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ORIGINAL ARTICLE

Clinical Findings Arising from the Use of Silver Diamine Fluoride to Prevent or Treat Caries Lesions and Dentinal Hypersensitivity: A Data Mining Analysis

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ABSTRACT

Objective: To summarize data of clinical trials that used silver diamine fluoride (SDF) to prevent and treat caries lesions and dentinal hypersensitivity. **Material and Methods:** Six electronic databases were searched in May 2022. The concentration of SDF, type of usage (alone/combined), dentition, anterior/posterior teeth, tooth region, dental tissue, number of the treated surfaces, the intervention environment, participants' age, frequency and duration of SDF application, purpose, and outcome were the extracted variables. The type of study, year of publication, authors, journals, and country were also investigated. **Results:** From 8860 articles, 53 were selected. Most were randomized (n=38), that applied 38% SDF (n=43), alone (n=44), on multiple surfaces (n=44), only in dentin (n=36), of the crown (n=46) of anterior and posterior (n=36) primary teeth (n=39). The studies were preferably carried out outside the clinic (n=31), only in children (n=33), with reapplication of SDF (n=30), but did not inform the duration of application (n=19). SDF was most used to treat (n=46) only caries lesions (n=50). They were published between 2001 and 2022, mainly in the Journal of Dentistry (n=10). China (n=19) and Lo E.C.M (n=19) were the countries and authors that published the most, respectively. **Conclusion:** The silver diamine fluoride 38% alone was most used to treat caries lesions in the dentin of the crown of all primary teeth, preferably applied on multiple surfaces, requiring reapplication, and outside the clinic.

Keywords: Dental Caries; Dentin Sensitivity; Cariostatic Agents; Review.

Introduction

Dental caries in primary and permanent teeth is one of the most frequent oral conditions in the world, severely affecting the most economically disadvantaged populations [1]. Treatment with silver diamine fluoride (SDF) is one of the recommendations for public health intervention against early childhood caries (ECC) from the WHO Global Consultation on Public Health Intervention against ECC [2]. It is a non-invasive method of caries control that aims to reduce the negative impact of the untreated open cavity, avoiding more invasive treatments [3].

SDF is a low-cost and safe cariostatic agent with a simple application protocol and requires a short time to perform [4]. It is a good treatment alternative for patients with caries lesions in dentin who do not have immediate access to conventional restorative treatment [5]. Studies have shown that it is effective in stopping early-stage caries lesions from progressing to advanced cavitated lesions in dentin, besides preventing the development of new caries lesions [4,6]. Furthermore, it recently won the status of a safer treatment during the COVID-19 pandemic [7], as it does not require carious tissue removal and, consequently, reduces aerosol production.

SDF is also indicated for the treatment of dental hypersensitivity, as it has the property of blocking the dentinal tubules [8]. Although there are a variety of possible desensitizing agents for the treatment of dentinal hypersensitivity [9], in 2014, a review reported the need for non-invasive, permanent, and positively cost-effective therapies for both professionals and patients [10]. In the same year, the use of SDF as a desensitizing agent was approved by The Food and Drug Administration (FDA) [4].

Although darkening of the region where it is applied [11] is the most common disadvantage of this product, the SDF is usually well accepted by parents [12]. However, the involvement of an anterior tooth and the visualization of the color can influence this acceptance [13]. There is a strategy to reduce the darkening caused by SDF, which is the subsequent use of potassium iodide (KI); however, the evidence of this combination is still insufficient [14].

SDF application interval is still controversial in the literature since some clinical studies demonstrate different protocols, ranging from a single application [15] to regular intervals [16]. Therefore, it is necessary to identify the main characteristics of clinical studies quantitatively and descriptively with SDF to prevent and treat caries lesions or dentinal hypersensitivity, to draw an overview of what the clinical protocol has addressed worldwide and, consequently, assist the clinician in their decisions related to these interventions. The purpose of this study was to summarize clinical trial data regarding the use of silver diamine fluoride for preventing and treating caries lesions, as well as dentinal hypersensitivity.

Material and Methods

Search Strategy

The search for studies was performed in May 2022 without restriction on the language and year of publication. It was completed in the following electronic databases: MEDLINE via PubMed, Scopus, Web of Science, Cochrane Library, Embase, and Latin American and Caribbean Health Sciences Literature database (LILACS) via Virtual Health Library (VHL). A controlled vocabulary (MeSH and Entry terms) and accessible terms regarding dental caries, silver diamine fluoride, and clinical trials, together with Boolean operators "OR" and "AND," were used to make search keys. The search strategy was first performed in PubMed and then adapted according to the syntax rules for each database, as presented in Supplementary Table 1 (Table S1).

Eligibility Criteria

This study included randomized and quasi-randomized clinical trials that used the SDF to treat or prevent dental caries lesions or dentinal hypersensitivity. No restrictions were made regarding the participants' age, type of dentition, and follow-up time. Reports of cases, case series, retrospective studies, *in vitro*, animal studies, *ex vivo*, *in situ*, and reviews were excluded.

Study Selection

All articles retrieved from the electronic databases were exported to a reference manager software (Rayyan™), where duplicate articles were removed. Then, in the same software, the title and abstract of the remaining articles were read by two independent reviewers (GFR and LAJ) to select potentially eligible articles based on the inclusion criteria. If there was any disagreement between these two reviewers, a third reviewer (AF) was contacted to resolve the conflict.

Data Extraction

All eligible articles were transferred to the Microsoft Excel® 2010 (Microsoft, Redmond, WA, USA) program, where the data extraction record was performed.

The articles had the following data extracted about SDF applicability: (1) type of dentition in which SDF was applied (primary, permanent, or both) and (2) location of the treated teeth (anterior, posterior, or both); (3) the SDF application aim (prevention, treatment, or both); (4) outcome: if it was used in caries lesions and/or dentinal hypersensitivity and (5) in what concentration (10%, 30%, 38% or more than one concentration); (6) if the SDF was applied alone or associated with another type of product (eg: SDF + KI); (7) if the application was on a surface or on multiple surfaces (if the study applied the SDF in both situations, it was considered as multiple surfaces); (8) the dental tissue in which the treatment/prevention was carried out (enamel, dentin or both) and (9) the tooth region (crown, root or both situations); (10) the age group of the participants, according to the WHO classification [17] (the minimum and maximum age informed in the study was considered and, when this information was not explained, the mean age was used) – children, teens, adults and elderly (the same study may include participants from more than one age group); (11) if the SDF was applied in a single frequency protocol (only once or used for treatment/prevention in the same patient one week apart between applications), periodic protocol (reapplication) or if both protocols were tested in the same study. Furthermore, when a study reapplied the SDF only to caries lesions that were still active at follow-up, it was considered to have both protocols since some participants (with inactive caries lesions) received only one application of the SDF; (12) Duration of SDF application, which could be: a – 1 minute, b – 3 minutes or c – immediately removed (application up to 10 seconds), d – other duration of application than those mentioned, e – more than one application time that were compared within the same study or f – those studies without information; and (13) the place where the treatment was carried out, whether in a clinical setting (the use of a portable dental office was also considered in this category) or not (e.g., kindergarten, schools, nursing homes, etc.).

Regarding the characteristics of the studies, information was collected such as journal and year of publication, authors, the country where the study was carried out (according to the information in the article methodology), keywords, and type of study (randomized and quasi-randomized). The articles' publication year was stratified into four time periods, from 2001 to 2022 (2001-2005, 2006-2010, 2011-2016, 2017-2022). Authors with three or more publications were considered the top authors, and, concerning the journal, those with two or more published articles were called the top journals. Only keywords mentioned four or more times (top

keywords) were included in this review, excluding those used in the search strategy. Most authors have published up to two articles, so we consider all those above this number of publications as the top authors. The same criteria were adopted for keywords.

The extracted data was transferred to the VantagePoint™ program to make the analyses. In addition, the objective of the articles and the intervention groups studied, the final follow-up time, the main conclusion related to arrest/prevention of caries lesions and the treatment of dentinal hypersensitivity were also tabled in a descriptive way using the Microsoft Excel® 2010 (Microsoft, Redmond, WA, USA) program.

Data Analysis

Data analysis was conducted using VantagePoint™ (Search Technology, Inc., Florida, USA) and Microsoft Excel®.

Descriptive analyses were done for the type of study and some of its clinical characteristics, such as whether SDF was applied on single or multiple surfaces, a crown or root, and a primary or permanent tooth. Comparisons were also made to observe the different SDF application protocols.

The cluster maps strategy was used to show the relationship between tooth tissue (enamel/dentin) and the concentration of SDF, the location of the treated tooth, and whether only SDF or some other associated product was used, as well as whether it was used for dental caries or dentin hypersensitivity and in what concentration. In this type of graph, the number of studies in each node, represented by each intersection between the studied variables, corresponds to the number of small balls within them.

Regarding the age of the groups included in the studies and whether it was performed in a clinical setting, this link was demonstrated through a matrix viewer. It is important to note that the larger the circle of each variable, the more it was present in the studies, and the thicker the line connecting one variable to another, the greater the relationship between them.

Furthermore, a word cloud was generated in the VantagePoint™ considering the top keywords, so the more significant the word, the more cited it was. To identify the countries where the studies were published, a world map was generated in Microsoft Excel® through a table with the number of studies carried out in each country; the greater the number of studies carried out in each country, the darker its color tone on the map. Countries with gray color do not have any of the included studies. A graph was also used to numerically demonstrate these publications according to each country.

The top authors were represented on a donut chart, highlighting the partnership in publications, which was demonstrated through a cross-correlation map, in which the thicker the line connecting these authors, the more significant the correlation between them. The absence of a line connecting one author to another shows no collaboration. The frequency of articles published in top journals (two or more publications), according to the time intervals of publication of the studies, was represented by a bubble chart. So, the larger the circle, the greater the number of published studies in a given journal by year.

Results

Database searches initially retrieved 8860 studies, of which 4487 were duplicates and were excluded. The remaining 4373 articles were evaluated according to the study's eligibility criteria by reading the titles and abstract. Thus, 4305 were excluded, and 65 were selected for a full reading. Finally, from 65 articles, 53 were included in the present study (Figure 1). Descriptive data and the author's conclusion of each study related to the use of SDF in caries lesions and dentinal hypersensitivity are shown in Supplementary Table 2 (Table S2).

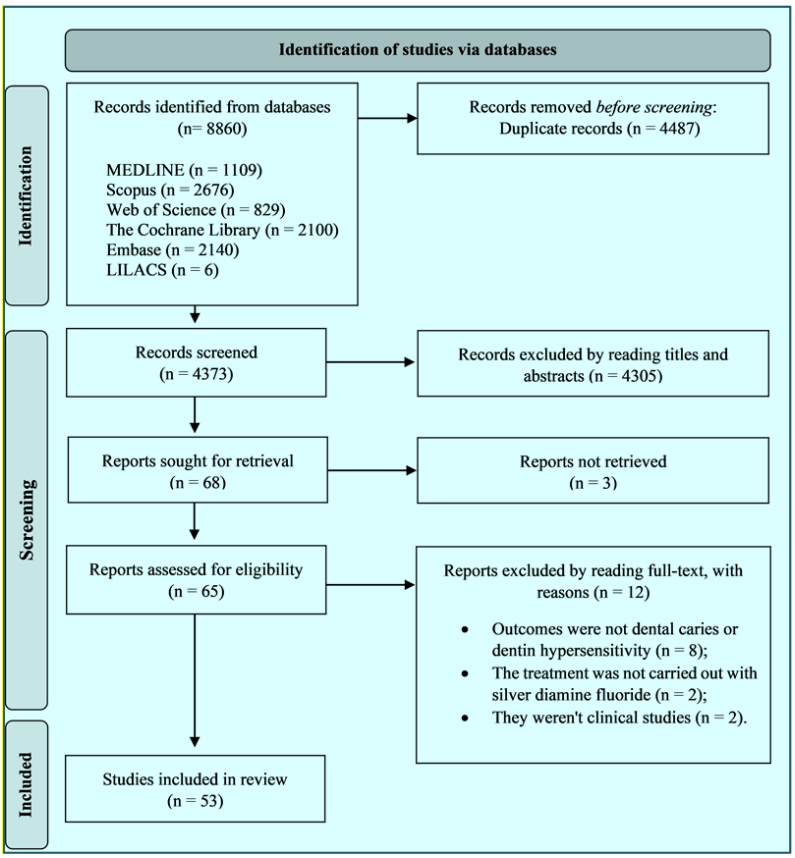

Figure 1. Flow chart of search results in databases.

Type of Study and Clinical Characteristics

Most of the articles included were randomized controlled clinical trials (n=38; 71.70%), 39 (73.58%) referred to interventions performed only on primary teeth, SDF mainly was applied only in the crown (n=46; 86.79%) and in multiple surfaces (n=44; 83.01%) (Figure 2).

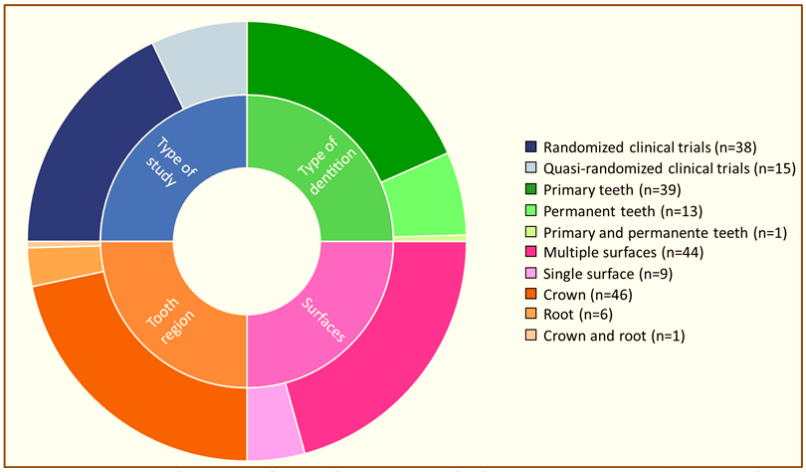

Figure 2. Donut chart with study type and characteristics of treated teeth.

Correlation Between Age Range and Environment

The relationship between the age range of the participants and the environment in which SDF was applied is shown in Figure 3. Most of the studies (n=31; 58.49%) were performed outside dental clinics and were accomplished only with children (n=33; 62.26%).

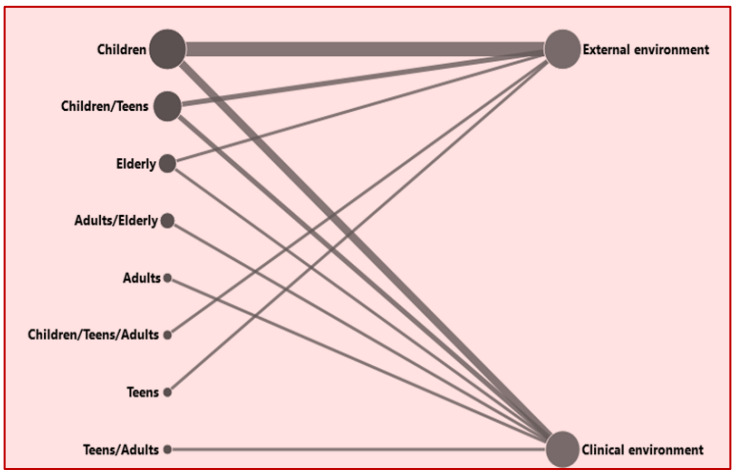

Figure 3. Correlation between the age group of the study participants and the environment in which the treatment was carried out.

Relationship Between (1) SDF Concentration and Outcome, Dental Tissue; (2) Combined or Non-Combined Use of SDF and Tooth Location, Outcome

Most of the studies used 38% SDF (n=43; 81.13%) in the management of caries (n=40; 75.47%) in dentin (n=30; 56.60%). On the other hand, 10% SDF was the least used (n=2; 3.77%) and only to treat enamel caries lesions. Furthermore, it was possible to observe that almost all articles addressed the management of dental caries (n=50; 94.34%). In addition, one study that addressed the management of teeth with molar incisor hypomineralization used 38% SDF for both caries and dentin hypersensitivity (1.89%) (Figure 4a, b).

Considering the position of the teeth in the arch, 37 studies (69.81%) covered posterior and anterior teeth. The SDF application associated with another product was performed in 9 (16.98%) articles, mainly for managing dental caries (n=7; 13.21%). Regarding dentinal hypersensitivity, the treatment was performed with SDF associated with another product in one study, while in the other study, SDF was used alone. (Figure 4c, d).

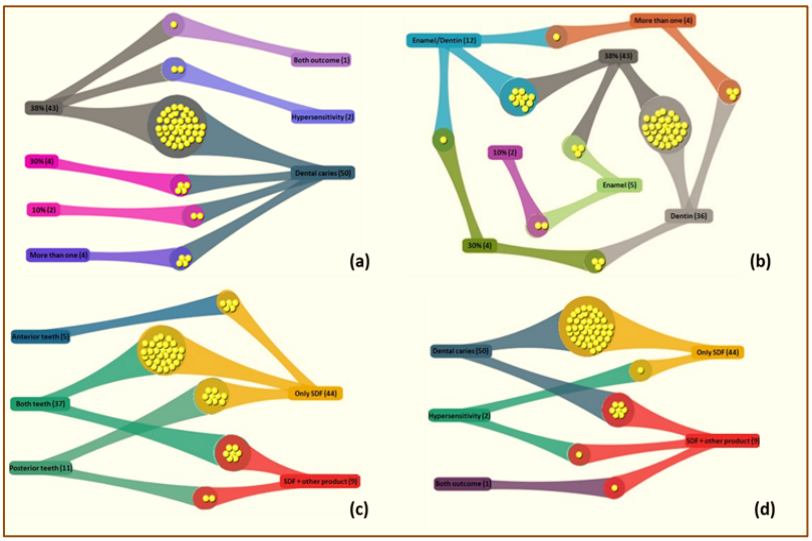

Figure 4. (a) Cluster map of the relationship between the concentration of SDF and the outcome; (b) Cluster map of the relationship between the concentration of SDF and the dental tissue to which it was applied; (c) Cluster map of the relationship between the location of the treated tooth and whether SDF was applied alone or in combination with another product; (d) Relationship between the outcome and the use of SDF alone or combined with another product.

Distribution of Different SDF Application Intervals According to Each Study

Among the 53 included studies, 19 (35.85%) performed only a single application of SDF. In contrast, 30 (56.60%) performed periodic reapplication of this cariostatic, and 4 (7.55%) performed both protocols within the same study, a group with periodic reapplication and another with a single application. It is important to note that reapplications every 1 or 2-3 weeks (weekly intervals) were considered a single application. Thus, studies that reapplied the SDF at short and longer intervals were classified as having both a single and a periodic reapplication protocol (both protocols).

Considering the studies that addressed both application protocols (n=4), in one [18], the SDF was reapplied approximately after two/three weeks (single application) and after three months if the caries lesion was active (periodic reapplication). In another study [19], the application was single or after six months (periodic reapplication), also in active lesions. In the other two studies [20,21], with the same sample, the SDF was applied three times at a weekly interval (single application) or every 12 months, independently of the caries activity (periodic reapplication).

In studies with only periodic reapplication of the SDF (n=30), the following reapplication protocols were performed: (a) every three months; (b) every four months; (c) every six months; (d) every six months or other intervals if the caries lesion had not been arrested in the first application; (e) every six months, one monthly interval for three months and three monthly intervals for six months; (f) every 6 and 12 months and (g) every 12 months. SDF reapplication every six months was the most frequent interval, considering both studies that only reapplied in this period (n=14) and those that tested more than one interval within the same study, one of them being six months (n=7), totaling 21 (39.62%) studies (Figure 5).

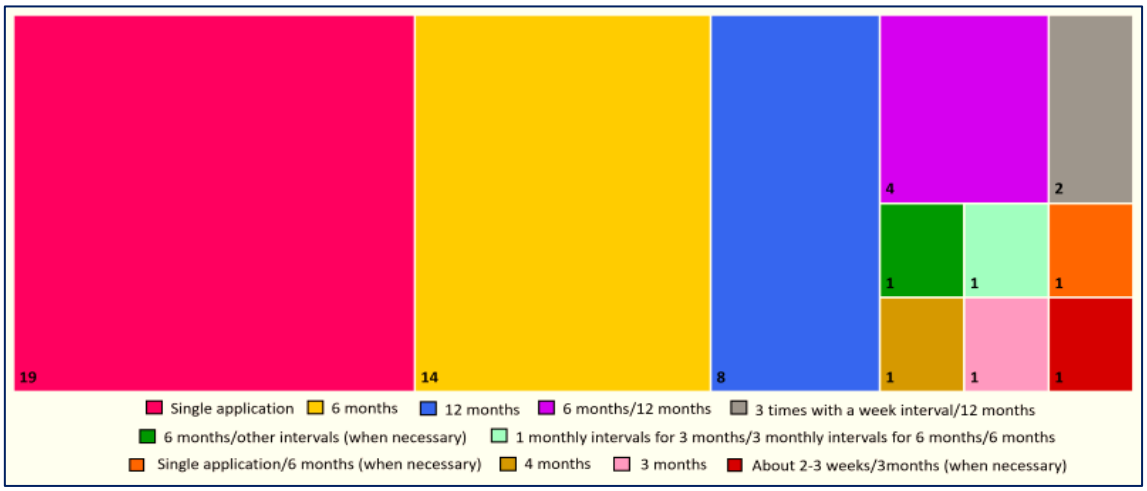

Figure 5. The treemap chart shows the SDF application intervals used in the studies. The number present in each rectangle/square indicates the number of studies that applied the protocol in question.

Distribution of Application Interval Protocol According to Concentration and Duration of Application

Most studies applied SDF periodically (n=30; 56.60%); that is, there was reapplication, but without reporting the duration of application (n=14; 26.41%). Among these, the studies that used 38% SDF stand out (n=12; 22.64%), followed by those that the time, although informed, was classified as "other time" (n=5; 9.43%) since none of the predetermined times was found (Figure 6).

Articles with a single SDF application protocol (n=19; 35.85%) were mainly represented by those that used 38% SDF during a 1-minute application (n=6; 11.32%). The studies that involved more than one application protocol (n=4; 7.55%) were those in which the application of 30% SDF was with immediate removal (n=2; 3.77%), 38% SDF with different duration of application (n=1; 1.89%) and 38% SDF applied for 1 minute (n=1; 1.89%) (Figure 6).

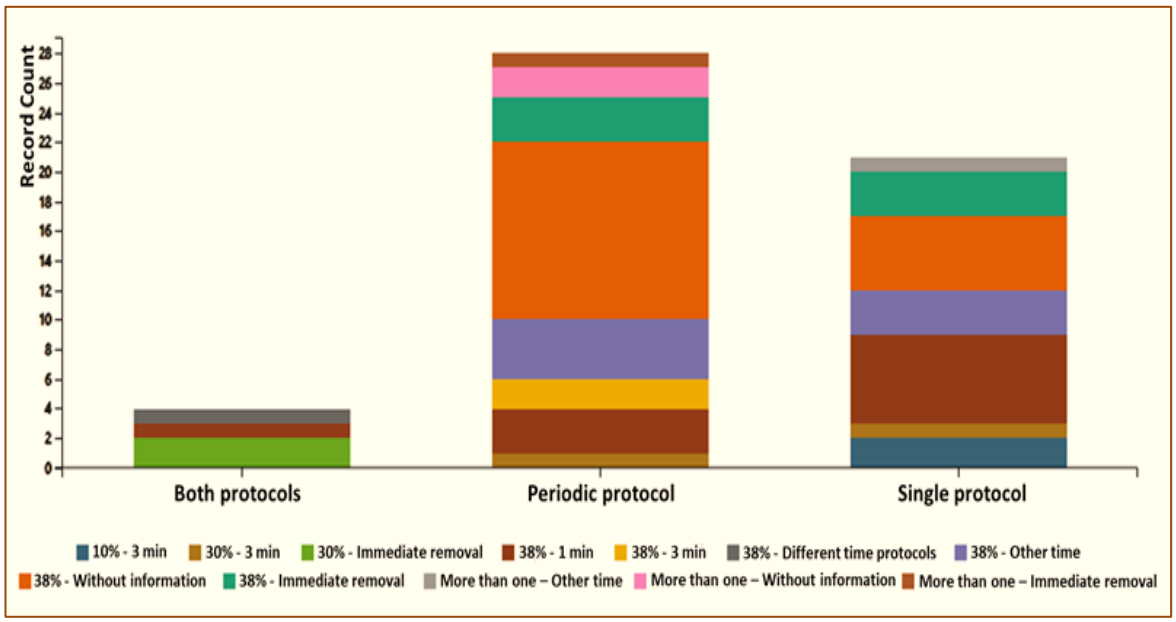

Figure 6. Stacked bar chart showing the interval protocols of SDF application according to the concentration of this product and their respective duration of application.

Relationship Between Outcome, Duration of Application and Purpose

Table 1 shows the number of studies that presented dental caries, hypersensitivity, or both as outcomes, considering the time of application and the purpose of SDF usage. The only study that used both outcomes investigated was treatment with SDF, and the duration of application was not reported.

Among the studies in which the duration of application was classified as "other times," most of them (n=6; 11.32%) applied the SDF for 2 minutes, 1 applied it from 30 to 60 seconds, and another for more than 3 minutes.

Table 1. Number of studies considering data related to the outcome, duration of application, and purpose.

Outcome	Duration of Application	Purpose			Total
		Prevention	Treatment	Prevention and Treatment	
		N (%)	N (%)	N (%)	N (%)
Dental Caries	Immediate removal	-	8 (15.09)	-	8 (15.09)
	1 min.	-	9 (16.98)	1 (1.89)	10 (18.87)
	3 min.	1 (1.89)	4 (7.55)	1 (1.89)	6 (11.32)
	Different protocols	-	1 (1.89)	-	1 (1.89)
	Other time	-	7 (13.21)	-	7 (13.21)
	Without information	1 (1.89)	14 (26.41)	3 (5.66)	18 (33.96)
Dentin Hypersensitivity	Immediate removal	-	1 (1.89)	-	1 (1.89)
	Without information	-	1 (1.89)	-	1 (1.89)
Dental Caries and Dentin Hypersensitivity	Without information	-	1 (1.89)	-	1 (1.89)
Total		2 (3.77)	46 (86.79)	5 (9.43)	53 (100.0)

Keywords and Countries

The 33 most cited keywords by the studies were demonstrated in a word cloud, which was "fluorides," "humans," and "child," being cited in 39, 23, and 20 articles, respectively (Figure 7a).

The included studies were carried out in 18 different countries, with China being the country that published the most, with 19 (35.85%) articles, followed by India (n=6; 11.32%), Brazil (n=4; 7.55%) and The United States of America (n=4; 7.55%) (Figure 7b and 7c).

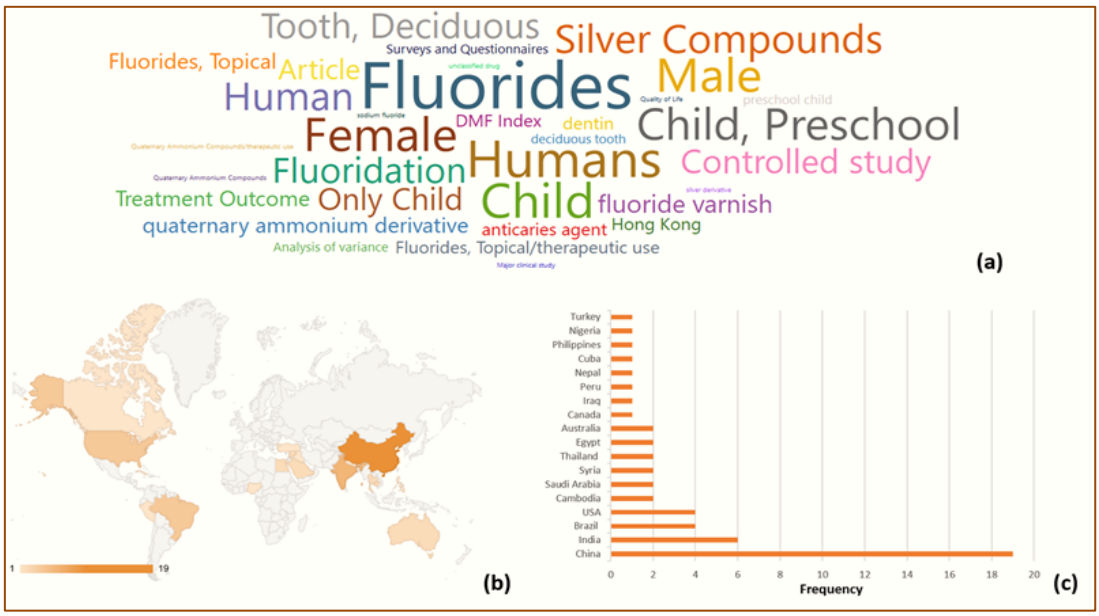

Figure 7. (a) Word cloud with the terms that have been reported four or more times; (b) Word map with the countries that published studies on the topic; (c) The countries represented on the world map and the number of studies carried out in each of them.

Journals, Authors, and Year of Publication

The top authors are shown in Figure 8a. The correlation between these authors shows they usually have a strong partnership. Lo, E.C.M are closely related to different authors, followed by Chu, C.H and Wong, M.C.M (Figure 8b).

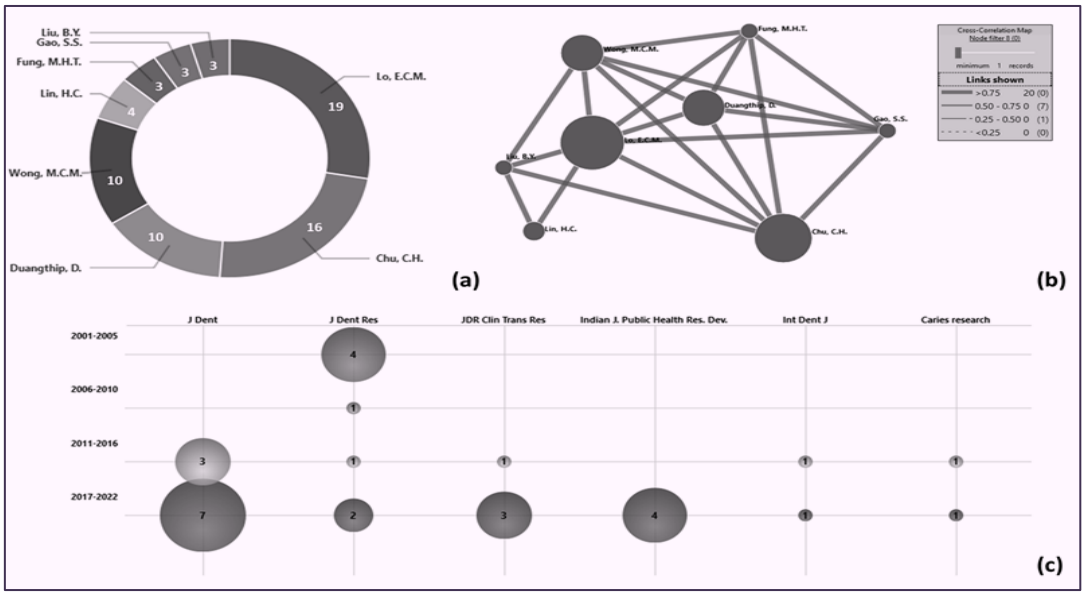

Figure 8. (a) Donut chart of the top author with three or more publications; (b) Cross-correlation map between the top authors;(c) Bubble chart representing the number of publications between 2001 and 2022, considering the top journals.

Top journals with two or more articles published by year of publication are highlighted in Figure 8c. Journal of Dentistry is the journal that published the most articles on the investigated subject. Furthermore, an increase in the number of clinical trials between the years 2017 and 2022 can be noticed compared to the other periods evaluated (Figure 8c).

Discussion

The data obtained from this study contains essential information about a given subject for the clinician. It can also help researchers seeking to develop studies, such as a protocol or clinical trials, since it clearly shows what has already been studied about the theme and the gaps in the literature. The main clinical findings of this paper show that the vast majority of trials were related to the management of caries lesions, with studies mainly addressing the treatment of these lesions, followed by cases in which both treatment and prevention occurred within the same survey. Thus, the less frequent outcomes in the included studies were using SDF only to prevent caries lesions and treat dentin hypersensitivity. Following a periodic application protocol, SDF at 38% was the most used concentration with reapplication. In these cases, the SDF was reapplied mainly every six months, followed by studies that applied it every 12 months. In this context, studies showed that the biannual reapplication of SDF is more effective in controlling caries lesions [22,23]. Furthermore, most studies still need to provide information on the duration of SDF application. In those that reported it, 1 minute followed by immediate removal was the most prevalent.

Although an *in vitro* study that compared different times of application of SDF showed that the use of 38% with immediate removal is enough to arrest caries lesions [24], the diversity of protocols [25] and lack of consensus regarding the duration of application reinforces the need for clinical studies that compare different durations of applications. Studies from this perspective would be relevant to investigate the shortest time required for the SDF to achieve its effectiveness since it reduces the patient chair time, which is essential, especially for treating young children or non-cooperating patients.

Regarding the effectiveness of the SDF, Chibinski et al. [26] showed, through a systematic review, that this treatment, when compared to other treatments or placebo, is more effective in arresting caries lesions in primary teeth, presenting high-quality evidence. This action of SDF can be explained by inhibiting the adhesion of *Streptococcus Mutans* to the tooth surface, thus reducing its growth. In addition, SDF promotes an increase in the microhardness values of the surface where it was applied and inhibits matrix metalloproteinases and cathepsin activity, thus preventing collagen degradation [27].

China is the leading country that has published on this subject, followed by India, Brazil, and the United States of America. Recent systematic reviews have shown that China is one of the countries with the highest prevalence of caries in older adults [28] and in children [29]; thus, the implementation of services that use SDF is sought to increase access to control caries lesions [30]. These data agree with the top authors who publish the most on this topic since they are researchers from China's universities, mainly The University of Hong Kong, reiterating a previous study published by Jiang et al. [31]. This predominance of authors from the same school also justifies their strong publication partnership. Thus, each author has already published a study with at least two other top authors.

Studies carried out outside the dental environment, mainly in kindergartens, were observed. Consequently, these studies portray more management in primary teeth. An extension project developed by the University of Hong Kong, China, which provides dental services in kindergartens through the application of the SDF for preventing and controlling dental caries in children [30], favored the number of trials outside the clinics. Implementing projects like this increases access to oral health care, especially for disadvantaged populations and regions. These data also reflect the simple technique of applying SDF, which does not require significant costs and can be done outside the dental clinic [15].

Considering the investigated outcomes, only three studies addressed dentin hypersensitivity [32-34], while all others were about dental caries. Among these three studies, one addresses the treatment of caries lesions

and dentinal hypersensitivity, as they are teeth with molar incisor hypomineralization [34]. This small number demonstrated an unexpected lack of studies on using SDF to treat dentin hypersensitivity, as this was its initial FDA-approved indication [4]. On the other hand, an unesthetic result of SDF can explain this scarcity because treatment for dentin hypersensitivity is generally performed on permanent teeth, often on anterior teeth, where the esthetic is more relevant than when used in primary and posterior teeth. Furthermore, for dental caries and hypersensitivity, the most used concentration of SDF was 38%, corroborating a systematic review that reported that this concentration is the most used [35]. However, 38% of SDF was preferentially used alone for caries lesions, while for hypersensitivity, one study used it alone [32] and the other associated with KI [33].

In Brazil, 38% of SDF is available on the market only associated with KI. Considering the present study, it was also observed that the 10% concentration was used only in enamel [36,37]. In comparison, the 12% SDF was only used in studies comparing this concentration with 38%, and it was not as effective as 38% in arrest dentin caries lesions [22,23,38]. On the other hand, 30% SDF was used for treating caries lesions in 4 included studies and proved effective in all of them [15,20,21,39]. These data agree with the Contreras et al. [40], which shows that at concentrations of 30% and 38%, SDF is more effective than other preventive measures in controlling caries lesions in primary dentition, besides being a potential preventative treatment of caries lesions in permanent first molars, without serious adverse effects.

Although the use of KI associated with SDF is intended to reduce staining caused by the application of this product [14] and to improve the aesthetic issue, none of the included clinical trials of this treatment were conducted exclusively with anterior teeth. Another component that can be used combined with SDF is tannic acid, a reducing agent that accelerates the deposition of silver (Ag) after its application. A study has shown that it does not influence the efficacy of SDF [38]. In addition, it is important to emphasize that after the application of the SDF, the tooth can receive a restoration to rehabilitate the patient and restore function. In this context, one can opt for the SMART technique (atraumatic restorative treatment modified by silver), which consists of restoring the tooth with glass ionomer cement shortly after treatment with SDF, with the advantage of not removing decayed tissue [41].

Studies show that despite the darkening caused by SDF being its main adverse effect, what is more important is to promote disease control, making this procedure preferable to more invasive approaches, especially when they involve sedation, pain, or general anesthesia [13,42]. In addition, it is crucial to support the education, promote, and encourage the use of SDF by health professionals [43], as they seem to have more reservations about accepting this treatment due to its aesthetic issue than those responsible for children undergoing this treatment [12].

Conclusion

The number of studies related to the use of silver diamine fluoride for managing carious lesions and dentinal hypersensitivity has increased over the past five years. It has been published mainly in the Journal of Dentistry. The author who has published the most on the subject is from China, which is the country where the vast majority of studies were carried out. In general, the included studies were randomized controlled clinical trials carried out in children outside the clinical setting, in which the application of silver diamine fluoride occurred mainly on more than one surface of the crown of primary teeth, both anterior and posterior.

Concerning silver diamine fluoride, it was more commonly used without being associated with another product and at a 38% concentration for managing caries lesions in dentin and dentinal hypersensitivity. Furthermore, in most of the studies, this product was reapplied, and the duration of application was not specified,

and when informed, it was preferably 1 minute. Almost all the studies included addressed using SDF for caries lesion treatment. The use of silver diamine fluoride to treat dentin hypersensitivity was the less-discussed outcome in the studies.

Authors' Contributions

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study or access to supplementary materials can be made available upon request to the corresponding author.

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