dentists' primary ethical, moral and legal duty is to the child" (54). Even the Gillick Competent principle assumes that "the child has the maturity and ability to understand what the treatment involve as determined by medical practitioner, i.e., they have been assessed to have adequate capacity (i.e., intelligence, competence and understanding) to be able to make an informed decision about their treatment". Although subjective, the dental practitioner responsible to determine if the child is Gillick competent or not.

Many dental practitioners would like to apply the "best interest" principle in routine practice, thereby taking control of the decision making regarding treatment of minors. However, the responses from most countries confirmed that dentists may only act in the best interest of the patient and treat the patient without formal consent if it is a life threatening situation and/or there is no legal person available to give consent. However, in Nigeria children are primarily considered the property of the State and parents are custodians of children on behalf of the State (55). This rights-oriented model for child care limits absolute parental control over the child and gives the State the right to interfere in the care of the child (44). The Health Professions Council of South African guidelines states that the "best interest" principle does not apply to patients who are competent, have sufficient maturity and mental capacity (53). With the exception of Pakistan, dental practitioners globally are dependent on consent for dental treatment obtained by a legal parent/guardian or the child of age for routine dental care. Informed consent therefore requires a dynamic interaction between the dentist, patient and parent/legal guardian. Dentist must provide sufficient information and education to enable parents and children who can self-consent to make the right decisions.

Although some countries' laws mention the dentists' authority to act in emergency situations, what constitutes an emergency in the dental setting is not specified or defined. Most laws only refer to "emergency" or "life threatening" situations, which leaves room for individual interpretation regarding dental conditions. Examples of dental emergencies are trauma, abscess formation (without facial swelling) or a lost filling among other. However, it is debatable if these dental conditions can be considered as "emergencies" for which dentist may overrule consent/assent or even act in the best interest of the child regardless of consent.

A limitation of this study is that it only includes 13 countries and a larger follow up study involving more or all countries should be done. The results of this pilot study can therefore not be safely generalized.

5 Conclusion

The policies and guidelines enabling children to self-consent for dental treatment varies globally. Some countries make use of a combination of age and Gillick Competency, whereas others strictly adhere to age as determining factor for competency. Obtaining assent from a child-patient is compulsory in some countries, but not specified in laws or regulations in all countries. Many countries' laws and regulations do not specify when a dentist may act in the "best interest" of the child- overruling general consent rules. Taking into consideration the aesthetic implications of SDF/SF treatments, obtaining informed consent plays a crucial role in successful management of caries with these products.

It is recommended at three areas are clarified to help dentists in providing appropriate dental care; first, when a dentist may act in the "best interest" of the child. Second, guidance what constitutes a dental emergency and third, clarity within the law with regard to overruling consent. A larger follow up study is recommended to include more or all countries around the world.

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.

Author contributions

NP: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft. GB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. ME: Data curation, Investigation, Writing – original draft, Writing – review & editing. MF: Data curation, Investigation, Writing – original draft, Writing – review & editing. SG: Data curation, Investigation, Writing – original draft, Writing – review & editing. SG: Data curation, Investigation, Writing – original draft, Writing – review & editing. AJ: Data curation, Investigation, Writing – original draft, Writing – review

& editing. AK: Data curation, Investigation, Writing – original draft, Writing – review & editing. DL: Data curation, Investigation, Writing – original draft, Writing – review & editing. PL: Data curation, Investigation, Writing – original draft, Writing – review & editing. SM: Data curation, Investigation, Writing – original draft, Writing – review & editing. RM: Data curation, Investigation, Writing – original draft, Writing – review & editing. JM: Data curation, Investigation, Writing – original draft, Writing – review & editing. MM: Data curation, Investigation, Writing – original draft, Writing – review & editing. AQ: Data curation, Writing – original draft, Writing – review & editing. NT: Data curation, Investigation, Writing – original draft, Writing – review & editing.

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Remineralization and inactivation of carious lesions treated with silver fluoride in Brazilian children with special healthcare needs

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Introduction: Providing conventional, restorative dental care to children with special healthcare needs (CSHCN) often requires sedation using general anesthesia. Saliva consistency, diet, and oral hygiene practice are different for CSHCN, and limited evidence is available on the efficacy of silver fluoride (SF) for the management of carious lesions for this vulnerable population.
Methods: Parents of CSHCN were educated about silver fluoride as a treatment option for caries. In total, 550 carious lesions from 100 participants were identified and scored according to the Nyvad Caries criteria. A total of 100 lesions with Nyvad scores 1, 2, and 3 were treated with a single application of silver fluoride and observed postoperatively at 1, 3, and 6 weeks.
Result: The results indicate statistically significant ($p < 0.05$) differences in lesion remineralization over the 6-week follow-up period. At the 6-week follow-up, more than 85% of all lesions were remineralized across all children, regardless of condition or original Nyvad score of 1, 2, or 3.
Conclusion: A single application of silver fluoride has demonstrated effectiveness in remineralization and inactivation of carious lesions over 6 weeks among Brazilian CSHCN. Silver fluoride should be considered an option for the management of carious lesions among CSHCN. Further studies are recommended, including larger sample sizes, longer follow-up times, a second application of SF, and different special needs conditions.

KEYWORDS

silver diamine fluoride (SDF), silver fluoride, caries remineralization, caries inactivation, children with special care needs

1 Introduction

Children with special healthcare needs (CSHCN) often experience functional impairment, impacting their oral health, as well as facial growth and development, making conventional dental care more challenging. CSHCN often also have impaired intellectual development and communication skills, and therefore do not have the ability to interpret and express dental pain. It has been reported that CSHCN require more complex restorative treatments as the affected children do not report pain as

Abbreviations
ASD, autism spectrum disorder; CP, cerebral palsy; CSHCN, children with special healthcare needs; DS, Down syndrome; SDF, silver diamine fluoride; SF, silver fluoride; WHO, World Health Organization.

easily (1). Several investigations have highlighted the difficulties of performing conventional dental care on children with cognitive impairment (2–4).

Providing dental care to CSHCN often requires hospitalization to receive dental treatment under general anesthesia. Minimally invasive dentistry has shifted the focus to remineralization or inactivating caries as an alternative to conventional restorations. The ideal caries management technique for CSHCN should be a simple, non-invasive dental procedure that lasts and that is able to remineralize the tooth surfaces below and around restorations. The atraumatic restorative technique (ART) has proven to be a viable option for some patients; however, the ART procedure still requires moderate cooperation and is considered a temporary solution. As described by Rosenblatt et al. (5), products containing silver fluoride (SF) have become a non-invasive alternative to dental restorations. In vitro studies suggested that silver fluoride regimens also inhibit the growth of *Streptococcus mutans* (4). SF is a new generation of the well-known silver diamine fluoride (SDF) with improved properties. SF is ammonia-free and therefore has less risk for tissue burn and irritation, improved smell, has a more physiological pH, and has more stability, therefore not requiring refrigeration (6). If disease progression can be halted through remineralization/inactivation of carious lesions, it might assist in the overall management and oral health of CSHCN without the need for repeat sedation or general anesthesia appointments.

Therefore, the aim of this study was to evaluate the clinical remineralization and inactivation of active carious lesions among Brazilian CSHCN after being treated with a single application of silver fluoride.

TABLE 1 Description of Nyvad caries criteria (7).

Score	Diagnostic	Criteria
0	Sound	Normal translucency and enamel texture (possible light pigmentation in a sound fissure).
1	Active caries (intact surface)	Enamel surface opaque, no shiny surface, whitish/yellowish enamel surface, rough on probing, usually covered with bacterial plaque. There is no detectable loss of substance. On a smooth surface, the carious lesion is located close to the gingival margin. In pits and fissures, the morphology is intact and the lesion extends along its walls.
2	Active caries (surface discontinued)	Same criteria for score 1. Superficial defect. Localized (microcavity) only in enamel. Absence of soft enamel.
3	Active caries (cavitation)	Enamel/dentin cavitated easily visualized by eye; surface of cavity softened on gentle probing. It might have or not pulp involvement
4	Inactive caries (intact surface)	White, brownish or dark enamel surface. Enamel can became shiny hard and smooth on gentle probing. There is no clinically detectable loss of substance. On a smooth surface, the carious lesion is typically located to some distance from gingival margin. In pits and fissures, an intact morphology is observed with the lesion extending along the cleft walls.
5	Inactive caries (surface discontinuity)	Same criteria for score 4. Superficial defect localized (microcavitaded) in enamel. Without enamel softened on probing.
6	Inactive caries (cavitation)	Enamel/dentin cavity easily visible clinically—cavity can be shiny and hardened on probing with light pressure. Without pulp involvement.
7	Restoration with sound surface	Normal translucency and enamel texture (possible light pigmentation in a sound fissure).
8	Restoration + active caries	Caries active lesion could be cavitated or not
9	Restoration + inactive caries	Caries inactive lesion could be cavitated or not

2 Materials and methods

Approval from the Ethical Committee was obtained (CEP, Brazilian Association of Dentistry, Duke de Caxias, Rio de Janeiro, Brazil) before the study. The study was conducted at the Brazilian Association of Dentistry Caxias, State of Rio de Janeiro, Brazil.

In total, 125 CSHCN diagnosed with autism spectrum disorder (ASD), Down syndrome (DS), or cerebral palsy (CP) at the age of 7–12 years and their parents were invited to participate in the study. The children had to have at least one carious lesion indicated for conventional restoration [caries limited to dentin, according to Nyvad et al. (7)] (Table 1).

Parents were informed about SF by making use of the patient information leaflet adapted from the British Society of Paediatric Dentistry (8). The information included the following: use of silver compounds in medicine and dentistry; composition of SF and its mechanism of action; the indications for SF treatment; the procedure of application; effectiveness and possible concerns; and photographs of lesions treated with SF. Written consent was obtained by parents/legal guardians as well as assent from the participating children aged over 12 years. This is the age for obtaining assent for research purposes in Brazil. The parents who did not authorize their child to be in the study or did not accept the terms of consent, still received dental treatment in the conventional away as offered by the facility. All identified children received additional and/or emergency treatment if needed before commencement of the study.

2.1 Clinical procedures and follow-up

Active carious lesion from each participant were identified for the study and scored according to the Nyvad system to obtain baseline data (Table 1) (7). All clinical procedures were performed by qualified, experienced single operators and all Nyvad scoring was carried out by an additional single operator. An experienced expert in the Nyvad scoring system, who was calibrated by Bent Nyvad in 2012, trained the principal investigator who conducted all examinations and Nyvad scoring. Interrater reliability between the expert and principal investigator was Kappa = 0.81 and intracalibration of the principal investigator was Kappa was 0.89 (Cohen's Kappa coefficient).

After baseline scoring, the SF was applied to the active carious lesions (Nyvad scores 1, 2, or 3) as per the manufacturer's instructions (9):

FIGURE 1
SF being applied in a lesion, with cotton roll isolation.

(1) Isolation: cocoa butter was applied to the lips and surrounding gingival tissues, and care was taken not to inadvertently coat the surfaces of the caries lesions. Isolation of the tooth was achieved with cotton rolls and the lesion was lightly dried with compressed air (Figure 1);
(2) SF application: one drop of SF (Riva Star Aqua, SDI, VIC, Australia, product registration code: D349082 / K172047/ GMDN code 45232 Class IIa) was dispensed into a glass Dappen dish and the microbrush was dipped into the solution. The SF was directly applied to the carious lesion. The lesion was then dabbed with a clean cotton pellet to remove any excess SF, and a gentle flow of compressed air was applied until the medicament was dry. The second step, the application of potassium iodide, was not done in this study, as the aim of this study was remineralization and not limiting discoloration.

No local anesthesia, sedation, or general anesthesia was used during the visit.

Patients were recalled at 1, 3, and 6 weeks after the single application of SF and the lesions were evaluated again according to the Nyvad scoring system at each visit to record remineralization within and around the treated lesions.

2.2 Statistical analysis

The results are reported with a descriptive analysis in the form of percentages. Differences in remineralization levels were evaluated with the Friedman test between weeks 1, 3, and 6. Pairwise comparisons were made with the paired Wilcoxon signed-rank test. p-Values were adjusted using the Bonferroni multiple testing correction method, and $p = 0.05$ was considered to be statistically significant. The statistical analysis was conducted using R Project 4.3.2 software (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 2 Baseline Nyvad scores or lesions observed in 100 children.

Score	Nyvad caries criteria	*N*	Percentage
1	Active caries (intact surface)	171	31.1
2	Active caries (surface discontinued)	111	20.2
3	Active caries (cavitation)	100	18.1
4	Inactive caries (intact surface)	25	4.5
5	Inactive caries (surface discontinuity)	84	15.3
6	Inactive caries (cavitation)	3	0.6
7	Restoration with sound surface	0	0
8	Restoration + Active caries	12	2.2
9	Restoration + Inactive caries	44	8
Total		550	100

3 Results

In total, 125 children aged 7–12 years and their parents were invited to participate in the clinical study; however, only 100 children took part in this study; 25 were excluded because they did not obtain consent from their parents/guardians to participate. Of the 100 participating children, 28 had DS, 27 had CP, and 45 had ASD. In total, 550 carious lesions were identified and scored according to the Nyvad criteria, as reported in Table 2.

Among the lesions, 300 active carious lesions had Nyvad scores of 1 ($n = 100$), 2 ($n = 100$), and 3 ($n = 100$), and were selected and treated with a single application of SF and analyzed for 6 weeks. Teeth with a baseline Nyvad score of 8 would also have been eligible for treatment but had a low prevalence ($n = 12$); therefore, they were excluded from the analysis in this study.

Follow-up evaluations, after a single application of SF at 1, 3, and 6 weeks, are reported in Table 3. The results indicate that the majority of the carious lesions remineralized or inactivated (Nyvad criteria: 4–6 grouped together) throughout the observation period. After 6 weeks, of those carious lesions with a Nyvad score of 1, only 11% did not remineralize; of those lesions with a Nyvad score of 2, only 10% did not remineralize; and of those lesions with a Nyvad score of 3, only 14% did not remineralize. The same pattern was found for all conditions, indicating that one single application of SF was able to promote a quick remineralization/inactivation of the active carious lesions, therefore avoiding progression of the disease. Figure 2 shows the increase of remineralization from week 1 to week 3 and from week 3 to week 6, with the exception of lesions with a Nyvad score of 3 that had a small, non-significant decrease from week 3 to week 6 (from 87% to 86%, i.e., −1 percentage point) but kept a steady increase from week 1 (78% remineralized/inactivated). Statistical tests (Friedman test and paired Wilcoxon signed-rank test) reported statistically significant differences ($p < 0.05$) between the weeks for the total sample and for most of the Nyvad scores in each condition. The most prominent differences have been between week 1 and week 6, also indicating the continuous effect of a single application of SF.

TABLE 3 Baseline and follow-up Nyvad scores of all lesions.

Group	Nyvad caries criteria		Base line	Remineralized Nyvad criteria: 4, 5 or 6			Variation w3-w1	Variation w6-w3	Frieadman *p*-value
	Score	Diagnostic		1 week	3 weeks	6 weeks			
Total ($N = 100$)	1	Active caries (intact surface)	100	54 (54%)[a]	70 (70%)[b]	88 (88%)[c]	16 (16 pp)	18 (18 pp)	<0.001*
	2	Active caries (surface discontinued)	100	77 (77%)[a]	82 (82%)[a]	89 (89%)[b]	5 (5 pp)	7 (7 pp)	<0.001*
	3	Active caries (cavitation)	100	78 (78%)[a]	87 (87%)[b]	86 (86%)[b]	9 (9 pp)	−1 (−1 pp)	<0.001*
	1, 2, 3	Total active carious lesions	300	211 (70%)[a]	244 (81%)[b]	265 (88%)[c]	33 (11 pp)	21 (7 pp)	<0.001*
Autism ($N = 45$)	1	Active caries (intact surface)	45	25 (56%)[a]	32 (71%)[b]	40 (89%)[c]	7 (16 pp)	8 (18 pp)	<0.001*
	2	Active caries (surface discontinued)	45	35 (78%)[a]	37 (82%)[a,b]	40 (89%)[b]	2 (4 pp)	3 (7 pp)	0.022*
	3	Active caries (cavitation)	45	35 (78%)[a]	39 (87%)[a]	39 (87%)[a]	4 (9 pp)	0 (0 pp)	0.072
	1, 2, 3	Total active carious lesions	135	95 (70%)[a]	108 (80%)[b]	119 (88%)[c]	13 (10 pp)	11 (8 pp)	<0.001*
Down Syndrome ($N = 28$)	1	Active caries (intact surface)	28	15 (54%)[a]	19 (68%)[a,b]	24 (86%)[b]	4 (14 pp)	5 (18 pp)	0.001*
	2	Active caries (surface discontinued)	28	21 (75%)[a]	23 (82%)[a]	25 (89%)[a]	2 (7 pp)	2 (7 pp)	0.052
	3	Active caries (cavitation)	28	22 (79%)[a]	24 (86%)[a,b]	24 (86%)[b]	2 (7 pp)	0 (0 pp)	0.001*
	1, 2, 3	Total active carious lesions	84	58 (69%)[a]	66 (79%)[b]	73 (87%)[c]	8 (10 pp)	7 (8 pp)	0.001*
Cerebral Palsy ($N = 27$)	1	Active caries (intact surface)	27	14 (52%)[a]	19 (70%)[a,b]	24 (89%)[c]	5 (19 pp)	5 (19 pp)	<0.001*
	2	Active caries (surface discontinued)	27	21 (78%)[a]	22 (81%)[a]	24 (89%)[a]	1 (4 pp)	2 (7 pp)	0.097
	3	Active caries (cavitation)	27	21 (78%)[a]	24 (89%)[a]	23 (85%)[a]	3 (11 pp)	−1 (−4 pp)	0.097
	1, 2, 3	Total active carious lesions	81	56 (69%)[a]	65 (80%)[b]	71 (88%)[b]	9 (11 pp)	6 (7 pp)	<0.001*

pp, percentage points.

[a,b,c]Different letters indicate significative differences between observations with the paired Wilcoxon signed-rank test ($p < 0.05$).

*$p < 0.05$.

4 Discussion

It has been proven *in vitro* that silver and fluoride ions can remineralize demineralized enamel and dentin (10, 11). Clinical studies have suggested SDF's efficacy in preventing caries in both the primary and permanent dentition and is being widely implemented worldwide for the treatment (arresting) of dental caries (12, 13). SDF has been proven to be safe, effective, patient-centered, timely, efficient, and equitable (14). However, limited scientific evidence is available on the efficacy of SF. Although SDF has an ammonia base and SF is ammonia-free, they contain the same active ingredients—38% silver fluoride and 5% fluoride (SDI, Riva Aqua Product information leaflet)—and the results of this study can therefore be compared with previous studies on SDF. The reason for using SF in this particular study was its improved properties. It was of the authors' opinion that the improved properties would make the treatment more tolerable for children who are sensitive to oral stimulus, taste, or smell. Comparing the patients' acceptance and experience between SDF and SF is an area for future research. Rosenblatt et al. (5) highlighted the need to increase access to care, improve

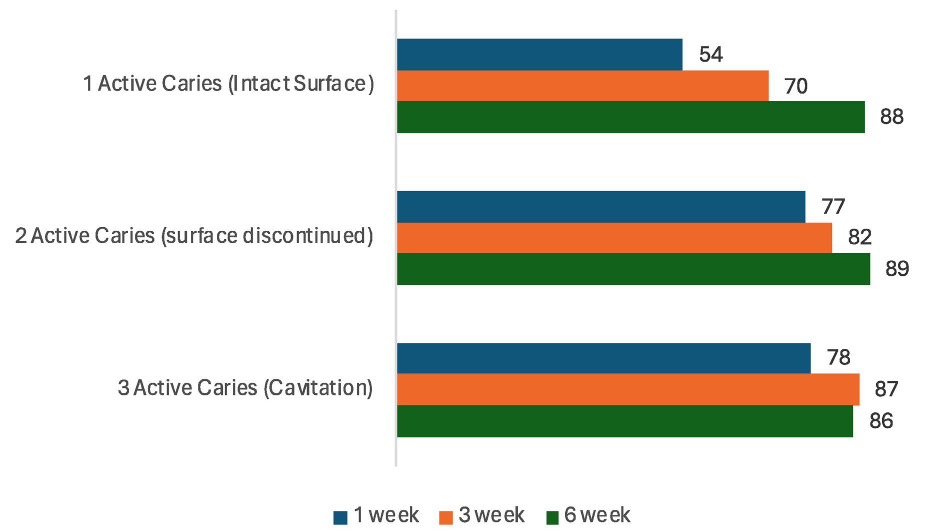

FIGURE 2
Percentage of lesions that remineralized/inactivated (Nyvad criteria 4–6), after 1, 3 and 6 weeks ($N = 300$ lesions, 100 per score).

oral health, and ultimately reduce the need for emergency care for CSHCN. However, there is limited evidence on the efficacy of SDF/SF among CSHCN. The authors wanted to explore if the efficacy of SF will differ among CSHCN as they often have different diets, saliva consistency/quantity, and cooperation regarding home oral hygiene practice.

The baseline Nyvad scores of this study (Table 2) report the high number of untreated active carious lesions (Nyvad scores of 1, 2, and 3: $n = 382$) among this group of CSHCN. This prevalence of untreated carious lesions is similar to the results among schoolchildren, as reported by Machiulskiene et al. (15). The possible reasons for untreated carious lesions can include challenges associated with transport, access to care, communication from the child, as well as some practitioners not being comfortable managing CSHCN. Regarding caries treated with restorations, it is notable that no restorations with sound surfaces were reported (Nyvad score 7), 12 restorations had active caries (Nyvad score 8), and 44 restorations presented with inactive caries (Nyvad score 9). These findings suggest that restorations are not stopping disease progression within this population group.

This study did not only focus on the management of cavitated lesions (Nyvad score 3) but also included initial, demineralized lesions (Nyvad score 1, 2) to evaluate the remineralization of these lesions in this vulnerable group of children. Focusing on early intervention and prevention shifts the focus from treating cavities (e.g., fillings) to rather managing the disease and its progression.

Without proper and timely intervention, dental caries and other oral diseases can lead to severe systemic infections, may negatively affect oral health-related quality of life (oral Health Profile-OHRQoL), and are associated with decreased academic performance and school attendance of a child (16, 17). To address the high rate of untreated caries in high-risk populations, the Centers for Disease Control and Prevention recommends school-based sealant programs, which have demonstrated clinical effectiveness and cost effectiveness (18). Furthermore, a review on the effect of SDF in preventing caries in primary dentition showed significant reductions in the development of new caries vs. placebo after 24 months and was not more or less effective after 12 months compared with glass ionomer sealants (19).

The results of this study show that SF has a high prevention rate, as 88% of Nyvad score 1 and 89% of Nyvad score 2 lesions remineralized within 6 weeks (Table 2). No significant differences were found between the different special needs groups as all lesions remineralized (>85%) regardless of the specific condition. These results suggest that SF might be the ideal, cost-effective option for not only treating active carious lesions but also preventing caries among CSHCN. SF requires fewer steps and is less techniques-sensitive than application of fissure sealants, which makes it even more ideal with children with neurological and associated behavioral challenges. It is the authors' opinion that existing sealant programs may benefit from SF as an alternative to fissure sealants or to be used in a combination of placing sealants and treating active carious lesions with SF.

Overall, this study showed inactivation of cavitated lesions at 1 (78%), 3 (87%), and 6 (86%) weeks postoperatively (Table 2). These findings are comparable to those from other controlled clinical trials with longer follow-up times, which indicated no differences in the 6- and 12-month caries inactivation rates comparing SDF vs. atraumatic restorative treatment (19). With limited cooperation associated with CSHCN, even the atraumatic restorative technique can be a challenge. It is important to note that the findings reported in this study are after a single application of SF and that the results might improve with a second application as part of the care plan.

The results of this study indicated that SF could become a key element for prevention and comprehensive management programs that meet the World Health Organization (WHO) Millennium Goals (20). SDF has also recently been added to the WHO's essential medicine list. The limitations of this study include a small sample size and that it was limited to a follow-up period of 6 weeks after a single application. Further research is recommended to support the findings of this study and to confirm the long-term benefits to this population group.

5 Conclusion

A single application of silver fluoride has demonstrated effectiveness in the remineralization and inactivation of carious lesions over 6 weeks among Brazilian CSHCN. Silver fluoride should be considered an option for the management of carious lesions among CSHCN. Further studies are recommended, including larger sample sizes, longer follow-up times, a second application of SF, and different special needs conditions.

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 humans were approved by Comitê de Ética em Pesquisa—Universidade Federal do Rio de Janeiro.

The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardians/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

NP: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. VP: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal Analysis, Data curation. RE: Writing – review & editing, Writing – original draft, Investigation, Formal Analysis, Data curation. SC: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal Analysis, Data curation. SG: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization.

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Comparing cytocompatibility of two fluoride-containing solutions and two resin-based restorative materials—a pilot study

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Background: Cytocompatibility should always be considered, especially if the surface of treated carious lesions is close to soft tissue or is accidentally exposed to the oral soft tissue by the clinician.
Methods: The aim of the present study was to compare the cytocompatibility of two fluoride-containing liquids and two resin-containing restorative materials with buccal mucosa fibroblasts. The fluoride-containing materials were silver diamine fluoride and water-based silver fluoride.
Results: The statistical analysis was completed by comparing the positive control growth of the buccal mucosa fibroblasts to the growth of cells exposed to various materials. The one-way ANOVA with Tukey's HSD result was completed. All the assessed materials compared to the control wells for both the 24 and 48 h time intervals indicated a significant cytocompatibility result, except for the test wells with Stela (SDI) at the 24 h time interval. There was no significant difference between the step 2 liquids and the two dental materials in cytocompatibility at the 24 h interval. All four materials indicated no significant differences between the cytocompatibility of any dental materials for 48 h.
Conclusion: The cytocompatibility assessment for Riva Star and Riva Star Aqua with the direct method in a full dispensing drop is not viable for step 1 of the fluoride-containing liquids. The use of Stela Light Cure is a suitable material that will be in contact with buccal mucosa as it showed potential for increased cytocompatibility compared to Riva Light Cure. Riva Star Aqua is more cytocompatible than Riva Star.

KEYWORDS

silver diamine fluoride, silver fluoride, resin restorative material, buccal fibroblast cells, resin modified glass ionomer

1 Introduction

The use of silver diamine fluoride (SDF) has been well established for preventing the progression of dental caries and has shown promise in vulnerable populations as well as an intervention to caries progression (1). The ease of use is useful in treating large numbers of patients as a treatment modality for the prevention of caries (2). Various formulations of SDF have been assessed in the literature for caries remineralization, and the subsequent acid resistance of treated teeth (3) improved changes in the surface's micro-hardness (4, 5); the management of carious lesions as a result of molar incisor hypomineralization have been recorded (6). It has been realized that teeth usually treated with various SDF products have large active cavitated carious lesions, with the tooth very well at the end of its life span. SDF products are, in most cases, the last chance for the survival of the tooth pulp. Some teeth might additionally receive a restoration that would inevitably have prolonged contact with the buccal mucosa; hence we have included two resin-based restorative materials for their cytocompatibility to buccal fibroblasts. Very deep pre-molar cavities of an *in vivo* study showed that Riva Light Cure (Southern Dental Industries (SDI) Limited, Australia) produced more damage to the pulp than Riva Self Cure Glass Ionomer (7). The *in vitro* material cytocompatibility results on pulp stem cells for Riva Light Cure indicated a significantly lower cytocompatibility to the pulpal stem cells compared to the control cells for all time intervals (24, 48, and 72 h of exposure) (8). However, these materials are deemed to be biocompatible (7) and are therefore the ideal comparative control materials for the assessment of cytocompatibility.

Initially, with the advent of SDF, pulpal cytocompatibility was debated (9, 10). The SDF products are not indicated for direct pulp application nor teeth with clinical signs of pulp involvement (11). However, the proximity of the carious lesion to the pulp cannot be ignored, hence the various cytocompatibility assessments that have been completed in the literature. The translation of *in vitro* studies toward the clinical sphere is represented by a clinical trial with a similar incidence of pulpal reactions in the patient groups for both the primary and secondary SDF-treated teeth groups (12). This pilot study is more focused toward the surrounding soft tissue of the oral cavity represented by buccal fibroblasts. In the initial stages of SDF use, it was predicted that oral tissue upon contact would present with reversible oral lesions (13). The importance of the buccal fibroblast cytocompatibility with SDF (Riva Star, SDI Limited, Australia) and water-based silver fluoride (AgF; Riva Star Aqua, SDI, Australia) gives further insight into the effect of these materials when they inadvertently come into contact with the oral soft tissue. In the literature, diluted versions of SDF showed inhibitory effects on cultured gingival fibroblasts with dilutions of 1,000 and 10,000 times (14). The clinician, however, uses an application brush and the volume of liquid is much bigger than the large dilutions used for *in vitro* studies. During SDF use and inadvertent contact with the soft tissue, the clinician will immediately start rinsing the affected area to reduce the tissue interaction and contact time. This technique was performed in a clinical trial and 3 of the 373 patients presented with small, mildly painful white lesions on the mucosa. There was complete resolution in 48 h (12). In another trial of 888 children, gum bleaching occurred in 38 children as a result of contact with SDF and resolved within 2 days (15). *In vitro* research has shown that there was a pH-induced chemical burn or at the very minimum mucosal corrosion with both 3 min and 1 h exposures of epithelial simulations. The authors also indicated that SDF was still less damaging than phosphoric acid etchant (16), which is widely used. SDF temporarily stains the skin as it does not penetrate the dermis; however, desquamation of skin results in skin pigmentation after 14 days with the shedding of keratinocytes (17, 18). The aim of this pilot study was to assess the long-term exposure, e.g., 24 and 48 h intervals, of these materials on buccal fibroblasts.

The use of the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide] assay provides a sensitive and quantitative colorimetric assay that measures the proliferation and viability of the cells' mitochondrial activity based on the conversion of the MTT reagent into formazan crystals. These assessments of cell viability provide insight to potential cellular interaction; in particular to the buccal mucosa, simulated by buccal fibroblasts. This pilot study present results with a clinically relevant volume of a single drop from each step of the SDF and AgF bottles. The two formulations, namely SDF (Riva Star, SDI, Australia) and AgF (Riva Star Aqua, SDI, Australia), were assessed previously by the authors of this pilot study for the penetration of materials into carious tooth structure toward affected dentine. The neutral pH of AgF also resulted in remineralization, and a depth of ion penetration was found to be similar to that of SDF (Riva Star). It was also noted that the surface of the carious lesion exposed to the oral environment and inevitably the buccal mucosa has the highest concentrations of ions derived from the SDF and AgF materials (19). With the current SDF literature only utilizing microtiter volumes (14), a full dispensing drop would be used in this pilot study as per the volume dispensed from the dispenser bottle. This study hypothesized that the cytocompatibility of the caries remineralization products of SDF and AgF would be no different to the restorative materials that contact the buccal mucosal fibroblasts. The aim of this study was to compare the cytocompatibility with buccal mucosa fibroblasts directly exposed to SDF, AgF, and two control materials, namely Riva Light Cure (SDI) and Stela Light Cure (SDI).

2 Materials and methods

2.1 Sample preparation

Five restorative material samples (height of 1 mm and diameter of 3 mm) were produced according to the manufacturer's recommendations for Stela (SDI) and Riva Light Cure (SDI). Two time periods would be assessed for the direct exposure of the restorative materials to the buccal mucosa fibroblasts in Dulbecco's Modified Eagle's Medium (DMEM), namely 24 and 48 h. The restorative material samples were sterilized with ethylene gas (Steri-Vac 4XL gas sterilizer, Model 400DGP; 3M Center, St Paul, MN, USA) stored at room temperature. The samples were assessed after 72 h to ensure the ethylene gas would not influence the cytocompatibility assay. The prepared restorative sample was placed directly in the well for direct contact with the medium and buccal fibroblast cells. Riva Star (SDF, SDI) and Riva Star Aqua (AgF, SDI) were used in their respective step 1 and 2 formulations to the volume of one dispensed drop, as that would be the clinical scenario. Each drop from the dispensing bottle (approximately 30 µl) (20) was placed directly into each well in the well plate.

2.2 Cytocompatibility assay

The cell viability assays were completed following an established method (21). This human oral fibroblast cell line was established in the Oral and Dental Research Institute, University of the Western Cape, as these fibroblasts were well suited to simulate the cells that would be exposed to the Riva Star and Aqua formulations as well as the restorative materials for the oral environment. Stocks of these cells were kept frozen in liquid nitrogen and retrieved for use. Cells were maintained and cultured in standard conditions. The viability of cells after the 24 and 48 h intervals of exposure was evaluated using the MTT assay.

To test the cytocompatibility of the products toward these buccal mucosa fibroblasts, the cells were first grown to near confluence and then were seeded in 96-well microtiter plates at a density of 1×10^5 cells per well. The cells were maintained in DMEM containing 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin cocktail (penstrep) HyClone™; Cytiva, Marlborough, MA, USA) in a 37°C humidified incubator with 5% CO_2 saturation. After 24 h cells, were microscopically checked for strong cell growth and the culture medium was replaced with fresh medium containing the different samples (22). Two 96-well plates were produced with samples for a 24 and 48 h assessment period for cytocompatibility. The sample distribution in each 96-well plate therefore consisted of each well containing one material sample per time (e.g., SDF bottle 1: $n = 5$; SDF bottle 2: $n = 5$; AGF bottle 1: $n = 5$; AGF bottle 2: $n = 5$; Rival Light Cure: $n = 5$; and Stela Light Cure: $n = 5$) as well as 20 untreated control wells containing only buccal mucosa fibroblasts.

Cells were exposed to the sample/medium mix for 24 and 48 h after which the MTT assay was completed (21). A total of 100 µl of the MTT reagent [prepared from 5.0 mg/ml stock solution and diluted with DMEM medium using a dilution factor of 1:10 (Sigma)] was added to each well. The plates were incubated again at 37°C for 4 h. The MTT reagent was then removed and replaced with 100 µl alkaline dimethyl sulfoxide to dissolve the purple formazan crystals (23). The restorative material samples remaining in the wells were removed at this point. After a 15 min incubation period at 37°C, the absorbance of the samples was measured at 540 nm using the microtiter plate reader. The absorbance at 630 nm was used as a reference wavelength (SPECTROstar Nano; BMG LABTECH) (21). The percentage of cell viability was calculated to the control wells. Control values were taken as 100% of the average control-wells values and subsequently expressed as a percentage of 100% using the following formula: [100/(Optical density of the control buccal fibroblast cells × Optical density of the fibroblast cells exposed to the test materials)] – 100.

3 Results

The statistical analysis was completed by comparing the control growth as 100% of the buccal mucosa fibroblasts to the growth of cells exposed to the various materials. The one-way ANOVA with Tukey's HSD result was completed. A p-value <0.05 indicated that significant differences were present. In the 96-well plate, the addition of the drop in step 1 from the Riva Star and Riva Star Aqua bottles resulted in an immediate change in medium color. This is indicative of a pH change in the medium. This resulted in a shock of the cells; upon completion of the cell culture, the wells were black and could not be read by the spectrophotometer. However, step 2 of both SDI products did not show a change in color in the wells, indicating that the change in pH only occurred with step 1 of both the SDF and AgF liquids.

Regarding the cells of the control wells, both the 24 and 48 h time intervals indicated a significant difference between the fluoride-containing liquids and the dental materials assessed, except for the test wells with the dental material Stela at the 24 h time interval. The comparison between both the step 2 liquids and the two dental materials showed that no significant difference in cytocompatibility was present at both the 24 and 48 h intervals (Table 1). Cytocompatibility improved from the 24 h interval to the 48 h interval and indicated that the Riva Star Aqua step 2 (42.74%) is comparable to Stela Light Cure at 53.09%. Riva Light Cure decreased in cytocompatibility from the 24 to the 48 h time interval.

TABLE 1 Cytocompatibility survival rate at different time intervals in percentage of the control wells.

	Riva Star step 1	Riva Star step 2	Riva Star Aqua step 1	Riva Star Aqua step 2	Riva Light Cure	Stela Light Cure
24 h	N/A	16.9	N/A	19.7	46.18	53.09
48 h	N/A	26.08	N/A	42.74	27.41	57.66

4 Discussion

The hypothesis of this study was accepted since the cytocompatibility of the caries remineralization SDF and AgF products were not significantly different to the biocompatible restorative materials in contact with the buccal mucosal fibroblasts.

The water-based Riva Star Aqua (AgF) uses water as the suspension medium instead of ammonia (SDF); otherwise, the formulation to Riva Star is similar to fluoride (5%), silver (25%), and ammonium iodide (8%). The difference became visible in the 48 h results where the cytocompatibility of the AgF (42.74) improved compared to SDF (26.08). This pilot study specifically focused on the effect of the SDF and AgF that would be in contact with the buccal mucosa, hence the use of the fibroblasts. Based on the comparison and the result showing no statistical significance, the SDF and AgF materials can be considered biocompatible. In clinical trials, a very small percentage of participants experienced oral lesions (12) and gum bleaching (15), further supporting the low incidence when the products are handled correctly.

There is a clear transition of ions from the surface of the treated tooth toward the pulpal cells. The weight percentage of ions decreases as the SDF and AgF move through the tooth structures (19). Step 1 for both materials could not be assessed for buccal fibroblast compatibility due to the silver precipitation of the material. In the literature, step 1 of Riva Star was assessed in a study of SDF exposure to primary tooth stem cells. The results indicated cell viability and the proliferation assay revealed that the clinical concentration of SDF (38%) was not cytocompatible on primary tooth stem cells. However, closer to the concentration that will diffuse toward the pulp and the dentine bridge that covers it, a concentration of 0.0038% SDF promoted cell proliferation and osteogenic differentiation. That study revealed that with the ELISA experiment, the dentine exposed to 38% SDF released TGF β-1, indicating that SDF could promote reactionary dentinogenesis (24). It is important to keep in mind that a dentine bridge of 1.5 mm is considered sufficient to limit the negative effects from eluates from dental materials, and with the carious structure above the pulp that will be remineralized with the SDF products, the possible exposure to the dental pulp also becomes more limited. In addition, the SDF products usually work as a step 1 and step 2 protocol, resulting in a more favorable result for cytocompatibility when combined (25, 26).

Stela Light Cure as a restorative material compared to Riva Light Cure presented a non-significant better cytocompatibility at both time intervals, with the 48 h time interval having a greater cytocompatibility of 57.66% compared to the 27.41% cytocompatibility of Riva Light Cure. Riva Star Aqua step 2 is more cytocompatible than Riva Star step 2. The results in Table 1 indicate that Riva Star Aqua step 2 at the 48 h interval is comparable to Stela Light cure. The cytocompatibility results therefore infer that the clinician should use their clinical judgment to prevent direct pulp contact if the healthy or carious dentine covering the pulp has a thickness of less than 1.5 mm. Riva Star, representing an SDF product in this pilot study, showed better cytocompatibility than other assessed SDF products from the literature (25). Therefore, Riva Star Aqua, from a cytocompatibility point of view, is a suitable clinical choice in addition to the other advantage it possesses over Riva Star of not containing ammonium iodide.

5 Conclusion

The limitation of the study was that step 1 of Riva Star and Riva Star Aqua was unable to provide a result due to the silver precipitation. In addition, mixing the two components (steps 1 and 2) of both materials and then exposing the buccal fibroblasts could have been assessed to evaluate their combined effect, but the premise of silver precipitation is still likely considering the current results. The assessment of cytocompatibility for Riva Star and Riva Star Aqua is ideal as per the dentine disc method and therefore presents a clinically relevant cytocompatibility assessment of the materials (26). The use of Stela Light Cure is a suitable material as it showed potential for increased cytocompatibility compared to Riva Light Cure.

6 Limitations of the study

This study is *in vitro* and is limited by not being able to capture the inherent complexity of the pulp system and its reaction to external stimulus, e.g., dental material constituents interacting with the cells. The liquids from step 1 of the Riva Star and Riva Star Aqua could not be evaluated. This is therefore a pilot study, and further research with larger sample sizes and adapted methodologies to overcome the limitations could be conducted.

7 Data management plan

Only the researchers have access to the data and they will not be shared with third parties. Data management practices will be compliant with the POPI Act. Data were stored securely in a durable and accessible format and in a manner that ensures its authenticity and integrity as well as meeting all legal and confidentiality requirements. The data will be retained securely within the department, in the researcher's own office, and stored on a hard drive as a password-protected file. The data might have long-term value and will be appropriately preserved and accessible for future research. Anonymized datasets will be stored for a minimum of 5 years and be deposited in the Institutional Research Data Repository on completion of the study (Kikapu data repository; https://eresearch.uwc.ac.za/kikapu/). The principal investigator will use an ORCID identifier when depositing data. Data management and storage will be done as per UWC guidelines. Research data remain the property of the university. The data management plan is therefore in line with UWC policies. Data security and management are in place on a secure Google Drive Folder and a soft copy back-up on a hard drive in a locked office at Tygerberg Oral Health Centre.

Data availability statement

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

Author contributions

RM: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. NN: Writing – review & editing. NP: Writing – review & editing, Resources, Funding acquisition, Conceptualization.

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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.

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Chemical kinetics of silver diammine fluoride in demineralization and remineralization solutions—an *in vitro* study

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Introduction: Silver Diammine Fluoride (SDF) is a clinical minimal intervention to manage dentin caries. Its chemistry in demineralization conditions has been investigated widely, but far less in remineralization conditions. The aim was to investigate and compare the chemical reactions when SDF is added to remineralization and demineralization solutions.
Methods: 0.01 ml SDF (Riva Star) was added to deionized water (DW); demineralization (DS = pH4) and remineralization (RS = pH7.0) solutions. The time sequence of concentrations of NH_4^+, F^-, and Ag^+ were measured using ion selective electrodes (ISEs) every 2 min. The pH was also measured. Precipitates were characterized using x-ray Diffraction (XRD) and, ^{31}P and ^{19}F nuclear magnetic resonance spectroscopy (NMR).
Results: The concentrations of NH_4^+ and Ag^+ showed decreasing trends in DW (–0.12 and –0.08 mM/h respectively), and in DS (–1.06 and –0.5 mM/h respectively); with corresponding increase in F^- concentration (0.04 and 0.7 mM/h respectively). However, in RS, NH_4^+ concentration showed little change (0.001 mM/h), and Ag^+ and F^- concentrations were negligible. XRD results showed that precipitates (in RS only) contained AgCl, and metallic Ag. NMR showed that fluorapatite/carbonated fluorapatite (FAP/CFAP) were formed. The pH increased after SDF addition in all three solutions.
Discussion: SDF dissolved to release NH_4^+, F^- and Ag^+. In DW and DS, NH_4^+ combined with Ag^+ to form diamminesilver, causing an increase of F^- and pH. In RS, F^- reacted with Ca^{2+} and $(PO)_4^{3-}$ to form FAP/CFAP, and Ag^+ reacted with Cl^- to form AgCl/Ag. These suggests why SDF is effective in managing dentin caries.

KEYWORDS
SDF, demineralization, remineralization, XRD, NMR, AgCl

Introduction

Demineralization and remineralization studies serve as crucial tools in investigating the efficacy of therapeutic interventions on dental substrates such as hydroxyapatite (HA) discs, enamel, or dentin. These investigations simulate

Abbreviations
Ag^+, silver ion; AgCl, silver chloride; Ca^{2+}, calcium ion; CaF_2, calcium fluoride; Cl^-, chloride ion; DS, demineralizing solution; DW, de-ionized water; F^-, fluoride ion; FAP, fluorapatite; g, gram; h, hour; HAp, hydroxyapatite; ISE, ion-selective electrodes; kHz, kilo hertz; L, litre; mM, millimolar; M, Mol; MAS-NMR, magic angle spinning nuclear magnetic resonance spectroscopy; ml, milli litre; mm, millimetre; MHz, mega hertz; NH^{4+}, ammonium ion; RM, remineralizing solution; XRD, x-ray diffraction.

the cariogenic challenges encountered in the oral cavity and provide valuable insights into potential treatments for caries prevention and management.

While various models have been employed in cariology research to replicate the caries process, chemical models offer distinct advantages in terms of efficiency, cost-effectiveness, and reproducibility. Among these models, chemical approaches utilizing acid or acid buffers to mimic demineralization and remineralization mechanisms have gained prominence. Notably, Yu et al. (1) observed that 62% of mechanistic studies utilize simple mineralization models, while 38% employ pH cycling models.

Silver diammine fluoride (SDF) is a colorless liquid and is a promising agent for dentin caries management. Its application involves painting it onto carious lesions for a brief duration. Therefore, understanding the chemical interaction of SDF in both acidic and remineralization environments is important.

Ion-selective electrodes (ISEs) are an analytical tool for determining the concentration of specific free ions in solution. In dental research, ISEs have a proven efficacy in various studies. For example, Huang et al. (2) demonstrated that calcium ISEs is a reliable method for real-time quantification of mineral loss during demineralization using a hydroxyapatite model system.

While numerous investigations have explored the effect of SDF on HA during demineralization, but there are noticeably fewer investigating its impact during remineralization (3). The aim of this study was to compare the chemical kinetics of SDF following dissolution in water, demineralization solutions, and in remineralization solutions. The emphasis was to investigate the chemical reactions in real-time of following addition of SDF into de- and re-mineralization solutions rather than its reactions directly on tooth tissues.

Materials and methods

Commercially available SDF ($Ag(NH_4)_2F$) (Riva Star, SDI, Australia) was used which has a concentration of 3.16M. Demineralization solutions of buffered 0.1M acetic acid at pH4.0 were prepared. Remineralization solutions comprising of 0.222 g/L $CaCl_2$, 0.163 g/L KH_2PO_4, 8.7 g/L NaCl at pH7 were also prepared (4). 0.01 ml of SDF was added to 50 ml of: deionized water, demineralization solution, and remineralization solutions, thus resulting in a concentration of 0.632 mM of SDF in each. ISEs (Nico2000, UK) were used to measure initial, and also to continually monitor NH_4^+ Ag^+ and F^- concentrations at intervals of 2 min (2) for a period of 2 h. All the experiments were carried out at 37 °C (repeated three times). The pH of the solution was measured before addition of SDF, and at the end of the experiment using a calibrated pH meter (Mettler Toledo portable pH meter).

Any precipitates were collected and dried in an incubator and characterized using x-ray diffraction (XRD), and ^{31}P and ^{19}F solid state Magic Angle Spinning nuclear magnetic resonance (MAS-NMR) spectroscopy. XRD spectra were collected using a x-ray powder diffractometer (PANalytical CubiX^3, UK). The theta-2theta scan measurements were carried out in standard reflection mode, using Cu K radiation, with sample holders spinning on the stage during the scan. ^{31}P MAS-NMR was conducted using a 14.1 Tesla spectrometer (600 MHz Bruker, UK) at a Larmor frequency of 242.94 MHz. ^{19}F MAS NMR analysis was conducted using a 14.1 Tesla spectrometer at a Larmor frequency of 564.658 MHz. All spectra were obtained with a 2.5 mm probe under spinning conditions of 20 kHz.

Results

The ISE results of the real-time changes of free NH_4^+, F^- and Ag^+ in the water, demineralization and remineralization solutions are shown in Figure 1. The trends after initial values were similar in deionized water and the demineralization solutions, i.e., decreasing concentration with time for NH_4^+, and Ag^+, but increasing for F^-. Whereas, for remineralization solution, after initial solubilization, following addition of SDF, the trend was no change in NH_4^+ and very low with virtually no change in Ag^+ and F^- concentrations.

Ammonium ions

Following addition of SDF into deionized water, the initial NH_4^+ concentration increased immediately to 1.2 mM, and then subsequently decreased linearly by 0.12 mM/h. Following addition of SDF into demineralization solution the NH_4^+ concentration increased rapidly to 9.0 mM, and then subsequently decreased linearly by 1.06 mM/h. However, following addition of SDF into remineralization solution, the initial NH_4^+ concentration increased to 1.0 mM but subsequently did not change much over time.

Fluoride ions

The initial F^- concentration in deionized water was 0.6 mM on addition of SDF, and then increased by 0.04 mM/h. The initial F^- in demineralizing solution was 6 mM on addition of SDF, and then increased by 0.7 mM/h. In the remineralization solution, the F^- concentration was between 0.025 and 0.045 mM on addition of SDF, and did not change subsequently.

Silver ions

The initial Ag^+ concentration in deionized water was 0.6 mM on addition SDF, and then decreased by 0.08 mM/h. Following addition of SDF in demineralization solution, the concentration of Ag^+ was 4.5 mM, and then decreased by 0.5 mM/h. Whereas, following addition of SDF to the remineralization solution, the Ag^+ concentration did not rise above the minimum detection limit of the ISE electrode.

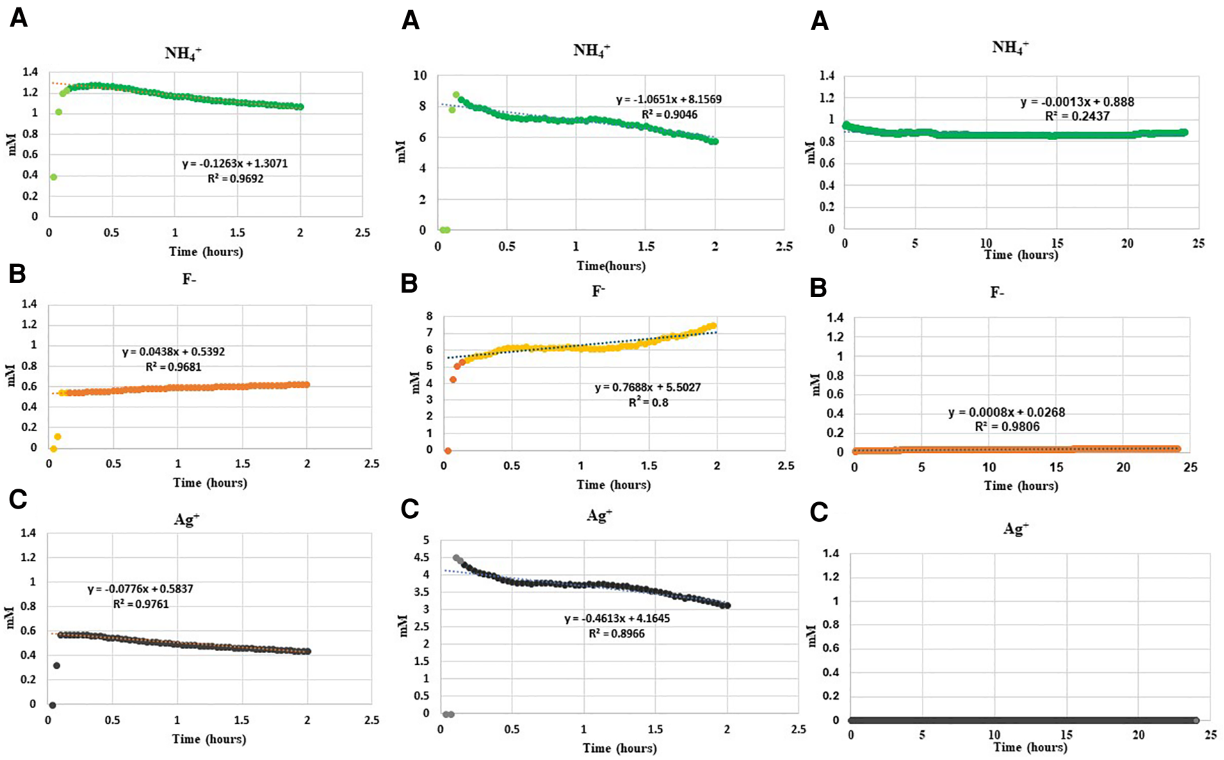

FIGURE 1
Changes in concentration of (A) NH_4^+, (B) F^- and (C) Ag^+ ions on addition of 0.01 ml SDF (3.16 M) to 50 ml deionized water, demineralization solution at pH4, and remineralization solution at pH7 in a time series. *Please note that the concentration of Ag^+ ions in the remineralization solution was below the lowest detection limit of ISE as a result of immediate precipitation.

Precipitation of solids

No precipitate was seen when SDF was added to either deionized water or demineralization solution. However, when SDF was added to remineralization solution, there was a rapid change in color from clear to white and a white precipitate was formed. XRD pattern of the precipitate (Figure 2) showed peaks at 27.9°, 32.3°, 46.3°, 54.9° and 57.6° that could be assigned to silver chloride (AgCl, Reference code-04-007-3906). The small peaks at 38.3°, 44.3° and 64.4° are consistent with the formation of metallic silver (Reference code: 04-006-1881). The ^{19}F MAS-NMR spectrum (Figure 3A) shows a peak at −102 ppm suggesting the formation of fluorapatite (FAP); and the peak at −88 ppm suggesting the formation of carbonated fluorapatite (CFAP) (5, 6). The ^{31}P MAS-NMR spectrum peak at 2.7 ppm indicates the presence of calcium hydroxyapatite (Figure 3B).

pH

The change of pH in the solutions is presented in Table 1. The pH increased after the addition of SDF in all solutions. The greatest increase in pH was in deionized water and the least was in demineralization solution.

Discussion

The complete dissolution of SDF in any of the solutions would result in concentrations of 1.2 mM NH_4^+, 0.6 mM F^-, and 0.6 mM Ag^+ calculated from the stoichiometry and concentration and volumes of SDF used, and assuming complete dissociation. SDF is known to be soluble in water (7). The ISE results in deionized water showed that it completely dissociated to give rise to around 1.2 mM NH_4^+ and 0.6 mM Ag^+ and F^- ions after adding 0.01 ml of 3.16 mM SDF in 50 ml of water. The subsequent small decrease of NH_4^+ and Ag^+ in the following 2 h indicated that an aqueous ammonia-silver ion complex, likely to be diamminesilver $[Ag(NH)_3)_2^+]$ (8, 9), leading to a corresponding increase in F^- in the solution, which might be the cause for the pH increase.

This situation was similar for SDF dissolved in demineralization solution as the gradients of the decrease of NH_4^+ and Ag^+ concentrations, and the corresponding gradient of increase for F^-, were similar to that in deionized water. As $Ag(NH)_3)_2^+$ is a stable aqueous species, and its ammonia-silver covalent bonds prevent the photo-reduction of silver, no precipitate was formed and the solution remained clear.

However, when SDF was dissolved in remineralization solution, the NH_4^+ concentration remained constant at about the stoichiometric value, but the concentrations of F^- and Ag^+ were

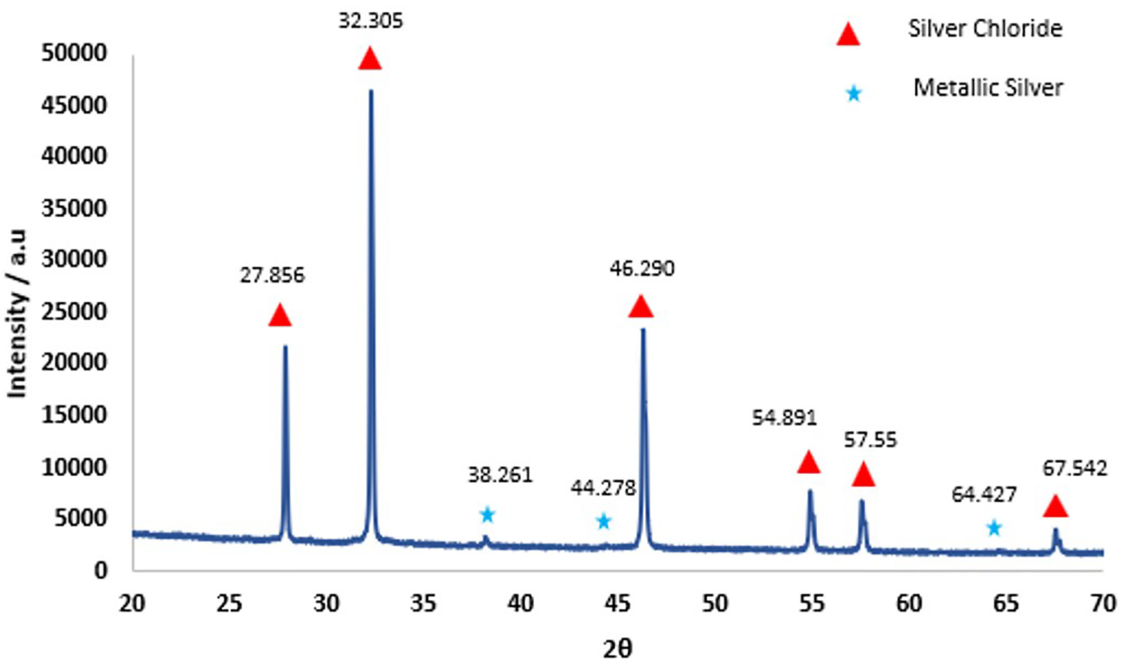

FIGURE 2
X-ray diffraction results obtained from the precipitate formed as a result of interaction of SDF with remineralization solution. The sharp diffraction lines and the pattern seen above indicate AgCl crystal (Reference Code: 04-007-3906) and small amount of metallic silver (Reference code: 04-006-1881).

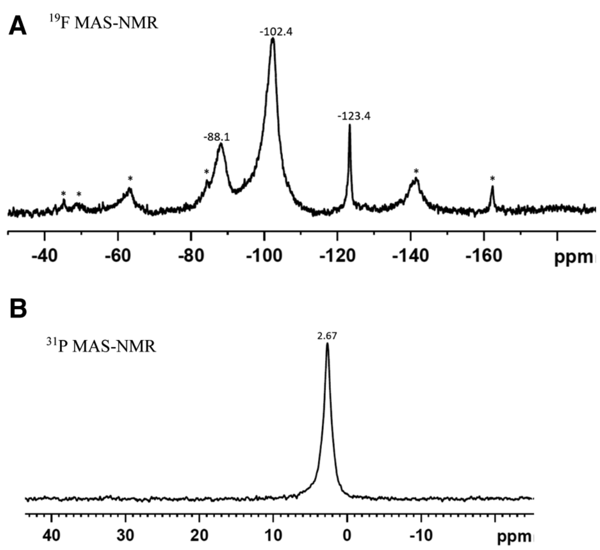

FIGURE 3
(A) ^{19}F MAS-NMR, and (B) ^{31}P MAS-NMR spectra of the precipitate formed as a result of interaction of SDF with remineralisation solution. The Asterix denote the sidebands. (A) The peak at −102.4 ppm indicates the formation of fluorapatite and at −88.1 ppm, carbonated complex. (B) The peak at 2.67 ppm signifies formation of apatite.

both very low. This indicated that these ions were taken up immediately to form the precipitate. The XRD and NMR analyses (Figures 2, 3) showed that these precipitates contained a mixture of AgCl, metallic silver, and fluorapatites, which are all insoluble compounds. As the remineralization solution contained $CaCl_2$, KH_2PO_4, and NaCl, this suggests that the dissociated Ag^+ reacted rapidly with the Cl^- to form AgCl as a white precipitate, thus reducing the Ag^+ concentration in the solution to a negligible amount. Subsequently, when the AgCl precipitate was exposed to light, a small amount was then photo-reduced to metallic silver, which was also seen in the XRD analysis. The F^- would react immediately with Ca^{2+} to form CaF_2 (10, 11), another white precipitate, which in the presence of phosphate, would form insoluble fluorapatite, (and therefore was not seen in the NMR spectra). Thus, the F^- concentration was also very little (Figure 1C).

This *in vitro* study, investigating the kinetics of the chemical reactions of SDF in demineralization and remineralization conditions can be used to predict the effects of SDF in the oral environment. As saliva contains Ca^{2+}, $(PO_4)^{3-}$ and Cl^-, these ions would also react with SDF to form insoluble FAP/CFAP and AgCl. These precipitates would then be retained for example in exposed dentinal tubules and not be washed away. The formation of the FAP would render the dentin to be less susceptible to acid demineralization (12–14). AgCl is photo-reduced to metallic Ag (giving the black appearance seen when SDF is used in dentin treatments) which will hinder bacterial growth and degradation of dentin collagen (15, 16). As the components of SDF also increase the pH in the oral environment, this will further reduce the damage caused by acid challenges. Furthermore, as the AgCl and FAP/CFAP precipitate within the dental tubules, these precipitated compounds may occlude the tubular lumens and

TABLE 1 Change of pH in solutions on interaction with SDF before and after experimental period.

Change in pH	Deionised water	Demineralisation solution	Remineralisation solution
Before SDF	7.7	4.0	7.0
After SDF	10.3	4.4	8.4

minimize pain by reducing direct communication of the pulp with external stimuli. However, in enamel, these precipitates could only be retained in demineralized porous lesions, and not on sound smooth surface. Therefore, clinically, the SDF protective benefit against acidic challenge for enamel (17) is reduced compared to dentin (13). Other studies [e.g., (14)] also demonstrated that the use of SDF/NaF had a remineralizing effect on a dentin surface under acid challenge.

Clearly, this *in vitro* study is limited if compared to the complexity of the *in vivo* oral environment, where there are a multitude of other charged species (ions and proteins) in saliva, all of which may partially interact with the ionic constituents of SDF. In the oral environment both demineralization and remineralization occur within the complex biological fluid that is saliva (18). Enamel biodemineralization (19, 20) has been proposed as the process by which tooth mineral is lost within a chemically interacting environment. Nevertheless, this *in vitro* study does demonstrate that complexes are formed when SDF is dissolved, especially when other ions including Cl^- are present, which is a major component of saliva.

Conclusion

In remineralizing solutions which contain chloride ions (and therefore likely to be the case in saliva), SDF reacts rapidly with calcium, phosphate, and chloride ions, leading to the formation of fluorapatite, carbonated fluorapatite, and silver chloride precipitates. The silver chloride precipitate will undergo photo-reduction, resulting in black discoloration. These precipitates, which would be retained inside dentinal tubes, with the increases of pH, suggests why SDF is beneficial in clinical treatments for dentin caries.

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.

Author contributions

MK: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. PA: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing. SS: Conceptualization, Methodology, Supervision, Writing – review & editing. FW: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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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.

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Acceptance of the use of silver fluoride among Brazilian parents of children with special health care needs

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Background: Children with special health care needs including Down Syndrome, Autism Spectrum Disorder and Down Syndrome experience difficulties in receiving dental treatment. Silver Diamine Fluoride (SDF) and Silver Fluoride (SF) are a minimally invasive treatments options to arrest dental caries without sedation; local or general anaesthesia (GA).
Aim: Evaluation of Brazilian's parents' acceptance of the use of SF in CSHCN.
Methods: After receiving education on SF, 100 Parents of CSHCN completed a questionnaire concerning their acceptance of SF, in different dental situation.
Result: Majority of parents (74,5%) agreed to the use of SF for their children. SF was more acceptable on posterior teeth (74,5%) when compared to its use on anterior teeth (43,1%). Parents accepted to use SF in order: to reduce infection and pain (82,4%); to avoid dental injection (72,5%) and treatment under GA (84,3%). The Majority of parents accepted the properties of SF (82,4%) and Silver (80,4%).
Conclusion: Silver Fluoride was accepted as a treatment option for caries, by Brazilian parents of CSHCN. SF should be considered as a treatment option for caries limited to dentine for CSHCN, taking into consideration the individual needs and opinions with regard to aesthetics and exposure to fluoride and silver.

KEYWORDS
silver diamine fluoride (SDF), silver fluoride, parental acceptance, children with special health care needs (CSHCN), caries arrest

1 Introduction

According World Health Organization (WHO), approximately 15% of global population lives with disabilities or special needs, indicating more than 1 billion people (1).

The Centers for Disease Control and Prevention, described that 1 in 68 children suffer from autism spectrum disorder (ASD) in the United States (2). The increase in prevalence could be due to better diagnostic criteria, as well genetic diagnosis (3, 4). Several studies

Abbreviation
CSHCNm, Children with Special Health Care Needs; SDF, Silver Diamine Fluoride; SF, Silver Fluoride; GA, General Anaesthesia.

have highlighted the difficulties of performing dental care on children with a serious mental disability like Cerebral Paralysis (CP), Down Syndrome (DS) and Autism Spectrum Disorder (ASD) (2, 4–6). CSHCN, tends to receive less oral health care than general population, which can lead to a poorer oral health outcomes, impacting nutrition, general diseases and quality of life (7).

Delivering good oral care to CSHCN has many challenges, not only concerning their medical status, but also the family's involvement in attaining proper oral care, transportation difficulties among others (8). The most common reason cited for not taking children to the dentist for DS group was "Not aware of the dental problems of their children" and for non- DS groups "No awareness of the importance of dental visit" (61.2% and 53%, respectively) (8). It has also being reported that individuals with special needs demonstrate exaggerated responses to physical stimulation, especially with regards to oral sensitivity (9, 10). This hypersensitivity to oral stimulation poses a challenge for dentists in providing proper dental treatment.

Silver Diamine Fluoride (SDF), is a product that has gained popularity as a minimally invasive treatment option and has demonstrated effectiveness in arresting dental caries in clinical trials (11). The product was originally used for desensitization but has proven effectiveness in arresting dental caries (11). SDF is also cost effective, requires limited instruments and does not require anaesthesia or cause severe pain during application (11).

The new generation ammonia free Silver Fluoride (SF) has added benefits, including less risk for tissue burn and irritation, improved smell, and improved product stability (12). Both Silver Diamine Fluoride (Riva Star, SDI Limited, Australia) and Silver Fluoride (Riva Star Aqua, SDI Limited, Australia) is approved for medical use with product registration numbers (D349082/K172047/GMDN code 45232 Class iia), and the qualities are summarized in Table 1 (12).

The improved properties of SF makes it even more ideal for CSHCN as the oral stimulation is less than SDF with regards to taste, smell and the "burning" sensation. Limited research is available on the acceptancy of parents or caregivers, concerning the use of SF as well as the efficacy of the treatment in CSHCN. The aim of this study was to identify whether there is parental acceptance of SF as a treatment option for CSHCN in Rio de Janeiro, Brazil. A subsequent study then evaluated the clinical success of SF application to carious lesions among this vulnerable group of our population.

TABLE 1 A comparative summary of riva star and riva star aqua.

	Riva star (SDF)	Riva star aqua (SF)
Formulation	38% Silver Fluoride in an ammonia solution; 5% Fluoride	38% Silver Fluoride in water; 5% Fluoride
pH levels	High (+-pH = 10)	Physiological (+-pH = 7)
Storage requirements	Refrigerated	Room temperature
Odour/Taste	Ammonia taste and odour	No ammonia taste and odour
Tissue irritation	Mild	None

Duque de Caxias, is a Brazilian Municipality in the State of Rio de Janeiro, southeast Region of the country. It is located in Baixada Fluminense, in the Metropolitan Region of Rio de Janeiro, 16 km from the state capital. Its population in 2023 according to National Census is 808,152 inhabitants, making it the most populous in the state and 22nd most populous in the country (13). In Duke de Caxias, 18,07% of individual received 2,6 minimum salary and 37.8% of the population recives half minimum salary per month 2010 (14). The minimum Salary is the lowest national wage mandatory by Brazilian by Law, and one minumum salary in Brazil is 272,30 Euros (15).

2 Materials and methods

The aim of this *in vivo* study was to determine the acceptance of the parents/legal guardians of SF application as treatment option for Brazilian CSHCN.

Ethical approval was obtained by the Ethical Committee Approval (CEP-Dental Association of Duque de Caxias).

This cross-sectional, questionnaire based study included 100 participants. All the participants self-reported to the Association of Dentistry: Duque de Caxias-Rio de Janeiro, Brazil for dental treatment. This association is dedicated to provide treatment to any patient, including patients without medical insurance. The study was conducted over a period 6 months from January 8th 2022–June 7th 2022.

Parents of children diagnosed with DS, CP and ASD, that required dental treatment, with at least one cavity indicated for restoration, were invited to participate in the study. All participants were informed about the purpose and nature of the study. All participants where from the same municipality with the same socio-economic status, therefore no statistical test was performed to observed if might be same variable that could affected the results of the acceptance of SF.

Once written informed consent was obtained for participation, the parents were educated about the treatment option of SF by making use of a patient information leaflet adapted from the British Society of Paediatric Dentistry's (16). The questionnaire was printed in English but a translator was available when necessary. The questionnaire was adapted from Crystal et al. (17), and evaluated the general acceptance of SF as a treatment option for caries, aesthetic concerns and concerns related to the composition of the SF treatment option. Responses were captured on a Microsoft Excell sheet and descriptively reported in percentages.

3 Results

100 questionnaires were analysed in this study with a 100% participation rate. The parental/guardian acceptance with regards to the use of silver fluoride is reported in Table 2. Majority of parents (74,5%) definitely agreed to the use of SF for their children. The use of SF on posterior teeth was more acceptable (74,5%) as opposed to its use on anterior teeth (43,1%). Parents

TABLE 2 Parental acceptance of SDF.

Variable	Definitely disagree	Neutral	Definitely agree
I would use silver diamine fluoride on my child.	9.8%	15.7%	74.5%
I would use silver diamine fluoride on my child to treat front teeth even if it turns teeth dark until it falls off.	31.3%	25.5%	43.1%
I would use silver diamine fluoride on my child to treat back teeth even if it turns teeth dark until it falls off.	17.6%	7.8%	74.5%
I would use silver diamine fluoride on my child if it can reduce the chances of infection and pain	-	13.7%	82.4%
I will use silver diamine fluoride on my child if it means avoiding treatment under general anesthesia	-	11.8%	84.3%
I would use silver diamine fluoride if my child can avoid having an injection	15.7%	11.8%	72.5%
I would use silver diamine fluoride if it reduces cost of treatment when compared to traditional fillings	17.6%	29.4%	52.9%
I would use silver diamine fluoride on my child even though it contains fluoride (within safety limits)	11.8%	-	82.4%
I would use silver diamine fluoride on my child even though it contains silver (within safety limits)	13.7%	-	80.4%

agreed to the use of SF to reduce infection and pain (82,4%); avoid treatment under GA (84,3%); and to avoid an injection (72,5%). 52,9% of parents indicated their agreement in using SF not only because it has a reduced cost when compared to other treatments options but also because of its minimally invasive nature. The use of SF, even with Fluoride (82,4%) or Silver (80,4%) is almost totally accepted by parents and caregivers.

4 Discussion

SDF and SF are similar products with SF having some different clinical properties (12). Limited literature is available on SF as it is a recent newer generation. Parental acceptance of SF in this study, will therefore also be discussed with parental acceptance of SDF from previous literature.

Conventional dental procedures can often propagate fear due to the uncomfortable nature of some dental procedures and the ineffectiveness of certain behavioral management techniques among CSHCN. CSHCN suffering from caries can often only be treated under general anesthesia or sedation, thus predisposing them to multiple general anesthesia/sedation treatments in their lifetime (18, 19). Due to the medical conditions, sedation and general anaesthesia is often also considered high risk (19, 20). Brazilian parents indicated that they would consent to SF treatment if it will reduce infection/pain (82.4%), the need for injections (72.5%) and avoid the need for general anaesthesia (84.3%). Crystal et al. (21) and Hu et al. (17), reported similar results and demonstrated that parent's acceptance increases specifically to decrease their child's pain and suffering. Efforts should be made to optimize prevention and early management of carious lesions among CSHCN to limit pain and infection as well as the need for repeat sedation and general anaesthesia for dental treatments.

Authors corroborated that there is a higher acceptance of the use of SDF in primary teeth compared to permanent teeth, and posterior teeth compared to anterior teeth (22). Brazilian parents had similar views with only 43.1% definitely agreeing to the use of SF on anterior teeth but 74.5% on posterior teeth. The unaesthetic result (black colour) therefore remains a limitation of SDF/SF treatments on anterior teeth and should be discussed during patient education and obtaining consent.

Concerns with regards to the presence of fluoride and silver in SDF has been reported (23). The majority of Brazilian parents of CSHCN reported acceptance of the use of SF for caries management regardless of the product containing silver and fluoride. This is particularly relevant at this time when the safety of fluoride is under increased scrutiny, and prone to misinformation (24), which has the potential to reignite the debate of the use of fluoride to manage dental caries. It is important to note that there were however parents who were not comfortable with the use of silver (13.7%) and fluoride (11.8%), Efforts should be made to provide more awareness and education to parents on the constitution and safety of silver and fluoride in dental medicaments and should therefore also be included when obtaining informed consent for SDF/SF treatments.

Lastly, a limitation of the study is the small sample size and more research with a larger sample size is recommended to support the findings of this study. Secondly, the parental acceptance of SF was evaluated before the actual experience of the procedure. A previous study by Crystal et al. (21) has shown that when examining parental perception after SDF application, it was found that almost all of the respondents thought that SDF was acceptable when considering ease of application, providing more comfort for the child. Future studies could incorporate re-evaluation of the parents' acceptance after the child has undergone the SF treatment procedure.

5 Conclusion

Silver Fluoride was accepted by the majority of Brazilian parents of children with special health care needs. The positive response of parents and the minimally invasive nature of SF indicates that SF should be considered as a treatment option for caries limited to dentine for this vulnerable population. Patient education should include the unaesthetic result as well as product constitution to enable informed consent (25).

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 humans were approved by CEP-Dental Association of Duque de Caxias. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NP: Conceptualization, Writing – original draft, Writing – review & editing. VP: Data curation, Investigation, Writing – original draft, Writing – review & editing. RE: Data curation, Investigation, Writing – original draft, Writing – review & editing. SC: Data curation, Investigation, Writing – original draft, Writing – review & editing. SG: Data curation, Investigation, Writing – original draft, Writing – review & editing.

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Effects of silver diammine fluoride with/without potassium iodide on enamel and dentin carious lesions in primary teeth

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Aim: To assess the effects of SDF and SDF+KI treatment on enamel and dentin carious lesions in primary teeth using x-ray Microtomography (XMT) and back scattered scanning electron microscopy (BSE-SEM).

Methods: Artificial enamel caries of 3 caries free primary teeth were created by immersion of the samples in 50 ml demineralization solution for 72 h. Three other teeth with natural dentin caries were selected. Both groups were divided into 3 subgroups: EC–Enamel Control; ES–Enamel with SDF application; ESK–Enamel with SDF followed by KI application; DC–Dentin Control; DS–Dentin with SDF application; DSK–Dentin with SDF followed by KI application. Each tooth was imaged using XMT at 3 time points: (1) Pretreatment; (2) after immersion in remineralization solution for 120 h, with or without SDF or SDF+KI; (3) after subsequent immersion in demineralization solution for 72 h. The change of radiopacities of the lesions in these time points were assessed from the XMT images. After the XMT scans, all teeth were investigated microscopically using BSE-SEM.

Results: In EC, no change in linear attenuation coefficient (LAC) was observed after remineralization, but LAC reduction was observed after subsequent demineralization. For ES, thin layer of high LAC material was deposited on the enamel surface after remineralization, and further reduction of LAC was observed after demineralization. In ESK, the surface layer was lost after SDF +KI, and small reduction of LAC was observed after demineralization. In DC, no LAC change was observed after remineralization, but reduction of LAC was detected after demineralization. In DS, high LAC material was formed on the carious dentin surface and randomly inside the lesion. No further LAC change was found after demineralization. In DSK, thick layer of high LAC material was deposited on the carious surface and inside the dentinal tubules. No further LAC reduction was found after subsequent demineralization.

Conclusion: SDF and SDF+KI did not protect artificial enamel under acid attack even though Ag products were deposited in the porous enamel. However, SDF and SDF+KI shows protective properties against acid challenges and Ag products are deposited in carious dentin lesion without tubular structure randomly; and within dentinal tubules when these structures are retained.

KEYWORDS

SDF, KI, remineralization, XMT, SEM

1 Introduction

The application of Silver Diammine Fluoride (SDF) on carious dentin lesion has been shown to arrest caries progression by forming a black remineralized surface layer (1–3). This black discoloration is caused by metallic silver (Ag) which is a photo-reduced product from silver chloride (AgCl), a compound formed by SDF reacting with saliva (4). Riva Star (SDI, Australia), a commercial SDF brand, has an optional additional application of potassium iodide (KI) solution to remove the discolouration by binding the Ag ions with I ions to form AgI, thereby reducing metallic Ag formation (5–7). However, the effect of this combination of SDF and KI (SDF+KI) on remineralization, and on preventing further demineralization, has not been well researched. Therefore, the aims of this study were to investigate and compare the effects of SDF with SDF+KI on primary enamel and primary dentin lesions, under re- and de-mineralization conditions *in vitro*, using x-ray microtomography (XMT) and back scattered scanning electron microscopy (BSE-SEM).

2 Materials and methods

Six primary teeth were selected from the human tooth tissue bank at Queen Mary University of London (Ethics number- QMREC 0014/17). Three teeth with sound enamel, and three other teeth with natural dentin caries were selected for the experiment. Each sound enamel tooth was coated with nail varnish, leaving a 3 × 4 mm window and immersed in 50 ml demineralization solution (0.1M acetic acid buffered with sodium acetate at pH 4.5) for 72 h (8) in order to create an artificial enamel lesion. Both the enamel and dentin groups were divided into 3 subgroups: EC – Enamel Control; ES – Enamel with SDF application; ESK – Enamel with SDF followed by KI application; DC – Dentin Control; DS – Dentin with SDF application; DSK – Dentin with SDF followed by KI application. Each tooth had XMT scans using MUCAT2 (QMUL) at 90 keV and 180 μA for 18 h, at 3 timepoints: (1) Pretreatment; (2) after immersion in remineralization solution (2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 150 mM NaCl) for 120 h, with/without SDF (Riva Star), or SDF+KI (Riva Star) treatment; (3) after immersion in demineralization solution (as above) for 72 h (Figure 1). After image reconstructions, the three XMT images of the same sample in 3 timepoints were aligned, and their linear attenuation coefficients (LACs) were normalised to 40 KeV using in-house software so that they could be compared and analysed quantitatively. After the XMT scans, all teeth were embedded and sectioned. The region of interest was then investigated microscopically using BSE-SEM (9).

3 Results

3.1 Artificial enamel carious lesion

All the pre-treatment scans of the artificial demineralized enamel lesions show that each tooth had a subsurface

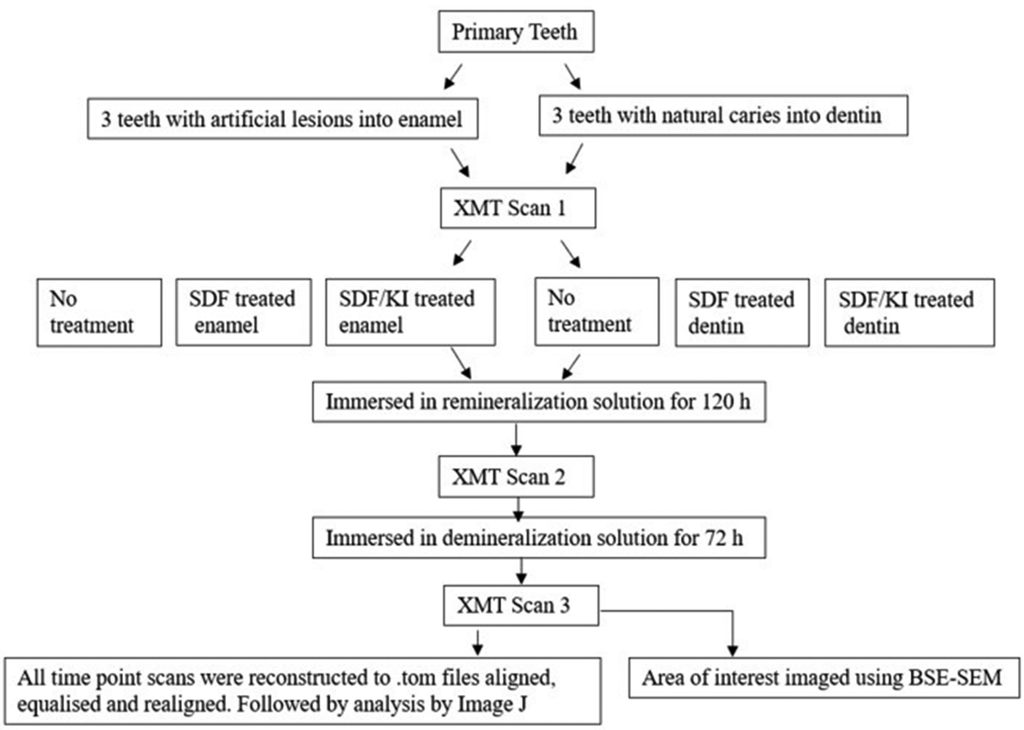

FIGURE 1
Schematic representation of the experimental method.

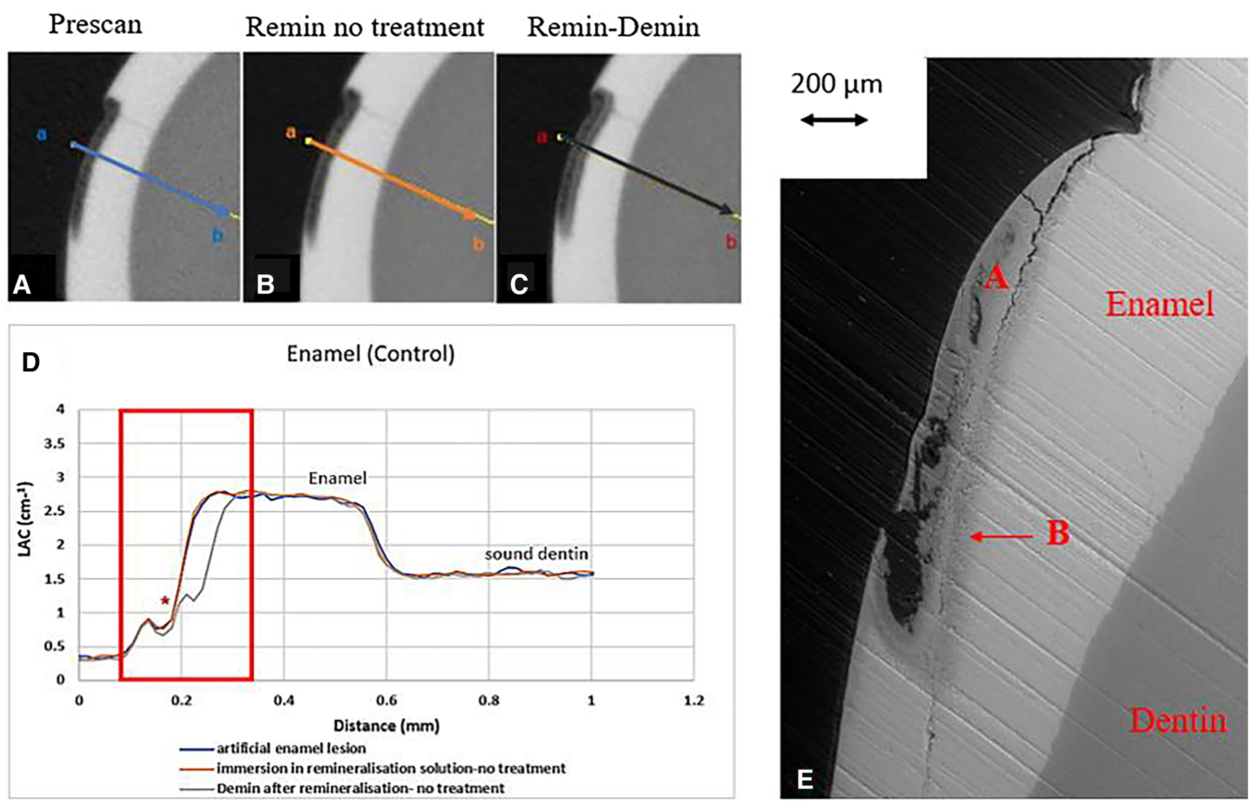

FIGURE 2
XMT slices of artificially created lesions in enamel with no SDF treatment showing no protection from demineralization in this control tooth. (A) Pretreatment scan; (B) after immersion in remineralization solution for 120 h; (C) subsequent immersion in demineralisation solution for 72 h; (D) line profiles of LACs for the 3 scans. (E) BSE-SEM image of the lesion in enamel: A- indicates the position of initial layer of demineralisation. B – extended demineralized region after subsequent immersion in demineralization solution.

demineralized lesion with a surface mineralized layer (Figures 2A, D, 3A,D, and 4A,D). With no SDF treatment, the lesion did not have any observable changes in LAC after immersion in remineralization solution for 120 h (Figures 2B,D). After subsequent demineralization for 72 h, the subsurface lesion extended further into enamel by about 0.06 mm (Figure 2C) and the line profile shows a second mineralized layer on the surface of the advancing front (Figure 2D). This feature could also be seen in the SEM image, which shows substantial loss of mineral (Figure 2E). With the application of SDF, there was a layer of high LAC (~3.2 cm^{-1}) material on the demineralized enamel surface, and into the lesion after remineralization (Figures 3B,D). After subsequent demineralization, the line profile (Figures 3C,D) shows that there was some loss of mineral in the depth of the lesion (indicated by the grey line shift to the right of the orange line). The radiopaque layer could be seen clearly in the BSE-SEM image covering the enamel, but it did not completely seal the surface. Therefore, a secondary demineralized layer could be detected (B in Figure 3E). With the application of SDF+KI, the initial surface mineralized layer was lost after remineralization (Figures 4B,D) and the normal enamel LAC was increased slightly from 2.6 to 2.8 cm^{-1}. After subsequent demineralization, there was a small loss of mineral in sound enamel (~0.02 mm).

3.2 Natural dentin carious lesion

In all the natural dentin carious lesions, there was no surface mineralized layer as observed in the artificial enamel lesions (Figures 5A,D, 6A,D, 7A,D). In the control sample without SDF application, remineralization did not seem to have an effect (Figures 5B,D). After subsequent demineralization, there was further loss of minerals in the sound dentin (Figures 5C,D). This could also be observed in the BSE-SEM image (B in Figure 5E). With the application of SDF, the DS sample had high LAC at the surface, and a speckled appearance with high LAC islands after remineralization inside the lesion (Figures 6B,D). After subsequent demineralization, no further loss of mineral was observed within the lesion or into the sound dentin (Figures 6C,E). In the BSE-SEM image, high density particles were observed inside the lesion (Figure 6E). No dentinal tubule structures were observed inside the lesion, but was apparent in the sound dentin. With the application of SDF+KI, the DSK sample had a thick layer of radiopaque material ($LAC > 3\ cm^{-1}$) from the carious dentin surface into the into the depth of the lesion (Figures 7B,D), after remineralisation. Even in the deeper part of the lesion, the LAC was increased to around 1.25 cm^{-1}, similar to that of sound dentin. After subsequent demineralization, there was no observable change

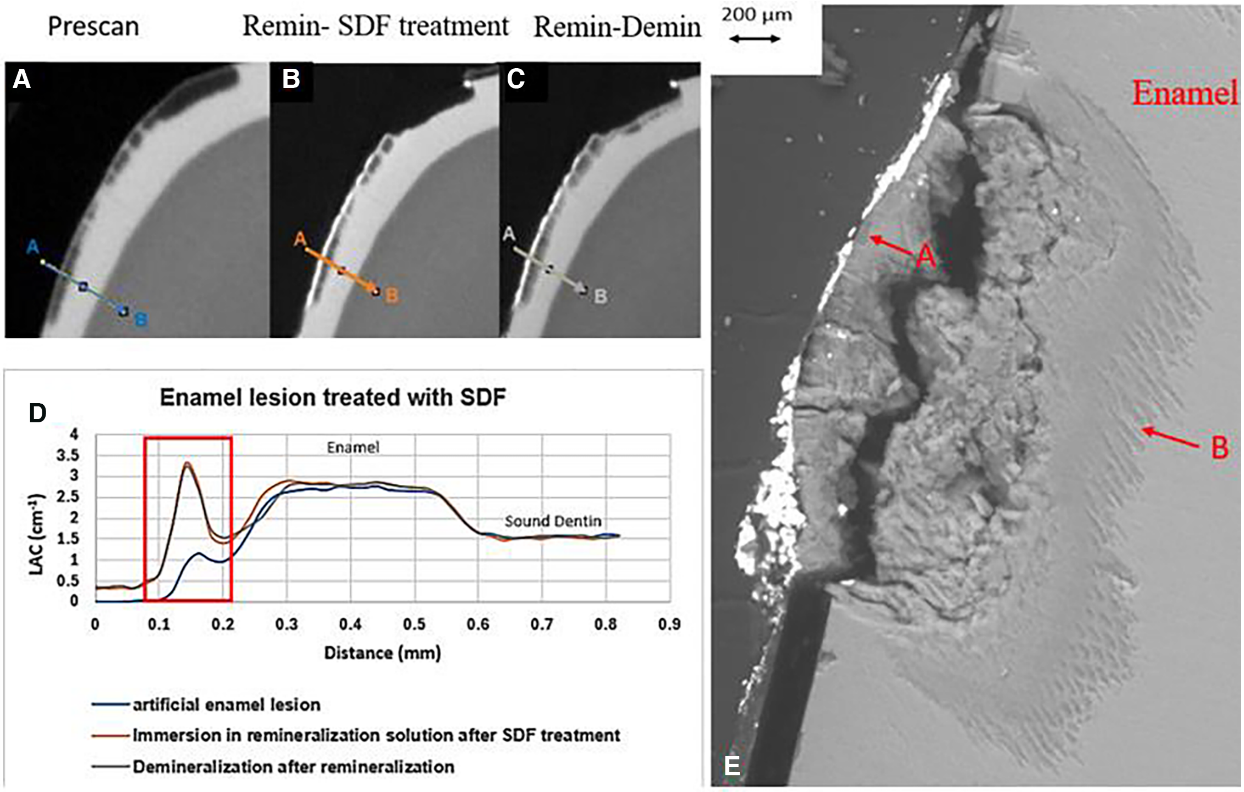

FIGURE 3
XMT slices of artificially created lesions in enamel with SDF treatment showing barrier formation on enamel surface with some penetration of SDF in porous enamel. **(A)** Pretreatment scan; **(B)** after SDF application and immersion in remineralization for 120 h; **(C)** subsequent immersion in demineralisation solution for 72 h; **(D)** line profiles of LACs for the 3 scans. **(E)** BSE-SEM image of the lesion in enamel: A- indicates the position of initial layer of demineralization; B – extended demineralized region.

of LACs in the lesion (Figures 7C,D). The BSE-SEM image (Figure 7E) showed that the lesion maintained some dentinal tubular structure and the high-density materials were deposited along the direction of the dentinal tubules.

4 Discussion

4.1 Enamel carious lesions

Artificial enamel lesions were used because it is difficult to standardise natural enamel carious lesions. Also, in natural early enamel carious lesion, there is usually a surface mineralised layer, possibly with high fluoride content that may prevent penetration of SDF into the lesion. It is confirmed in this study that even with the thinner surface mineralized layer, the penetration of the SDF was limited on the surface (Figure 2B). As the outer surface layer was smooth, the Ag particles did not retain well. This was shown in the ESK sample (Figure 4) which showed total loss of the surface after SDF+KI remineralization (Figure 4B). This might be due to the surface layer was very thin and was lost during the application of SDF+KI.

In the enamel control sample (EC), no increase of LAC (*i.e.*, no remineralization) was observed after immersion in remineralization solution for 120 h (Figure 2B). This might be due to the immersion time was too short; and/or the surface mineralized layer prevented any further exchange of ions in the deeper layer. However, when this tooth was re-immersed in demineralization solution for 72 h, there was further mineral loss in the body of the lesion, with an increase in depth (Figure 2C). It was noted the surface mineralized layer was intact and retained its LAC. Furthermore, there was a 2nd mineralized layer with the second wave of demineralization in the depth of enamel. This implies that clinically when enamel is subjected to cyclical de- and re-mineralization, the dynamics of ion exchange will create a complex enamel structure.

In the ES sample, after SDF application and remineralization, there was a very radiopaque layer on the enamel surface (Figure 3B). When SDF was in contact with the remineralization solution, AgCl is formed (4). From the high LAC value, this layer is due to the Ag content of AgCl. In this sample, the AgCl was retained, covering the surface of enamel. From the line profile (Figure 3D), the AgCl might have penetrated inside the lesion and increased LAC of the lesion. Although remineralization might also occur due to the high F content of

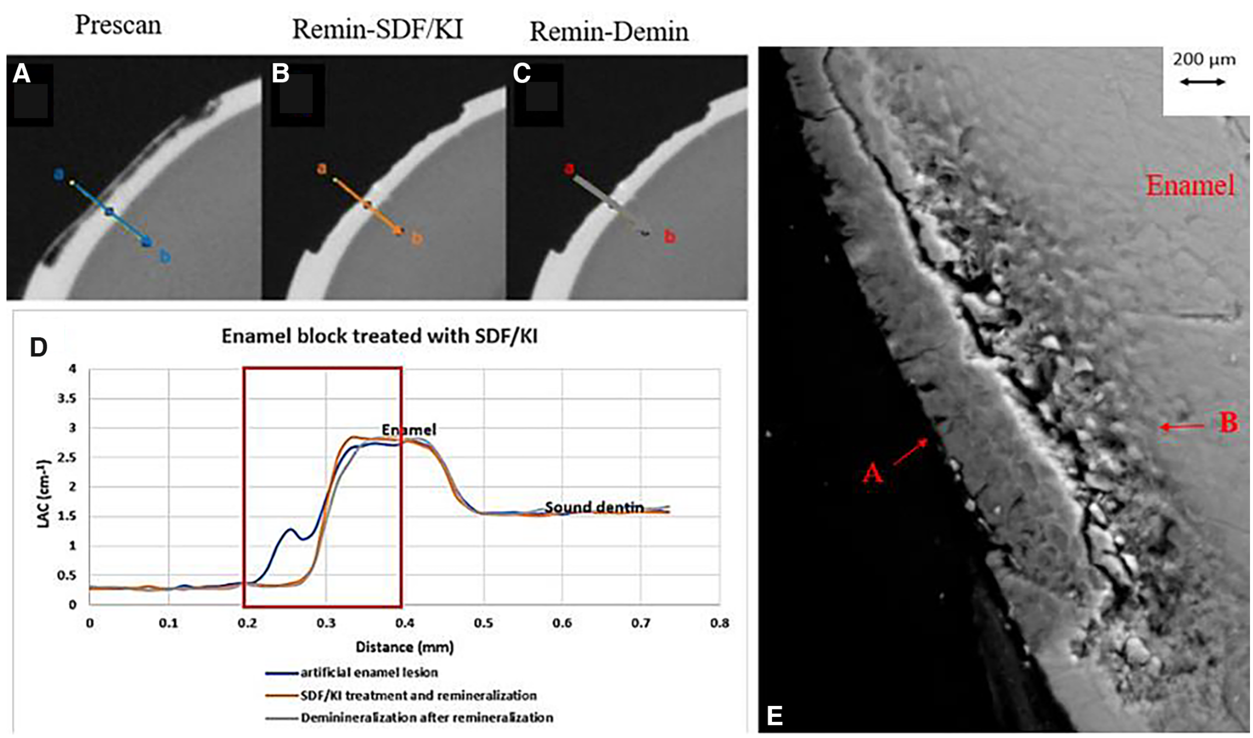

FIGURE 4
XMT slices of artificially created lesions in enamel with SDF+KI treatment showing no barrier formation and protection from demineralization. **(A)** Pretreatment scan; **(B)** after SDF+KI application and immersion in remineralization solution for 120 h; **(C)** subsequent immersion in demineralisation solution for 72 h; **(D)** line profiles of LACs for the 3 scans. **(E)** BSE-SEM image of the lesion in enamel: A- indicates the position of initial layer of demineralization B - extended demineralized region.

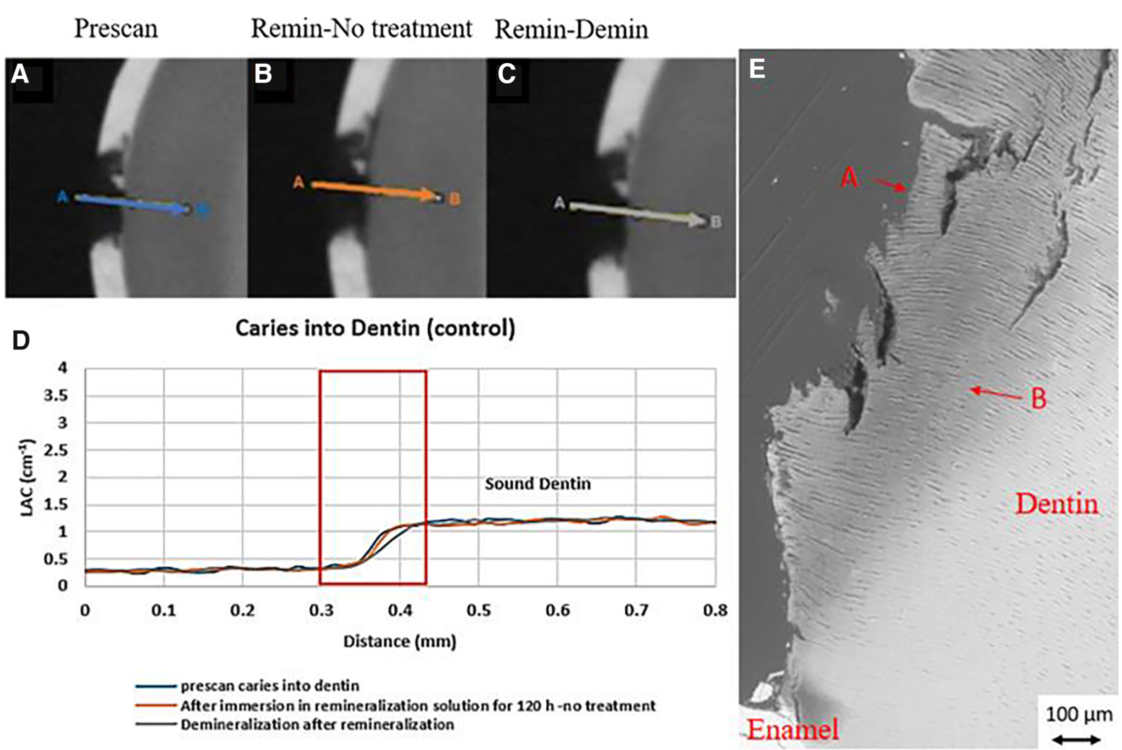

FIGURE 5
XMT slices of natural lesions in dentin with no SDF treatment showing no protection from demineralization in this control tooth. **(A)** Pretreatment scan; **(B)** after immersion in remineralization solution for 120 h; **(C)** subsequent immersion in demineralisation solution for 72 h; **(D)** line profiles of LACs for the 3 scans. **(E)** BSE-SEM image of the lesion in dentin showing dentinal tubules: A- indicates the position of initial layer of demineralization B – extended demineralized region in dentin.

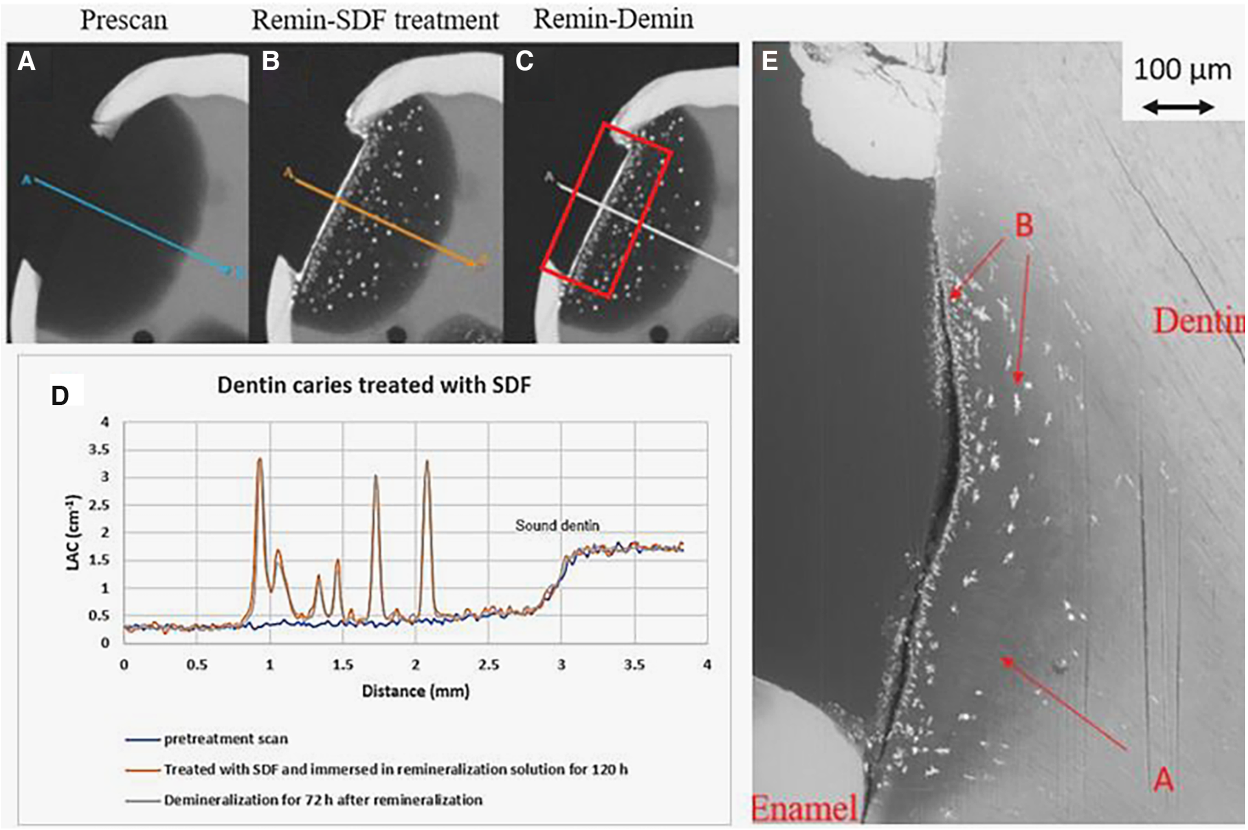

FIGURE 6
XMT slices of natural lesions in dentin with SDF treatment showing superficial radiopaque layer and Ag particles deposition in carious dentin matrix, protecting dentin from further demineralization. (A) Pretreatment scan; (B) after immersion in remineralization solution for 120 h; (C) subsequent immersion in demineralisation solution for 72 h; (D) line profiles of LACs for the three scans. The spikes indicate Ag deposition. (E) BSE-SEM image of the lesion in dentin showing no dentinal tubules: A - initial demineralized lesion; B - Ag particles in carious dentin matrix.

SDF, the immersion time is too short for this to happen, as shown in the EC sample. Also, after demineralization, there is some mineral loss beyond the original lesion into normal enamel, showing that SDF does not prevent demineralization in enamel.

After application of SDF+KI and after remineralization, the surface layer of the ESK seemed to be destroyed (Figure 4B). As there was no acidic component in SDF+KI, the destruction was likely caused by the mechanical brushing during the application since the surface was thin and weak. However, there was a small increase in LAC in the normal enamel, indicating that a small amount of AgI (a product formed when SDF is mixed with KI) managed to be deposited on the surface and partly into the enamel. Once again, this layer did not protect the enamel from subsequent demineralization indicating no formation of acid resistant fluorapatite or fluoride substituted hydroxyapatite (FA/FSHA).

These results suggest that the SDF will penetrate into the enamel only if some porosities exist. Li et al. (10), reported the movement of silver ions through the pellicle along the prism boundaries. However, this current study shows that the penetration of SDF is limited to the surface of the demineralized lesion. In natural enamel carious lesion, the porous structure could be different from the artificial lesion. Clinically, when the lesion becomes black after SDF application, it indicates that the lesion is porous enough to retain the SDF byproduct that is photo reduced to metallic Ag, which might offer protection from bacterial invasion.

4.2 Dentin carious lesion

In natural dentin carious lesion (DC sample), no change of LAC was observed after immersion in remineralization solution for 120 h (Figure 5B). This implies that dentin caries is difficult to remineralize without the presence of fluoride. Hence, there was no protection when the tooth was subsequently immersed in demineralization solution for 72 h, resulting in a loss of mineral and decrease in LAC (Figure 5D). When SDF was applied to the dentin carious lesion (DS sample), after remineralization, a layer of high LAC (up to 3.4 cm^{-3} material was deposited on the surface of the lesion. This material was likely to be AgCl. Some of this material also penetrated into the lesion and randomly deposited in the dentin lesion. After subsequent demineralization, the LAC was unchanged. This implies that

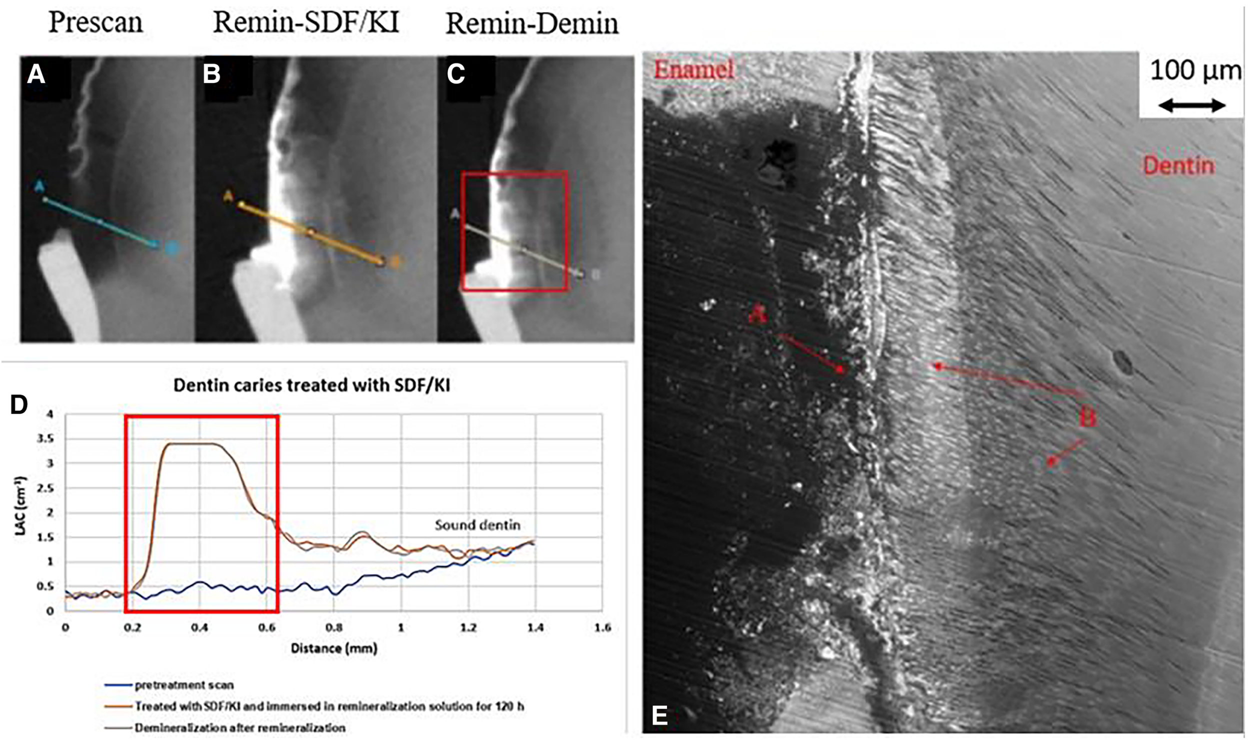

FIGURE 7
XMT slices of natural lesions in dentine with SDF+KI treatment showing thick superficial radiopaque layer and Ag particles deposition in carious dentin matrix, protecting dentin from further demineralization. **(A)** Pretreatment scan; **(B)** after immersion in remineralization solution for 120 h; **(C)** subsequent immersion in demineralisation solution for 72 h; **(D)** line profiles of LACs for the 3 scans. The high LAC layer are AgI. **(E)** BSE-SEM image of the lesion in dentin showing dentinal tubule structure: A- initial demineralized lesion with superficial Ag particles in carious dentin matrix B- Ag particles in carious dentin matrix and subsurface dentinal tubules.

unlike enamel, FA or FSHA might have been formed inside the dentin lesions but was masked by the high LAC of precipitated AgCl. This might explain the multiple peaks in the line profile (Figure 6D). As FA/FSHA are more acid resistant and harder, subsequent demineralization did not result in further loss of mineral (11).

Several studies have reported occlusion of dentin tubules with the application of silver ions (2, 10, 12–15). Seto et al. (13) reported the formation of microwires of silver within the dentinal tubules but Kiesow et al. (14) and Menzel et al. (15) found particles of Ag occluding the dentinal tubules. However, if the dentinal tubule structure is destroyed, as shown in the BSE-SEM image (Figure 6E), Ag particles could only be retained within space in the matrix. This might explain the random high LAC island appearance in Figure 6B.

In the DSK sample which had SDF+KI application, there was a thick layer of high LAC material on the surface. Unlike the DS sample, the penetrated material had a structural pattern (Figure 7B). The BSE-SEM image (Figure 7E) showed that the dentinal tubule structure within the lesion was not destroyed. Hence, this radiopaque material, most likely to be AgI, was deposited inside the dentinal tubules, as shown by others (14, 15). Hence, it does not indicate that SDF+KI application results in deeper penetration than SDF, it depends on the structure of the natural dentin carious lesion. Similar to SDF, SDF+KI application would have formed FA/FSHA to harden the dentin and prevent mineral loss in subsequent demineralization (Figure 7D).

Regarding the remineralization effect of SDF, Heukamp et al. (16) found that SDF to be less effective than Cervitec F varnish on artificial enamel caries lesion, which agrees with the results of present study. |With regard to SDF on dentin, Cifuentes-Jiménez et al. (3) found that SDF and NaF resulted in an increase in mineral content, the formation of a crystalline precipitate with high flexural strength. They found no effect of acid challenge on dentin blocks treated with SDF under pH cycling. This agrees with this current study which shows application of SDF with or without KI protects dentin from acid attack.

5 Conclusion

The study presented provides valuable insights into the remineralization potential of SDF and its KI adjunct on both enamel and dentin lesions in primary teeth. The findings from this *in vitro* study shows that silver ions penetrate the enamel structure only in the presence of porosities, suggesting that SDF treatment may benefit sound enamel to prevent demineralization. The SDF application is most effect in carious dentin where Ag containing material is deposited on the surface and inside dentin tubule, with F containing apatite formation. This can then protect the dentin from acidic challenge. The adjunct of KI, used for reducing formation of black metallic silver, does not seem to hamper its protective property.

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 humans were approved by Queen Mary University Of London (QMREC 0014/17). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. PA: Conceptualization, Investigation, Methodology, Writing – review & editing, Supervision. SS: Conceptualization, Supervision, Writing – review & editing. GD: Writing – review & editing, Methodology, Software. DM: Methodology, Software, Writing – review & editing. FW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors received the materials for the study from SDI Limited. The company played no role in the design, implementation, analysis, or preparation of the manuscript.

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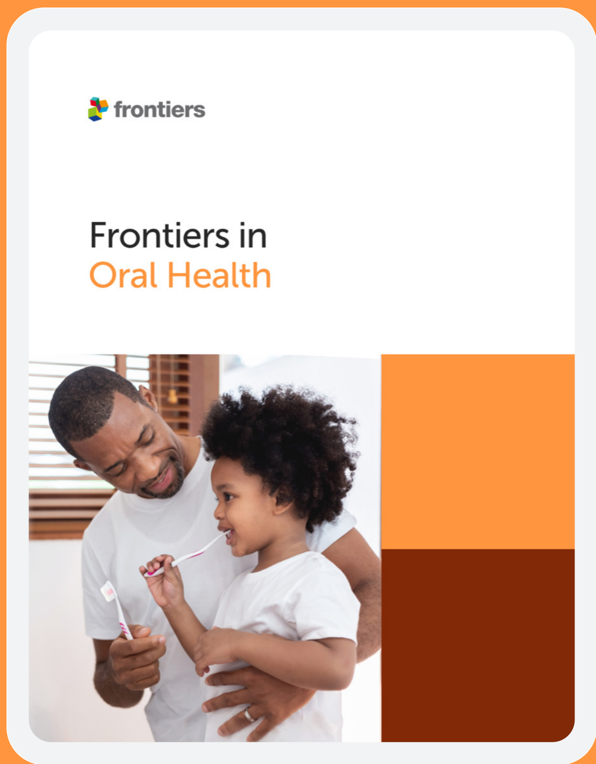

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