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Silver Diamine Fluoride Has Efficacy in Controlling Caries Progression in Primary Teeth: A Systematic Review and Meta-Analysis

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Cariostatic agents · Child · Dental caries · Systematic review

Abstract
A systematic review was performed to evaluate the efficacy of silver diamine fluoride (SDF) in controlling caries progression in children when compared with active treatments or placebos. A search for randomized clinical trials that evaluate the effectiveness of SDF for caries control in children compared to active treatments or placebos with follow-ups longer than 6 months was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library, and grey literature. The risk of bias tool from the Cochrane Collaboration was used for quality assessment of the studies. The quality of the evidence was evaluated using the GRADE approach. Meta-analysis was performed on studies considered at low risk of bias. A total of 5,980 articles were identified. Eleven remained in the qualitative synthesis. Five studies were at "low," 2 at "unclear," and 4 studies at "high" risk of bias in the key domains. The studies from which the information could be extracted were included for meta-analysis. The arrestment of caries at 12 months promoted by SDF was 66% higher (95% CI 41–91%; $p < 0.00001$) than by other active material, but it was 154% higher (95% CI 67–85%; $p < 0.00001$) than by placebos. Overall, the caries arrestment was 89% higher (95% CI 49–138%; $p < 0.00001$) than using active materials/placebo. No heterogeneity was detected. The evidence was graded as high quality. The use of SDF is 89% more effective in controlling/arresting caries than other treatments or placebos. The quality of the evidence was graded as high.

The water fluoridation [Koh et al., 2015] and the widespread use of fluoride toothpaste [dos Santos et al., 2013] have produced major reductions in the prevalence and incidence of dental caries leading to significant improvements in children's oral health status over the past decades [Pitts et al., 2011].

However, dental caries remains a major oral health problem. Preschool children, in contrast to other age groups, still exhibit a large number of untreated caries lesions, and the decayed number is the main component in the dmft index [Duangthip et al., 2015; Dye et al., 2015]. In Brazil, the prevalence of untreated caries lesions in 5-year-old children is very high (80%), based on the last national epidemiological survey [Brasil, 2010].

This scenario is particularly true among socioeconomically deprived groups [Pitts et al., 2011; McGrady et al., 2012; Engelmann et al., 2016; Splieth et al., 2016], and

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adverse outcomes, such as dental pain and need of extraction, are common [dos Santos et al., 2013] jeopardizing the quality of life of these children [Bönecker et al., 2012].

The required restorative treatments are usually not available due to poor access to dental care and/or limited financial resources [Craig et al., 2012]. Another barrier against treatment is that the dental treatment causes fear and anxiety in children at this age, and the general dentist may find it stressful to provide them the required dental care [Duangthip et al., 2015]. As a result, the cavities remain untreated and the caries activity persists, increasing the risk of caries in the permanent dentition, particularly in the first permanent molars that erupt around the age of 6–7 years [Kalnina and Care, 2016].

In order to reduce the inequality in oral health, it is necessary to identify potential synergies between public health strategies and clinical strategies [Pitts et al., 2011]. Noninvasive approaches may present alternatives to conventional surgical treatment in arresting or slowing the progression of caries lesions in primary and permanent teeth [Llodra et al., 2005; Liu et al., 2012]. These approaches include the use of fluoride, chlorhexidine and sealants, among others [Liu et al., 2012]. Besides them, silver diamine fluoride (SDF) has been used for more than 4 decades, and its advantages encourage its use in the public health meeting World Health Organization Millennium Goals for the 21st-century medical care [Chu et al., 2014].

SDF is the only dental material available that associates the remineralization of the dental structures provided by sodium fluoride with the antibacterial effect on the caries microorganisms by the action of silver nitrate. It has been shown in an "ex vivo" study that dentin carious lesions treated with SDF exhibited a remineralized zone rich in calcium and phosphate, similar to arrested carious lesions, with collagen fibrils protected by these minerals, avoiding further degradation [Mei et al., 2014].

SDF is easy to apply (even by dental assistants) and quite affordable. Since its application does not require dental equipment, it can be used outside the clinical environment [dos Santos et al., 2012b]. The product is well accepted even by young children [Chu and Lo, 2008] since it can be applied without caries removal [Chu et al., 2002b]. Therefore, SDF can be considered a user-friendly material for use in dental clinics as well as remote areas, schools or deprived communities.

The efficacy of SDF is documented in the literature. Compared to negative control groups like water and saline solution or no treatment at all, SDF is capable of arresting dentin carious lesions in primary teeth [Llodra et al., 2005; Yee et al., 2009b; dos Santos et al., 2014] or first permanent molars [Llodra et al., 2005].

But there is a unique characteristic that hampers a broader acceptance of this product: the staining of the teeth after SDF application. Therefore, it is important to determine if other noninvasive methods are as effective as SDF in arresting caries in primary teeth and first permanent molars. If so, these methods could substitute SDF without the disadvantages of teeth staining. The most common treatments that are compared to SDF are fluoride varnish and atraumatic restorative treatment (ART) sealants and restorations.

We are aware of the recent systematic reviews published on this subject by a group of Chinese researchers [Gao et al., 2016a, b]. However, we understand that the precision and robustness and quality of the evidence gathered by a systematic review depend on an extremely critical analysis of the clinical studies to produce the best available evidence. Unfortunately, the previous systematic reviews of the literature on this topic failed to compare similar outcomes and/or did not evaluate the risk of bias of the included studies [Gao et al., 2016a, b].

In this way, we collected and systematized data from randomized controlled clinical trials and evaluated the long-term effects of SDF application compared to negative controls or active treatments, focusing on a strict process that evaluates the risk of bias of the available studies and meta-analyzing only similar outcomes. Therefore, in summary the purpose of this systematic review and meta-analysis was to answer the following PICO (participant, intervention, comparator and outcome) question: is SDF more effective than other active treatments/placebo for controlling the progress of active carious lesions in primary teeth and first permanent molars?

Materials and Methods

Protocol and Registration

This study protocol was registered in the PROSPERO database (CRD42016035741) and the recommendations of the PRISMA statement were followed for the report of this study [Moher et al., 2010; Moher et al., 2015]. This study was accomplished from March to December 2016 at the State University of Ponta Grossa, Paraná, Brazil.

Information Sources and Search Strategy

We defined a search strategy based on controlled vocabulary (MeSH terms) of the PubMed database along with free keyword. These words were combined with the Boolean operator OR within each concept of the search strategy. The concepts from the PICO question (population and intervention) were then combined with the Boolean operator AND.

Table 1. Electronic databases and search strategy

PubMed = 1,743 (08/03/2016)			
#1 dental caries[MeSH Terms] OR dentin, carious[MeSH Terms] OR "enamel caries"[Title/Abstract] OR "dentin caries"[Title/Abstract] OR "dental cavity"[Title/Abstract] OR molar[MeSH Terms] OR tooth, deciduous[MeSH Terms] OR carious lesion*[Title/Abstract] OR caries lesion*[Title/Abstract] OR "deciduous dentition"[Title/Abstract] OR "primary dentition"[Title/Abstract] OR "primary teeth"[Title/Abstract] OR "primary tooth"[Title/Abstract] OR "first teeth"[Title/Abstract] OR "first tooth"[Title/Abstract] OR "first permanent molar"[Title/Abstract] OR "first permanent molars"[Title/Abstract]	#2 ((((((silver fluoride[Supplementary concept]) OR silver diamine fluoride[Supplementary concept]) OR SDF[Title/Abstract]) OR "silver fluoride"[Title/Abstract]) OR diamine fluoride*[Title/Abstract]) OR (fluorides[MeSH Terms] AND teeth[Title/Abstract]) OR "silver nitrate solution[Title/Abstract]) OR (cariostatic agents[MeSH Terms] AND teeth[Title/Abstract])	#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))	#1 AND #2 AND #3
Scopus = 4,201 (11/03/16)			
#1 (TITLE-ABS-KEY ("dental caries") OR TITLE-ABS-KEY ("dentin, carious") OR TITLE-ABS-KEY ("enamel caries") OR TITLE-ABS-KEY ("dentin caries") OR TITLE-ABS-KEY ("dental cavit*") OR TITLE-ABS-KEY (molar) OR TITLE-ABS-KEY ("t??th, deciduous") OR TITLE-ABS-KEY ("cari*s lesion") OR TITLE-ABS-KEY ("cari*s lesions") OR TITLE-ABS-KEY ("deciduous dentition") OR TITLE-ABS-KEY ("primary dentition") OR TITLE-ABS-KEY ("primary t??th") OR TITLE-ABS-KEY ("first t??th") OR TITLE-ABS-KEY ("first permanent molar*"))	#2 (TITLE-ABS-KEY ("silver fluoride") OR TITLE-ABS-KEY ("silver diamine fluoride") OR TITLE-ABS-KEY (sdf) OR TITLE-ABS-KEY ("diamine fluoride*")) #3 (TITLE-ABS-KEY (fluoride) AND TITLE-ABS-KEY (teeth)) #4 (TITLE-ABS-KEY ("cariostatic agents") AND TITLE-ABS-KEY (teeth)) #5 #2 OR #3 OR #4 AND (LIMIT-TO (SUBJAREA, "DENT"))	#1 AND #5
Web of Science = 1,480 (11/03/2016)			
#1 Tópico: ("dental caries") OR Tópico: ("dentin, carious") OR Tópico: ("enamel caries") OR Tópico: ("dentin caries") OR Tópico: ("dental cavit*") OR Tópico: ("t*th, deciduous") OR Tópico: (cari*s lesion*) OR Tópico: ("deciduous dentition") OR Tópico: ("primary dentition") OR Tópico: ("primary t*th") OR Tópico: ("first t*th") OR Tópico: ("first permanent molar/s")	#2 Tópico: ("silverfluoride") OR Tópico: ("silverdiaminefluoride") OR Tópico: (SDF) OR Tópico: ("diaminefluoride/s") #3 Tópico: (fluoride) AND Tópico: (teeth) #4 Tópico: ("cariostatic agents") AND Tópico: (teeth) #5 #4 OR #3 OR #2	#1 AND #5
LILACS and BBO = 98 (11/03/16)			
#1 (MH: "dental caries" OR MH: "dentin, caries" OR MH: molar OR "tooth, deciduous" OR "enamel caries" OR "cárie de esmalte" OR "caries de esmalte" OR "dentin caries" OR "cárie de dentina" OR "cárie dentinária" OR "caries de dentina" OR caries lesion/s OR "lesão cariosa" OR "lesiones cariosas" OR carious lesion/s OR "decidous dentition" OR "dentição decidua" OR "dentición temporal" OR "primary dentition" OR "dentadura decidua" OR "dentadura temporal" OR "primary teeth" OR "dentes decíduos" OR "dientes primarios" OR "primary tooth" OR "dente decíduo" OR "diente primario" OR "first teeth" OR "first tooth" OR first permanent molar/s OR "primeiros molares permanents" OR "primers molares permanents")	#2 (MH: "silver fluoride" OR MH: "silver diamine fluoride" OR SDF OR DFP OR diamine fluoride/s OR diaminofluoreto/s OR MH: fluorides OR MH: "cariostatic agents")	#1 AND #2
Cochrane Library = 518 (08/03/2016)			
#1 MeSH descriptor: [Dental Caries] explode all trees #2 MeSH descriptor: [Dental Caries] explode all trees #3 MeSH descriptor: [Molar] explode all trees #4 MeSH descriptor: [Tooth, Deciduous] explode all trees #5 #1 or #2 or #3 or #4 #6 enamel near caries:ti,ab,kw (Word variations have been searched) #7 dentin near caries:ti,ab,kw (Word variations have been searched) #8 dental near cavity:ti,ab,kw (Word variations have been searched) #9 "caries lesion":ti,ab,kw (Word variations have been searched) #10 "carious lesion":ti,ab,kw (Word variations have been searched) #11 "deciduous dentition":ti,ab,kw (Word variations have been searched) #12 "primary dentition":ti,ab,kw (Word variations have been searched) #13 "primary tooth":ti,ab,kw (Word variations have been searched) #14 "first tooth":ti,ab,kw (Word variations have been searched) #15 "first permanent molar":ti,ab,kw (Word variations have been searched) #16 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	#17 #5 or #16 #18 MeSH descriptor: [Cariostatic Agents] explode all trees #19 MeSH descriptor: [Fluorides] explode all trees #20 SDF:ti,ab,kw (Word variations have been searched) #21 "silver fluoride":ti,ab,kw (Word variations have been searched) #22 diamine near fluoride:ti,ab,kw (Word variations have been searched) #23 "silver nitrate solution":ti,ab,kw (Word variations have been searched) #24 teeth:ti,ab,kw (Word variations have been searched) #25 #18 and #24 #26 #19 and #24 #27 #20 or #21 or #22 or #23 or #25 or #26	#17 AND #27

Other electronic databases (Scopus, Web of Science, the Latin American and Caribbean Health Sciences Literature database (LILACS), the Brazilian Library in Dentistry (BBO) and the Cochrane Library) were also used to identify the trials to be included, after adaptation of the search strategy developed for PubMed (Table 1). We also hand-searched the reference lists of all primary studies for additional relevant publications and investigated the related article links for each primary study in the PubMed database. No restrictions on publication date or languages were involved.

Abstracts of the International Association for Dental Research and its regional divisions (1990–2015) were used; the authors of relevant abstracts were contacted for further information. The grey literature was explored using the database System for Information on Grey Literature in Europe and Google Scholar. Dissertations and theses were searched using the ProQuest Dissertations and Theses Full Text databases and the Periódicos Capes Theses database.

To locate unpublished and ongoing trials, the following clinical trials registries were searched: Current Controlled Trials (www.

Table 2. Summary of the studies selected for this systematic review

Study ID	Study design	Subjects' mean age ± SD and range, years	Teeth	Total number of patients	Test group – material, protocol (number of patients) [dropouts]	Control groups – material, use protocol (number of patients) [dropouts]	Follow-up period, months	Outcomes
Chu et al., 2002b	Parallel design	4±0.8 3–5	Deciduous upper anterior teeth with dentin carious lesion	375	SDF + excavation SDF 38%[a] – 1 application every 12 months (76) [15] Only SDF 38% (77) [15]	Varnish 5%[h] + excavation – 1 application every 3 months (76) [14] Varnish 5%[h] – 1 application every 3 months (73) [12] Water – 1 application at baseline (73) [11]	30	dmf-t, number of active carious surfaces, number of inactive carious surfaces
Duangthip et al., 2016	Parallel design	4.2±4 3–4	Deciduous teeth with active caries	304	SDF 30%[b] – once a year (100) [11] SDF 30%[b] – once a year or 3 weekly applications at baseline (97) [8]	Fluoride varnish[i] – 3 weekly applications at baseline (107) [10]	18	dmf-t, number of arrested carious surfaces
Dos Santos et al., 2014	Parallel design	6.31±0.6 n.r.	Deciduous teeth (anterior and posterior) with dentin carious lesion (ICDAS 5)	60	Nanosilver fluoride – 1 application at baseline (2 drops kept in contact with the teeth for 2 min) (n.r) [n.r.]	Water – 1 application at baseline (n.r.) [n.r.]	12	dmf-t, number of active carious surfaces
Dos Santos et al., 2012	Parallel design	n.r. *5–7	Deciduous teeth (anterior and posterior) with dentin carious lesion (ICDAS 5)	91	SDF 30%[b] – 1 application at baseline (48) [n.r.]	ART restorations[j] – restoration made with partial caries removal and with dentin conditioner (43) [n.r.]	12	dmft-t, number of teeth with inactive carious lesions
Liu et al., 2012	Parallel design	9.1±n.r. n.r.	Permanent first molars with incipient fissure caries lesions (ICDAS 2)	501	SDF 38%[a] – 1 application every 12 months (125) [2]	Resin sealant[k] – sealants were applied after conditioning of the pits and fissures with 37% phosphoric acid and photopolymerized (124) [n.r.] NaF varnish[l] – 1 application every 6 months (124) [n.r.] Water – 1 application every 12 months (124) [n.r.]	24	Number of teeth with new carious lesions
Llodra et al., 2005	Parallel design	6.3±0.5 6–15	Deciduous canines and molars; permanent first molars	452	SDF 38%[c] – 1 application every 6 months (225) [45]	No treatment (227) [34]	36	dmft-t, number of active carious surfaces, number of new active carious lesions, number of inactive surfaces in permanent first molars
Monse et al., 2012	Parallel design	6.7±0.8 6–8	First permanent molars	1,016	SDF 38%[a] – 1 application with tannic acid to precipitate the silver (288) [58]	ART sealant[m] (301) [56] No treatment – fluoride toothpaste (427) [198]	18	Number of active carious surfaces
Seberol and Ökte, 2013	Parallel design	n.r. 2–6	Deciduous upper anterior teeth	114	*SDF 38%[d] – 1 application at baseline (60) [0]	Saline solution (*54) [5]	18	dmft-t, number of active carious surfaces
Vasconcelos, 2011	Parallel design	n.r. 6	Deciduous teeth	227	SDF 12%[e] – 1 application at baseline (*120) [17]	*5% sodium fluoride varnish[n] – 1 application at baseline (*107) [11]	12	dmf-t, number of active carious surfaces, number of inactive carious surfaces
Yee et al., 2009	Parallel design	5.2±1.2 3–9	Deciduous teeth with dentin caries	976	SDF 38%[f] – 1 application for 2 min at baseline (243) [86] SDF 38%[f] + reducing agent (tannic acid) – 1 application for 2 min plus reducing agent at baseline (249) [93] SDF 12%[g] – 1 application for 2 min at baseline (243) [87]	No treatment (241) [86]	24	dmft-t, number of active carious surfaces, number of inactive carious surface

Table 2 (continued)

Study ID	Study design	Subjects' mean age ± SD and range, years	Teeth	Total number of patients	Test group – material, protocol (number of patients) [dropouts]	Control groups – material, use protocol (number of patients) [dropouts]	Follow-up period, months	Outcomes
Zhi et al., 2012	Parallel design	3.8±0.6 3–4	Deciduous (active dentin caries lesions) All groups: removal of infected dentin before designed treatment	212	SDF 38%[a] – 1 application every 12 months (71) [11] SDF 38%[a] – 1 application every 6 months (69) [10]	ART[o] – every 12 months (71) [10]	24	Number of inactive caries lesions

ID, identification; SD, standard deviation; n.r., not reported. * This information was obtained by e-mail contact with the author. [a] SDF 38% (J. Morita; Toyo Seiyaku Kasei Ltd., Japan). [b] SDF 30% (Cariestop Biodynamic, Ibiporã, Paraná, Brazil). [c] SDF 38% (Fluoroplat, Laboratorios Naf, Buenos Aires, Argentina). [d] SDF 38% (FAgamin, Tedequim SRL, Cordoba, Argentina). [e] SDF 12% (Biodinâmica, Paraná, Brazil). [f] SDF 38% (Bee Brand, Osaka, Japan). [g] SDF 12% (Probem, São Paulo, Brazil). [h] 5% sodium fluoride varnish (Duraphat, Inpharma GmbH, Cologne, Germany). [i] Fluoride varnish (Duraphat, Colgate Palmolive, USA). [j] Fuji IX GP (GC America Inc.). [k] Resin sealant (Clinpro Sealant, 3M ESPE, St. Paul, MN, USA). [l] NaF varnish (Duraphat, Colgate-Palmolive Ltd., Waltrop, Germany). [m] Ketac Molar Easy Mix (3M ESPE, St. Paul, MN, USA). [n] 5% sodium fluoride varnish (Duraflor, Medicom, Quebec, Canada). [o] Fuji VII (GC America Inc.).

controlled-trials.com), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), the ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

The search strategy and the search date for all databases were included in Table 1. Full-text versions of the papers that appeared to meet the inclusion criteria were retrieved for further assessment and data extraction.

Eligibility Criteria

We included randomized clinical trials (RCTs) with parallel design in humans that compared the efficacy of SDF application with other active treatments or placebo in arresting carious lesions in primary teeth or first permanent molars of children. The primary outcome was the arrestment of the carious lesion in enamel or dentin.

RCT studies were excluded if: (1) the follow-up was shorter than 6 months; (2) SDF was not compared with a control group or a placebo; (3) the participants from the study did not present active caries during enrolment.

Study Selection and Data Collection Process

The articles were selected by title and abstracts according to the described eligibility criteria. Articles appearing in more than 1 database were considered once. Full-text articles were obtained when there was insufficient information in the title and abstract to make a clear decision.

Two reviewers (A.C.R.C. and L.M.W.) classified the full texts that met the inclusion criteria. Each included study received an ID, combining first author and year of publication. Relevant information about the study design, participants, interventions and outcomes were extracted using customized extraction forms by 3 authors (A.C.R.C., L.M.W., and A.R.; Table 2).

When there were multiple reports of the same study (i.e., reports with different follow-ups), data from all reports were extracted directly into a single data collection form to avoid overlapping data. The collection form was pilot tested using a sample of study reports to ensure that the collection form was consistent with the research question.

Risk of Bias in Individual Studies

Quality assessments of the included trials were evaluated by 2 independent reviewers (A.C.R.C. and L.M.W.), using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials [Higgins et al., 2011]. The assessment criteria contained 6 items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias.

For each aspect of the quality assessment, the risk of bias was scored following the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry consisted of recording "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (either lack of information or uncertainty over the potential for bias).

We considered 2 out of the 6 domains in the Cochrane risk of bias tool as key domains [Higgins et al., 2011]. At the study level, studies were judged to be at low risk of bias if they were judged as at low risk in the key domains sequence generation and allocation concealment. If at least 1 of these 2 domains were at high risk, the study was classified as at high risk of bias. When the study was judged as "unclear" in at least one key domain, the study was at unclear risk of bias, unless we could obtain information from authors to allow a definitive judgment of low or high risk of bias.

Summary Measures and Synthesis of the Results

Data from eligible studies were dichotomous. Only studies classified at "low" or "unclear" risk of bias in the key domains were meta-analyzed. The outcomes were summarized by calculating the risk ratio and the 95% confidence interval (CI). The random-effects models were employed. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. All analyses were conducted using RevMan (version 3, the Cochrane Collaboration, USA).

Assessment of the Quality of Evidence Using GRADE

We graded the quality of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allows one to de-

termine the overall strength of evidence for each meta-analysis [Guyatt et al., 2011]. The GRADE approach grades the evidence in 4 levels: very low, low, moderate, high. The "high quality" suggests that we are very confident that the true effect lies close to the estimate of the effect. On the other extreme "very low quality" suggests that we have very little confidence in the effect estimate and the estimate reported can be substantially different from what it was measured.

For randomized clinical trials, the GRADE approach addresses 5 reasons (risk of bias, imprecision, inconsistency, indirectness of evidence and publication bias) to possibly rate down the quality of the evidence in 1 or 2 levels [Guyatt et al., 2011]. Each domain was assessed as "no limitation" (0), "serious limitations" (1 level downgraded), and "very serious limitations" (2 levels downgraded). The GRADE pro Guideline Development Tool, available online (www.gradepro.org), was used to create a summary of findings table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* [Schünemann et al., 2011].

Results

Additional information about the studies was requested from 6 authors [Chu et al., 2002b; Yee et al., 2009a; Vasconcelos, 2011; dos Santos et al., 2012a; Liu et al., 2012; Seberol and Ökte, 2013]. This procedure was done whenever we could not retrieve them from the papers and was specially directed to details of the study design to allow judgment of the risk of bias of the included studies. After contacting the authors by e-mail or social networks, 4 of them answered our requests [Yee et al., 2009a; Vasconcelos, 2011; dos Santos et al., 2012a; Seberol and Ökte, 2013]. Among them, 2 sent their thesis for analysis [Vasconcelos, 2011; Seberol and Ökte, 2013]. Therefore, the results described in this systematic review are also based on complementary data supplied by the authors.

Study Selection

The initial screening in databases and other sources resulted in 8,047 records (Fig. 1). The removal of the duplicates resulted in 5,980 records. After title screening, the number of records was reduced to 49. Thirty papers were excluded after abstract reading, resulting in 19 full-text articles for the assessment of eligibility. Eight papers were excluded due to: (1) follow-up period equal to or lower than 6 months [Craig et al., 2013; Nishino et al., 1969], (2) absence of control group [Almeida et al., 1994], (3) being an early report of another study already included [Lo et al., 2001; Nassar et al., 2010], (4) inadequate test group [McDonald and Sheiham, 1994; Vachirarojpisan et al., 2009] and (5) the method of evaluation was based on qualitative scores [Braga et al., 2009] (Fig. 1).

Characteristics of Included Articles

The characteristics of the 11 selected studies are listed in Tables 2–4. All eligible papers were clinical trials with a parallel design [Chu et al., 2002a; Llodra et al., 2005; Yee et al., 2009b; Vasconcelos, 2011; dos Santos et al., 2012b; Liu et al., 2012; Monse et al., 2012; Zhi et al., 2012; Seberol and Ökte, 2013; dos Santos et al., 2014; Duangthip et al., 2016].

The mean age of the patients in the included studies was 8 ± 0.5 years. There were 8 studies with samples composed only by primary teeth [Chu et al., 2002a; Yee et al., 2009b; Vasconcelos, 2011; dos Santos et al., 2012a; Zhi et al., 2012; Seberol and Ökte, 2013; dos Santos et al., 2014; Duangthip et al., 2016]; 2 papers used only permanent teeth [Liu et al., 2012; Monse et al., 2012], and 1 study used both teeth [Llodra et al., 2005].

The number of patients included in the studies ranged from 60 to 1,016 children. SDF was used in different concentrations and application protocols. The most common concentration was 38% [Chu et al., 2002a; Llodra et al., 2005; Yee et al., 2009b; Liu et al., 2012; Monse et al., 2012; Zhi et al., 2012; Seberol and Ökte, 2013] but concentrations of 30% [dos Santos et al., 2012a; Duangthip et al., 2016] and 12% [Vasconcelos, 2011] were also used. There was 1 study that used a solution of nanosilver fluoride, with a concentration of 34% (33.98 μg/mL) [dos Santos et al., 2014].

The protocol of application of the majority of the studies was 1 application of SDF at baseline [Chu et al., 2002a; Yee et al., 2009b; Vasconcelos, 2011; dos Santos et al., 2012a; Liu et al., 2012; Monse et al., 2012; Zhi et al., 2012; Seberol and Ökte, 2013; dos Santos et al., 2014; Duangthip et al., 2016]. SDF application was repeated every 6 months in 2 studies [Llodra et al., 2005; Zhi et al., 2012]. Tannic acid was used to precipitate SDF in 2 studies [Yee et al., 2009b; Monse et al., 2012]. One study included a group that used SDF in a 3-week application at baseline [Duangthip et al., 2016].

The control groups were quite variable. The ART was used by 3 studies as ART restorations in primary teeth [dos Santos et al., 2012a; Zhi et al., 2012] and ART sealants in first permanent molars [Monse et al., 2012]. Two studies used fluoride varnish [Vasconcelos, 2011; Duangthip et al., 2016]. In 4 studies, the patients from the control group did not receive any active treatment, no treatment at all [Llodra et al., 2005; Yee et al., 2009b], or saline solution/water application [Seberol and Ökte, 2013; dos Santos et al., 2014]. More than 1 control group was used in 2 studies. In one of them, SDF was compared with fluoride, resin sealants and water [Liu et al., 2012]

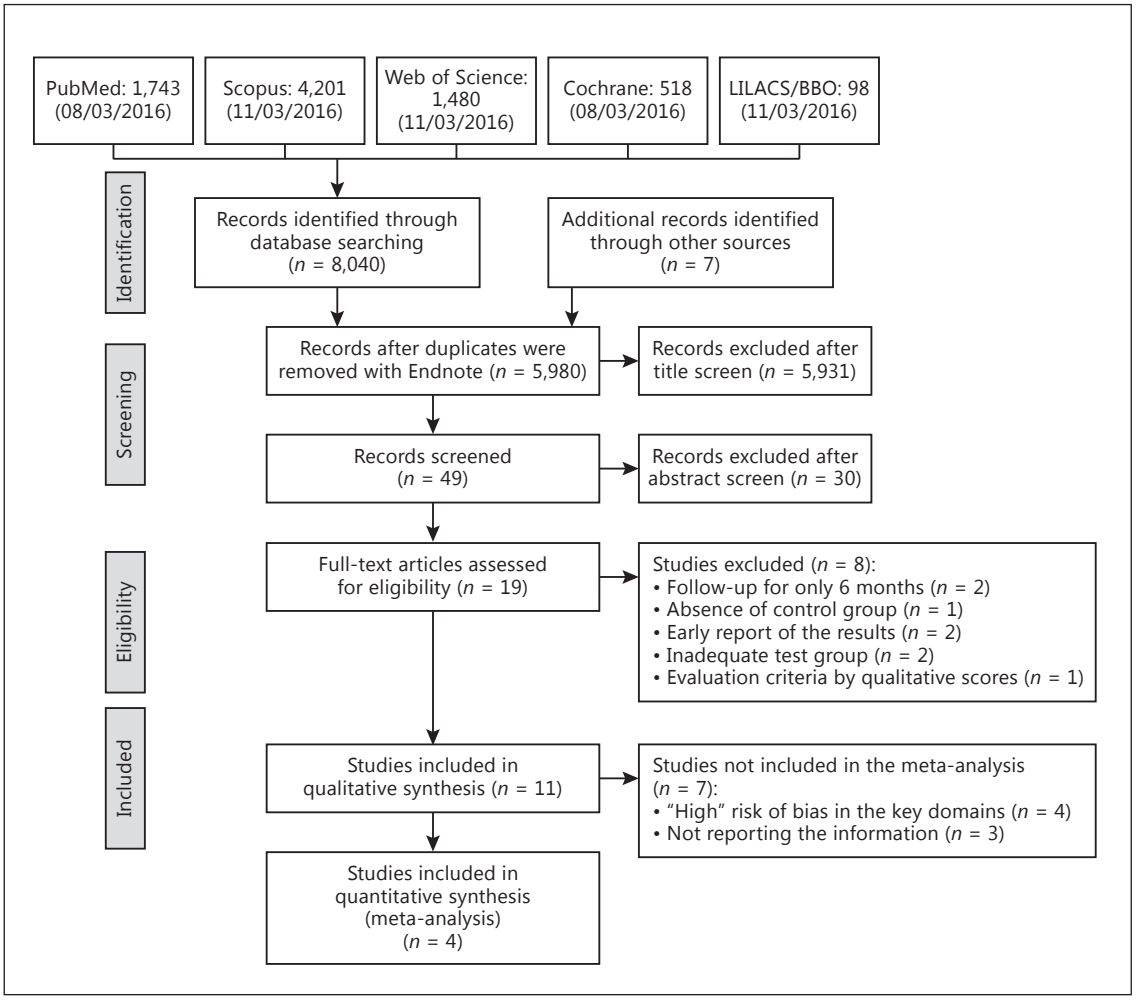

Fig. 1. Flow diagram of the study.

and in another with fluoride varnish and water [Chu et al., 2002a].

The follow-up periods ranged from 12 to 36 months: 12-month follow-up [Vasconcelos, 2011; dos Santos et al., 2012a; Zhi et al., 2012; dos Santos et al., 2014; Duangthip et al., 2016], 18-month follow-up [Monse et al., 2012; Seberol and Ökte, 2013; Duangthip et al., 2016], 24-month follow-up [Yee et al., 2009b; Liu et al., 2012; Zhi et al., 2012], 30-month follow-up [Chu et al., 2002a], 36-month follow-up [Llodra et al., 2005].

The most remarkable feature of the included papers is the great variation of the measured outcomes (Table 3). The outcomes were: (1) number of inactive carious surface [Chu et al., 2002a; Llodra et al., 2005; Yee et al., 2009b; Vasconcelos, 2011; Zhi et al., 2012; dos Santos et al., 2014; Duangthip et al., 2016]; (2) number of active carious surface [Llodra et al., 2005; Yee et al., 2009b; Vasconcelos, 2011; Liu et al., 2012; Monse et al., 2012; Seberol and Ökte, 2013; Chu et al., 2014; dos Santos et al., 2014]; (3) dmft index [Chu et al., 2002a; Llodra et al., 2005; Vasconcelos, 2011; dos Santos et al., 2012a; Seberol and Ökte, 2013]; (4) number of teeth with inactive carious lesions [dos Santos et al., 2012a]; (5) number of teeth with new carious lesions [Liu et al., 2012]; (6) number of inactive carious lesions in the first permanent molars [Llodra et al., 2005].

There was only 1 study that did not report the dmft index at baseline [Monse et al., 2012]. Two studies did not describe the number of active carious lesions at baseline or follow-up periods [dos Santos et al., 2012a; Zhi et al., 2012]. The number of inactive carious lesions was not reported in 3 studies [dos Santos et al., 2012a; Liu et al., 2012; Monse et al., 2012; Seberol and Ökte, 2013]. Two studies [Zhi et al., 2012; Duangthip et al., 2016] evaluated the number of arrested lesions at 12 months.

Table 3. Included studies in this systematic review: summary of the results reported

Study ID	Materials	dmf-t (baseline/ follow-up) [range]	Number of active carious surfaces (baseline/ follow-up) [range]	Number of inactive carious surfaces (baseline/follow-up) [range]	Number of teeth with inactive carious lesions (baseline/follow-up) [range]	Number of teeth with new carious lesions (baseline/ follow-up) [range]	Number of inactive surfaces in permanent first molars
Chu et al., 2002b (follow-up: 30 months)	SDF 38% + excavation	4.83±0.28 [4.61±0.29]	4.13±0.27 [3.82±0.27]	n.r. [2.49±0.27]	n.r.		
	SDF 38%	5.01±0.36 [5.35±0.42]	4.26±0.31 [4.32±0.34]	n.r. [2.82±0.3]	n.r.		
	Varnish + excavation	4.74±0.43 [4.77±0.42]	3.92±0.31 [3.82±0.34]	n.r. [1.45±0.19]	n.r.		
	Varnish	4.71±0.41 [4.33±0.43]	3.82±0.30 [3.54±0.30]	n.r. [1.54±0.27]	n.r.		
	Water	4.36±0.33 [4.24±0.36]	3.75±0.13 [3.76±0.34]	n.r. [1.27±0.19]	n.r.		
Duangthip et al., 2015 (follow-up: 12 months)	SDF 30% – 1 application/year	4.5±3.4 n.r.		91/463[a] n.r. 40% (181/458)			
	SDF 30% – 3 weekly applications at baseline	4.2.± 3.2 n.r.		118/429[a] n.r. 35% (149/426)			
	Fluoride varnish	4.6±3.7 n.r.		71/536[a] n.r. 27% (142/523)			
Dos Santos et al., 2014 (follow-up: 12 months)	NSF	4.76±2.65 n.r.	n.r./17	n.r. 34	n.r.		
	Water		n.r./32	n.r. 17	n.r.		
Dos Santos et al., 2012 (follow-up: 12 months*)	SDF 30%	4.71± 2.76 [5.92±2.83]	n.r.	n.r.	n.r./113		
	ART	*4.56±3.00 [5.58±3.22]	n.r.	n.r.	n.r./59		
Liu et al., 2012 (follow-up: 24 months)	SDF 38%	n.r./n.r.	280/n.r.			n.r./17	
	Sealant	n.r./n.r.	257/n.r.			n.r./11	
	Varnish	n.r./n.r.	267/n.r.			n.r./16	
	Water	n.r./n.r.	272/n.r.			n.r./28	
Llodra et al., 2005 (follow-up: 36 months)	SDF 38%	n.r. [3.6±0.2 [3.7±0.3]	n.r. 3.0±0.2 [3.3±0.3]	n.r. n.r. [2.8±0.3]	n.r.	n.r.	n.r. 0.3±0.0 [0.3±0.1]
	No treatment	n.r. 3.5±0.3 [3.4±0.3]	n.r. [2.9±0.3 [2.9±0.2]	n.r. n.r. [1.8±0.3]	n.r.	n.r.	n.r. 0.3±0.1 [0.1±0.0]
Monse et al., 2012 (follow-up: 18 months)	SDF 38%	n.r./ n.r.	96/78	n.r. n.r.[b]			
	ART sealant	n.r./n.r.	116/32	n.r.	n.r.	n.r.	n.r.
	No treatment	n.r./n.r.	139/101	n.r.	n.r.	n.r.	n.r.
Seberol and Ökte, 2013 (follow-up: 12 months)	SDF 38%	28.8±11.4* [39.2±10.2]	*60/23	n.r.	n.r.	n.r.	n.r.
	Saline solution	30.5±9.6* [35.8±10.1]	*53/43	n.r.	n.r.	n.r.	n.r.
Vasconcelos, 2011 (follow-up: 12 months)	SDF 12%	5.66±3.62 [5.05±3.12]	5.27±3.35 [2.51±2.24]	0 [1.62±1.48]			
	Varnish	5.42±3.45 [5.13±2.88]	5.10±3.25 [4.20±2.69]	0 [0]			
Yee et al., 2009 (follow-up: 24 months)	SDF 38%	4.5±3.1 n.r.	7.9 ±7.6 n.r.	6.6 ±6.4 [2.1±0.3]			
	SDF 38% + reducing agent	4.7±4.7 n.r.	8.3 ±8.5 n.r.	7.2 ±7.6 [2.2±0.3]			
	SDF 12%	5.3±1.2 n.r.	8.0 ±7.9 n.r.	6.8 ±7.0 [1.5±0.3]			
	No treatment	5.3±1.2 n.r.	8.0±8.5 n.r.	6.8±7.1 [1.0±0.2]			

Table 3 (continued)

Study ID	Materials	dmf-t (baseline/ follow-up) [range]	Number of active carious surfaces (baseline/ follow-up) [range]	Number of inactive carious surfaces (baseline/follow-up) [range]	Number of teeth with inactive carious lesions (baseline/follow-up) [range]	Number of teeth with new carious lesions (baseline/ follow-up) [range]	Number of inactive surfaces in permanent first molars
Zhi et al., 2012 (follow-up: 24 months)	SDF 38% annual application	4.8±4.0 n.r.		75/203[a] 0 [174]			
	SDF semiannual application	4.9±3.8 n.r.		109/206[a] 0 [205]			
	ART	5.5± 4.1		69/242[a] 0 [229]			

[a] Follow-up: 12 months; [b] Follow-up: 36 months.
ID, identification; SD, standard deviation; n.r., not reported. * This information was obtained by e-mail contact with the author.

Fig. 2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool.

Assessment of the Risk of Bias

The assessment of the risk of bias is presented in Figure 2. From the 11 eligible papers, 5 were at low risk of bias [Yee et al., 2009b; Liu et al., 2012; Zhi et al., 2012; dos Santos et al., 2014; Duangthip et al., 2016] since they fulfilled the required features for randomization and allocation. Four studies were at high risk of bias [Vasconcelos, 2011; dos Santos et al., 2012a; Monse et al., 2012; Chu et al., 2014], and 2 studies were at "unclear" risk of bias [Llodra et al., 2005; Seberol and Ökte, 2013].

Table 4. Summary of findings

SDF compared to other treatments for caries lesion arrestment	
Patient or population	Caries lesion arrestment
Intervention	SDF
Comparison	Other treatments
Outcomes	Caries arrestment follow-up: mean 12 months
Anticipated absolute effects*(95% CI)	
Risk with other treatments	186 per 1,000
Risk with SDF	351 per 1,000 (277–443)
Relative effect (95% CI)	RR 1.89 (1.49–2.38)
Number of participants (studies)	2,322 (4 RCTs)
Quality of the evidence (GRADE)	⊕⊕⊕⊕ High
Comments	Studies included in the meta-analysis were only conducted in deciduous teeth
GRADE Working Group grades of evidence	
High quality	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

CI, confidence interval; RR, risk ratio. * The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Meta-Analysis

Although there were 7 studies that could be included in the meta-analysis, only 4 were used in the meta-analysis as they reported similar outcomes. From these 4, 3 were at "low" risk of bias [Zhi et al., 2012; dos Santos et al., 2014; Duangthip et al., 2016] and 1 at "unclear" risk of bias [Seberol and Ökte, 2013]. Coincidently all these studies were conducted in primary teeth, and therefore we did not have data from permanent teeth.

Among the studies that were not included in the meta-analysis, one of them evaluated the number of teeth with new carious lesions over time [Liu et al., 2012]; the other 2 evaluated the number of teeth with inactive carious lesions but provided the results as continuous data reporting mean and standard deviation (which does not seem reasonable for such measurement) and we could not get the number of events versus total even after contacting the authors [Llodra et al., 2005; Yee et al., 2009b].

As the control groups used in these 4 studies were active treatments or placebos, we decided to run a meta-analysis with subgroup analysis so that the impact of the type of control group could be assessed.

Caries Arrestment – SDF versus Active Treatments

This analysis was based on 2 studies that compared SDF to fluoride varnish [Duangthip et al., 2016] or ART restorations [Zhi et al., 2012]. The risk ratio was 1.66, with a 95% confidence interval of 1.41 to 1.96 ($p < 0.00001$). This result showed that the use of SDF is 66% more effective in controlling/arresting dental caries than the active treatment tested (ART restorations and fluoride varnish). The data were not heterogeneous (χ^2 test; p = 0.45; $I^2 = 0\%$, Fig. 3).

Caries Arrestment – SDF versus Placebo

This analysis was based on 2 studies that compared SDF to saline solution [Seberol and Ökte, 2013] and no treatment [dos Santos et al., 2014]. The risk ratio was 2.54,

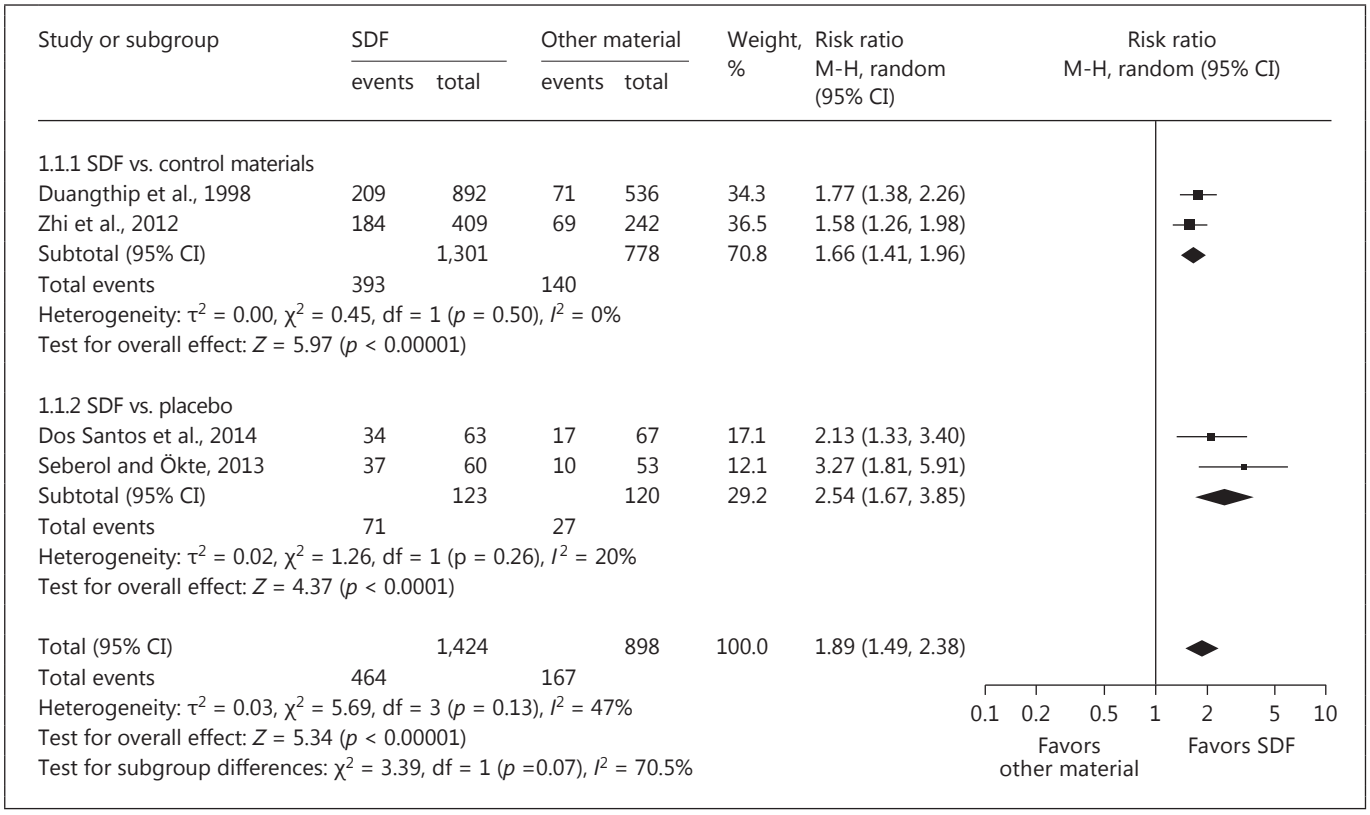

Fig. 3. Forest plot of caries arrestment at 12 months.

with a 95% CI of 1.67–3.85 ($p < 0.00001$). This result shows that the use of SDF is 154% more effective in controlling/arresting dental caries than the placebo treatment or no treatment. The data were not heterogeneous (χ^2 test; $p = 1.26$; $I^2 = 20\%$; Fig. 3).

Caries Arrestment – Overall Analysis

This analysis was based on the 4 studies that compared SDF to active treatments [Zhi et al., 2012; Duangthip et al., 2016] or placebos [Seberol and Ökte, 2013; dos Santos et al., 2014]. The risk ratio was 1.89, with a 95% CI of 1.49–2.38 ($p < 000001$). This result shows that the use of SDF is 89% (from 49 to 138%) more effective in controlling/arresting caries than the other treatments or no treatment. The data were not heterogeneous (χ^2 test; $p = 3.39$; $I^2 = 47\%$, Fig. 3).

Assessment of the Quality of Evidence Using GRADE

For the single outcome that could be analyzed in the present systematic review (caries arrestment at 12 months; Table 3), the GRADE quality of evidence was high as no "serious" limitations were found.

Discussion

This systematic review and meta-analysis showed that SDF was more effective than other active treatments or placebo for arresting caries in primary teeth after 12 months. The quality of the evidence produced in the present study was graded as high as most of the evidence came from RCTs with low risk of bias. Additionally, we did not observe data inconsistency in the results (heterogeneity), the risk ratio for the treatment effect was obtained from a high sample size with optimal information size, and all studies were conducted in similar populations. Based on that, one may be confident in the results herein presented.

The overall conclusion was the same presented individually by most of the primary studies included in this systematic review. The exceptions were related to first permanent molars, when SDF was considered to be as effective as ART sealants [Zhi et al., 2012] or fluoride varnish [Liu et al., 2012] and less effective than ART sealants [Monse et al., 2012] for caries arrestment.

A minimal follow-up period of 12 months was required for inclusion in the meta-analysis. There is data

showing that the caries arrestment effect of a single application of SDF is higher at the first 6 months being no different than controls after this period [Braga et al., 2009]. Therefore, since we proposed to compare SDF and other noninvasive methods for caries arrestment, it would not be reasonable to include short-term follow-ups. And if we had included them, they should be meta-analyzed in their respective follow-ups, contrary to what was done in other systematic reviews of the literature [Gao et al., 2016a, b].

Our search strategy included primary and permanent teeth. Three of the eligible studies employed SDF only in first permanent molars [Llodra et al., 2005; Liu et al., 2012; Monse et al., 2012]. Unfortunately, we could not run a meta-analysis with the data from permanent teeth. Although the studies exhibited the same design (parallel) and the same type of tooth (first permanent molars), they evaluated different outcomes (number of teeth with new carious lesions or with active carious lesions) and provided the data in different units of measurement (means and standard deviation and number of events). The contacts with the authors were not successful to overcome this problem. Therefore, the data about the effectiveness of SDF in permanent molars for caries control/arrestment could not be meta-analyzed.

SDF is not commonly used in permanent teeth, probably due to the staining potential of the substance. Even so, the ease of use and its low cost makes SDF an interesting alternative to arrest caries lesions in newly erupted first permanent molars [Braga et al., 2009; Liu et al., 2012]. Based on that, we strongly suggest the conduction of well-designed randomized controlled clinical trials to investigate the use of SDF in first permanent molars in eruption.

A larger number of papers was found using primary teeth, but the variability in the outcomes and in the way the results were described was quite high, which prevented us from including them in the meta-analysis. Only 4 studies, judged as low or unclear risk of bias, described similar outcomes for meta-analyses [Zhi et al., 2012; Seberol and Ökte, 2013; dos Santos et al., 2014; Duangthip et al., 2016].

We performed subgroup analysis to compare the caries arrestment effectiveness of SDF when compared to placebos or other active treatments. In both cases, SDF was more effective than their comparative groups. In the subgroup SDF versus other active treatments (fluoride varnish [Duangthip et al., 2016] and ART restorations with glass ionomer cement (GIC) [Zhi et al., 2012]), the meta-analysis showed that the application of SDF was 66% (95% CI 41–96%) more effective to arrest carious lesions (Fig. 3). Although SDF is not a sealing material, the product has several mechanisms of action that work synergistically and lead to caries arrestment. The silver component interacts with the sulfhydryl groups of proteins and DNA from the microorganisms, interfering in the bacterial metabolism. This results in bacterial killing and inhibition of biofilm formation [Rosenblatt et al., 2009]. Additionally, the silver salts formed on the dentin surface contribute to form a very resistant dentin outer layer [Fung et al., 2016], with silver phosphate blocking the dentin tubules [Knight et al., 2007]. Another advantage of the dentin tubule blockage is that it reduces tooth sensitivity during tooth brushing, which makes the brushing procedure less painful and increases adherence to this hygiene procedure [Willershausen et al., 2015].

The fluoride component of the SDF reacts with calcium phosphate and hydroxyapatite to form fluorapatite and calcium fluoride, which improves the acid resistance of the dental hard tissues. An increase in the mineral density and in the hardness of the carious dentin was observed in vitro [Mei et al., 2013], which is consistent with dentin remineralization [Mei et al., 2013]. SDF also inhibits the breakdown of the exposed collagen matrix, since it inhibits matrix metalloproteinases and cysteine cathepsins [Mei et al., 2013], probably due to the high concentration of silver [Thanatvarakorn et al., 2016]. This is very important, since the collagen network provides the scaffold for the new remineralization cores. This was observed in an ex vivo study, that showed a high content of calcium and phosphorus on collagen fibrils of the outermost layer of arrested carious dentin lesions in primary teeth [Mei et al., 2014]. The synergistic effect of fluoride and silver may be the main advantage of SDF in controlling dental caries when compared to the other active noninvasive methods such as fluoride varnish and ART restorations.

On the other hand, fluoride varnishes rely mainly on a single mechanism to control caries progression. It restores the mineral content that was lost during the active caries process through remineralization and makes the hard tissues more resistant to demineralization in future pH drops [Byeon et al., 2016; Naidu et al., 2016]. Similarly, partial caries removal followed by ART restorations with GIC controls caries progression by providing proper conditions for the reorganization of the carious dentin left at the cavity floor. Through cavity sealing, the biofilm removal becomes easier during tooth brushing [Hahnel et al., 2017]. Although GIC also releases fluoride, this release is very low when compared to SDF (38%, 44,800 parts per million, ppm, fluoride) and 5% fluoride varnish (22,600 ppm F). Therefore, ART restorations performed

with GIC probably control caries lesions by preventing biofilm retention and not by fluoride release.

It is worth mentioning that high viscosity GIC is recommended for ART restorations due to its better mechanical and physical properties that contribute to the restoration survival, maintaining a suitable cavity sealing [Kuhn et al., 2016]. However, the gold standard high viscosity glass ionomer FUJI IX (GC America Inc.), recommended by the WHO for ART restorations, costs almost 20 times more than SDF, and it is the major limitation for its use in underprivileged communities [dos Santos et al., 2012a].

Regarding the effectiveness of SDF, factors like the concentration of the fluorine and silver ions is very important for caries arrestment. The studies meta-analyzed in this paper employed high SDF concentrations of 38% (44,800 ppm F; 253,870 ppm Ag) [Zhi et al., 2012; Seberol and Ökte, 2013; Cheng, 2017] and 30% (35,400 ppm F; 200,400 ppm Ag) [Duangthip et al., 2016]. Higher concentrations of SDF provided better effectiveness in arresting dentin caries in primary teeth [Cheng, 2017] when compared to low SDF concentrations (12% – 14,150 ppm F; 80,170 ppm Ag) [Yee et al., 2009b; Fung et al., 2016; Horst et al., 2016].

Some countries like Argentina, Australia, Brazil, China, and Japan employ SDF at 38% [Cheng, 2017]. In Brazil, since the 1980s, SDF has been used for the treatment of early childhood caries in different concentrations (10, 12, 30, and 38%). Only recently (August 2014) was SDF treatment authorized by the Food and Drug Administration (FDA) for dental use in the USA. Nowadays, the FDA has cleared SDF as a treatment for tooth sensitivity and for off-label use to arrest and prevent dental caries [Horst et al., 2016].

The main disadvantage in using SDF is that the carious lesions will be stained black. The lack of esthetics may prevent the dentists to choose this treatment and the patients/parents to accept the procedure [Chu and Lo, 2008], regardless of its proven effectiveness in arresting dental caries. A recent research about the use of SDF in pediatric dentistry training programs showed that the most cited barrier by the directors of the programs was "the poor acceptance of esthetics following treatment" [Nelson et al., 2016]. Notwithstanding, this conclusion was based on the opinion of the professionals, and future RCTs should be designed focusing on the patient/parents reported outcome in order to clarify this aspect.

Recently, 2 systematic reviews have been published about professionally applied fluoride treatment [Gao et al., 2016b] and SDF [Gao et al., 2016a]. They both affirmed that SDF is effective in controlling caries progression. Despite the use of the same research question, the reviews included different sets of papers, due to distinct search strategies and eligibility criteria. We only included RCTs with at least a 12-month follow-up period, which resulted in 11 papers. The recently published review on SDF [Gao et al., 2016a] included 19 papers, but the authors did not set a minimum follow-up period, included the same study (with different follow-ups) in the same meta-analysis, and allowed studies without control groups to be included. Additionally, they included in their search data from the China National Knowledge Infrastructure and Ichusi-web databases resulting in the inclusion of papers written in Chinese and Japanese. These papers were not detected by our search strategy, since they were not indexed in PubMed, Scopus, or any other database used in our research strategy.

This explains the high number of included studies in the earlier systematic reviews [Gao et al., 2016a, b]. Equivocally, the authors [Gao et al., 2016a, b] included different follow-ups of the same study as new study entries, leading to an overestimation of the treatment effect. They also included in the same meta-analysis studies measuring different outcomes, which is not reasonable.

Another important difference is the subgroup analysis. Our option was to meta-analyze the SDF compared to active treatments or to placebo, including only papers judged as being at "low" or "unclear" risk of bias, unlike the former meta-analysis [Gao et al., 2016a] that centered the comparison on the follow-up periods and also used papers classified as being at "high" risk, leading to a high level of heterogeneity and reducing the confidence in the summary estimates. By including in the present study articles with low/unclear risk of bias and reporting the same outcome, we have not observed heterogeneity neither in the subgroup analysis nor in overall analysis. This is important because the results of a meta-analysis can only be generalized if they come from a consistent group of studies in terms of participants, interventions and outcomes [Higgins et al., 2003].

Finally, we must address that the greater variability in the outcomes and in the description of the obtained results prevented us from using data from other eligible studies at "low" risk of bias [Liu et al., 2012; Yee et al., 2009b]. This fact shows that there is an urgent need for standardization in the presentation of data between studies that focus on caries arrestment. Consequently, we encourage the development of new well-designed randomized clinical trials on SDF to produce studies with low risk of bias during planning, execution, and reporting of the research results.

Conclusion

SDF is more effective than other active treatments or placebo for caries arrestment in primary teeth. The body of evidence was of high quality for primary teeth. There is not enough evidence to draw a conclusion about caries arrestment in first permanent molars.

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Disclosure Statement

The authors declare no conflict of interest of any kind related to this study.

Author Contributions

Ana Cláudia Rodrigues Chibinski, Letícia Maíra Wambier, and Alessandra Reis: conception or design of the work; or acquisition, analysis, or interpretation of data for the work.

Juliana Feltrin and Denise Stadler Wambier: drafting the work and revising it critically for important intellectual content.

Alessandra Reis and Alessandro Dourado Loguercio: statistical analysis.

Ana Cláudia Rodrigues Chibinski, Letícia Maíra Wambier, Juliana Feltrin, Alessandro Dourado Loguercio, and Alessandra Reis: final approval of the manuscript.

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