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Effects of Low and Standard Fluoride Toothpastes on Caries and Fluorosis: Systematic Review and Meta-Analysis

A.P.P. Santos[a, b] B.H. Oliveira[a] P. Nadanovsky[b]

[a]Department of Community and Preventive Dentistry, School of Dentistry and [b]Department of Epidemiology, Institute of Social Medicine, Rio de Janeiro State University, Rio de Janeiro, Brazil

Key Words
Dental caries · Fluorosis · Meta-analysis · Preschool children · Toothpastes

Abstract
Although the anti-caries effects of standard fluoride (F) toothpastes are well established, their use by preschoolers (2- to 5-year-olds) has given rise to concerns regarding the development of dental fluorosis. Thus, a widespread support of low F toothpastes has been observed. The aim of this study was to assess the effects of low (<600 ppm) and standard (1,000–1,500 ppm) F toothpastes on the prevention of caries in the primary dentition and aesthetically objectionable (moderate to severe) fluorosis in the permanent dentition. A systematic review of clinical trials and meta-analyses were carried out. Two examiners independently screened 1,932 records and read 159 potentially eligible full-text articles. Data regarding characteristics of participants, interventions, outcomes, length of follow-up and potential of bias were independently extracted by two examiners and disagreements were solved by consensus after consulting a third examiner. In order to assess the effects of low and standard F toothpastes on the proportion of children developing caries and fluorosis, pooled relative risks (RR) and associated 95% confidence intervals were estimated using a fixed and a random-effects model, respectively. Five clinical trials fulfilled the inclusion criteria. Low F toothpastes significantly increased the risk of caries in primary teeth [RR = 1.13 (1.07–1.20); 4,634 participants in three studies] and did not significantly decrease the risk of aesthetically objectionable fluorosis in the upper anterior permanent teeth [RR = 0.32 (0.03–2.97); 1,968 participants in two studies]. There is no evidence to support the use of low F toothpastes by preschoolers regarding caries and fluorosis prevention.

The role of topical fluorides (F) in reducing dental caries in children and adolescents has been extensively studied [Ijaz et al., 2010] and, among these, F toothpastes are more likely to be used as toothbrushing is culturally approved and widespread [Burt, 1998; Marinho et al., 2004; Marinho, 2008]. Three systematic reviews have shown that standard F toothpastes, which contain from 1,000 to 1,500 ppm of F, reduce 24–29% of caries in permanent teeth when compared to a placebo and that larger reductions were associated with an increase in F concentration

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E-Mail karger@karger.com
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Ana Paula Pires dos Santos
Rio de Janeiro State University, School of Dentistry, Department of Community and Preventive Dentistry, Boulevard 28 de Setembro, 157, 2° andar, Vila Isabel
Rio de Janeiro, RJ 20551-030 (Brazil)
E-Mail ana.paulapires@uol.com.br

[Chaves and Vieira-da-Silva, 2002; Marinho et al., 2003; Twetman et al., 2003]. On the other hand, the use of standard F toothpastes by young children was significantly associated with an increase in fluorosis in the permanent anterior teeth [Wong et al., 2010].

Once there is F intake from any source during tooth development, a certain level of fluorosis will always exist [Aoba and Fejerskov, 2002]. Recently, both an increase and a decrease in the prevalence of fluorosis have been reported [Riordan, 2002; Whelton et al., 2006; Do and Spencer, 2007c; Beltran-Aguilar et al., 2010]; however, there is general agreement that moderate to severe forms of fluorosis in areas with non-fluoridated or optimally fluoridated drinking water are uncommon [Stephen et al., 2002; Bottenberg et al., 2004; Cochran et al., 2004a; Conway et al., 2005; Vallejos-Sanchez et al., 2006; Do and Spencer, 2007c; Beltran-Aguilar et al., 2010]. Also, mild fluorosis is of little concern for parents and has little or no effect on children's oral health-related quality of life [Sigurjons et al., 2004; Do and Spencer, 2007a; Chankanka et al., 2010; Browne et al., 2011].

Much concern has been raised regarding the use of F toothpastes by young children as they may swallow from 60 to 72% of the toothpaste applied to the toothbrush [Bentley et al., 1999; Cochran et al., 2004b; Franco et al., 2005; Moraes et al., 2007]. Dental and medical associations recommend different strategies to address this issue [Santos et al., 2010, 2011], among which is the reduction in the F concentration of the toothpaste. However, the anti-caries potential of low F toothpastes (<600 ppm) remains inconclusive [Ammari et al., 2003; Steiner et al., 2004; Walsh et al., 2010].

As low F toothpastes are targeted at young children in order to reduce the occurrence of fluorosis, it is more important to assess their effectiveness specifically in these younger children, who are at risk of developing it, than to assess their effectiveness in children in general, as has been the case in previous reviews [Ammari et al., 2003; Steiner et al., 2004; Walsh et al., 2010]. Moreover, as mild forms of fluorosis are not considered aesthetically objectionable, the question that has yet to be answered is the extent to which the anti-caries benefits of low F toothpastes in young children outweigh the theoretically smaller risks of developing moderate to severe forms of fluorosis.

The aim of this study was to evaluate the effects of low and standard F toothpastes on the prevention of caries in the primary dentition of preschoolers and moderate to severe forms of fluorosis in the permanent dentition.

Materials and Methods

Study Design

Systematic review of individual or cluster randomized/quasi-randomized clinical trials with a follow-up period of at least 1 year.

Participants

Children not older than 7 years when the outcome caries was assessed. There was no age limit for the assessment of fluorosis. Studies whose participants had special general or oral health conditions were excluded.

Interventions

Low (<600 ppm) and standard (1,000–1,500 ppm) F toothpastes, irrespective of formulation. Studies whose interventions included F gel, F varnish, F mouth rinse, chlorhexidine, xylitol or dental sealants were excluded.

Outcomes

Enamel and dentine caries in the primary dentition and moderate to severe fluorosis in the permanent dentition.

Search Strategy

The databases consulted from date of online availability to January 2010 were the following: The Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), MEDLINE via PubMed, EMBASE, Web of Science, LILACS and BBO (Brazilian Library of Dentistry). The electronic search was updated by one of the authors (A.P.P. Santos) in March 2012 and no additional studies were found. Additional sources included a Brazilian database of thesis and dissertations (Banco de Teses CAPES), a Brazilian register of ethically approved projects involving human beings (SISNEP) and two international registers of ongoing trials (Current Controlled Trials and ClinicalTrials.gov). The search strategy included controlled vocabulary and free terms. It was developed for MEDLINE (online suppl. appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159.000348492), without idiom restraints, and adapted for the other databases. Meeting abstracts of the International Association for Dental Research (2001–2012) and the European Organisation for Caries Research (1998–2012) were also searched. Sixteen dental journals that are also in the Cochrane Master List of Journals Being Searched [Bickley and Glenny, 2003] were handsearched. Two independent examiners handsearched these sixteen dental journals from the last date of the Cochrane Collaboration's handsearch until June 2010. References of eligible trials and systematic and narrative reviews on F were checked in order to detect potential studies. Finally, specialists in the field were contacted by e-mail.

Data Collection and Analysis

Two reviewers read the titles and abstracts (when available) of all studies identified. Whenever there was not enough information available, the full-text article was obtained. Two reviewers independently extracted the data using a data extraction form. Attempts were made to contact the authors to check for incomplete data. Missing standard deviations (SD) were calculated according to Higgins and Deeks [2008]. Any disagreement during study selection and data extraction was solved by consensus after consulting a third reviewer.

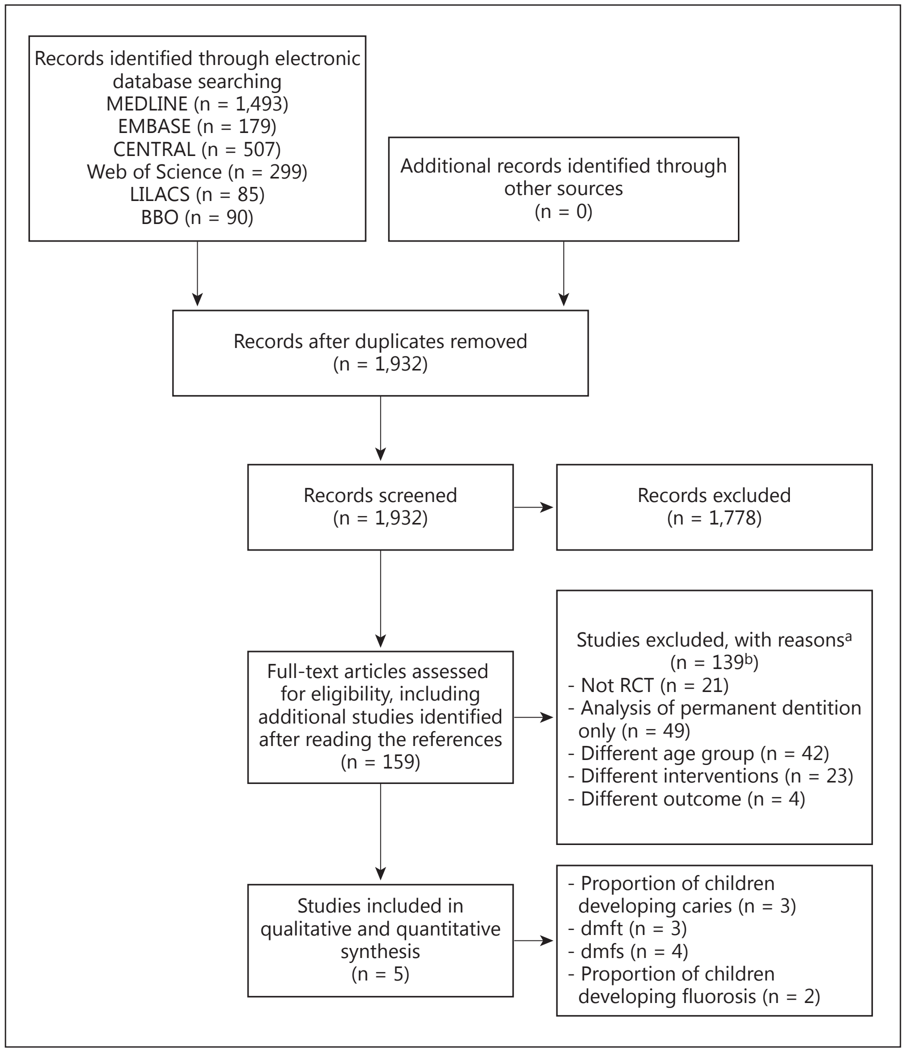

Fig. 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding and including the studies retrieved from the electronic search. RCT = Randomized controlled trials. [a] The reasons for exclusion were those firstly or most easily obtained. For instance, a study that was excluded because of a different age group (the first or easiest clue) could also have been excluded because of a different intervention. [b] The number of excluded studies does not add up to 154 (159 full-text articles assessed for eligibility minus the 5 included studies) because the results of some studies were published in several articles.

We used the Cochrane Collaboration's tool for assessing the risk of bias in included studies [Higgins and Altman, 2008]. The domains evaluated were sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain was classified as having low, high or uncertain risk of bias. For this review, non-blinding of participants was unlikely to introduce bias; therefore, when only the outcome assessors were blinded, studies were considered as having low risk of bias. Also, studies were considered to be free of selective outcome reporting when caries incidence was assessed at surface, tooth and individual level. Other possible sources of bias were: losses to follow-up (low risk of bias when less than 20%), diagnosis reliability (low risk of bias when good [Altman, 1991]), baseline balance (low risk of bias when data showed balance regarding age, gender, socioeconomic status and caries levels) and contamination (low risk of bias when strategies to avoid contamination between groups were reported).

Pooled relative risks (RR) and 95% confidence intervals (CIs) were estimated to assess the proportion of children who developed caries in primary teeth and aesthetically objectionable fluorosis in permanent teeth. Numbers needed to treat for an additional harmful outcome (NNTH), which corresponds to the number of children that needed to use low F toothpaste as opposed to standard F toothpaste in order for 1 child to be harmed, i.e. to develop at least 1 dentine caries lesion, were derived by applying the pooled RR of caries to three different scenarios [Ebrahim, 2001]: high (70%), medium (50%) and low (20%) 5-year caries incidence; 95% CIs were derived by applying the 95% CIs of the pooled RR [Altman, 1998]. No meta-analyses of the difference in means were performed as data regarding caries incidence at surface and tooth level were highly skewed [Altman and Bland, 1996].

Heterogeneity of studies was assessed by visual inspection of forest plots, χ^2 test for heterogeneity and Higgins index (I^2). A random effects model was used in the presence of heterogeneity (χ^2 with significance level <0.10 and I^2 >50%).

All analyses were carried out in Stata® 11.1 (StataCorp LP, College Station, Tex., USA). The paucity of studies prevented the use of meta-regression to assess the influence of study characteristics on the treatment effect, as well as the assessment of publication bias.

Table 1. Characteristics of the toothpastes tested in the included studies

Study	Low F toothpaste			Standard F toothpaste		
	ppm	pH	F agent and abrasive	ppm	pH	F agent and abrasive
Davies et al.[a] [2002]	440	neutral	NaF; silica	1,450	neutral	1,000 ppm SMFP + 450 ppm NaF; dicalcium phosphate dihydrate
Gerdin [1974]	250	5.5	KF; no abrasive	1,000	6.5	NaF; no abrasive
Sonju-Clasen et al. [1995]	250	6.5	NaF; silica	1,450	6.8	NaF; silica
Vilhena et al.[a] [2010]	550	4.5	NaF; silica	1,100	7.0	NaF; silica
Winter et al. [1989]	550	not reported	SMFP + NaF; calcium glycerophosphate	1,055	not reported	SMFP; calcium glycerophosphate

KF = Potassium fluoride; NaF = sodium fluoride; SMFP = sodium monofluorophosphate.
[a] Complete information was obtained after consulting the authors.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective outcome reporting?	Losses to follow-up <20%?	Adequate reliability?	Baseline balance?	Free of contamination?
Davies et al. [2002]	+	+	+	+	–	–	?	?	?
Gerdin [1974]	–	–	+	–	–	+	?	?	?
Sonju-Clasen et al. [1995]	?	?	+	–	+	–	+	?	+
Vilhena et al. [2010]	+	–	+	+	–	–	+	?	+
Winter et al. [1989]	?	?	+	–	+	–	–	?	+

Fig. 2. Ascertainment of the risk of bias in the included studies. + = Yes; – = no; ? = uncertain (the darker the shade of grey the higher the risk of bias).

Results

After excluding duplicates, 1,932 records were retrieved from the electronic search. No additional records were obtained after hand searching and searching for ongoing trials. Figure 1 shows a flow diagram of the reports that were identified, screened, assessed for eligibility, excluded and included in the review. The characteristics of included studies are described in online supplementary appendix 2.

Figure 2 shows the risk of bias in the included studies. The domain judged as having the lowest risk of bias was blinding, whereas high rates of losses to follow-up posed a threat to the validity for most studies. Ascertainment of baseline characteristics balance was uncertain in all studies.

Although all the interventions consisted of comparisons between low and standard F toothpastes, several differences were observed concerning their formulations (table 1). Tables 2 and 3 show the studies that reported caries incidence at surface level [Gerdin, 1974; Winter et al., 1989; Sonju-Clasen et al., 1995; Vilhena et al., 2010] and tooth level [Gerdin, 1974; Winter et al., 1989; Sonju-Clasen et al., 1995; Davies et al., 2002], respectively. All the means were smaller than twice the SD, suggesting that data were highly skewed, which prevented the calculation of a pooled weighted mean difference [Altman and Bland, 1996]. Only one study showed that children using low F toothpaste had a significant increase in the mean incidence of caries at tooth level compared to those using standard F toothpastes [Davies et al., 2002].

Three studies had data on the proportion of children developing caries [Winter et al., 1989; Sonju-Clasen et al., 1995; Davies et al., 2002]. One of them was a cluster randomized trial [Sonju-Clasen et al., 1995], so we used an extern estimate of an intraclass correlation coefficient to obtain the design effect [Campbell et al., 2000] and then the effective sample size [Higgins et al., 2008]. Figure 3 shows the pooled RR of 1.13 (1.07–1.20). NNTHs were 11 (7–20), 15 (10–28) and 38 (25–71) for scenarios of high, medium and low incidence of caries, respectively.

Two clinical trials [Winter et al., 1989; Davies et al., 2002] that assessed the incidence of caries in the primary

Table 2. Mean and SD of baseline and final dmfs and caries increment, and p values for the difference in caries increment between low and standard F groups

Study	Low F toothpaste				Standard F toothpaste				p value
	n	dmfs baseline	dmfs final	mean increment	n	dmfs baseline	dmfs final	mean increment	
Gerdin [1974]	108	2.87 (2.41)	–	3.83 (3.21)	105	2.95 (2.32)	–	4.23 (3.53)	0.39[c]
Sonju-Clasen et al. [1995]	46[a]	2.0 (5.5)	–	2.9 (5.1)	49[a]	2.4 (6.6)	–	1.7 (3.2)	0.18[c]
Vilhena et al. [2010]	259	5.24 (5.37)	7.29 (7.27)	2.05 (2.79)	270	5.05 (4.89)	7.13 (6.35)	2.08 (2.34)	0.89[c]
Winter et al. [1989]	1,104	0	2.45 (5.36)[b]	–	1,073	0	2.21 (5.36)[b]	–	0.296[c]

[a] This is the effective sample size. Original sample size is 83 (low F toothpaste) and 89 (standard F toothpaste).
[b] Other measure of dispersion reported; SD calculated by the authors of this review according to Higgins and Deeks [2008].
[c] Calculated by the authors of this review using t test with unequal variances.

Table 3. Mean and SD of baseline and final dmft and caries increment, and p values for the difference in caries increment between low and standard F groups

Study	Low F toothpaste				Standard F toothpaste				p value
	n	dmft baseline	dmft final	mean increment	n	dmft baseline	dmft final	mean increment	
Davies et al. [2002]	1,176	0	2.49 (3.16)	–	1,186	0	2.15 (2.96)	–	0.02
Gerdin [1974]	108	2.31 (1.78)	–	3.22 (2.81)	105	2.28 (1.82)	–	3.49 (3.16)	0.51[c]
Sonju-Clasen et al. [1995]	46[a]	1.0 (2.2)	–	1.2 (2.2)	49[a]	1.2 (2.8)	–	0.8 (1.4)	0.30[c]
Winter et al. [1989]	1,104	0	1.48 (2.62)[b]	–	1,073	0	1.29 (2.62)[b]	–	0.09[c]

[a] This is the effective sample size. Original sample size was 83 (low F toothpaste) and 89 (standard F toothpaste).
[b] Other measure of dispersion reported; SD calculated by the authors of this review according to Higgins and Deeks [2008].
[c] Calculated by the authors of this review using t test with unequal variances.

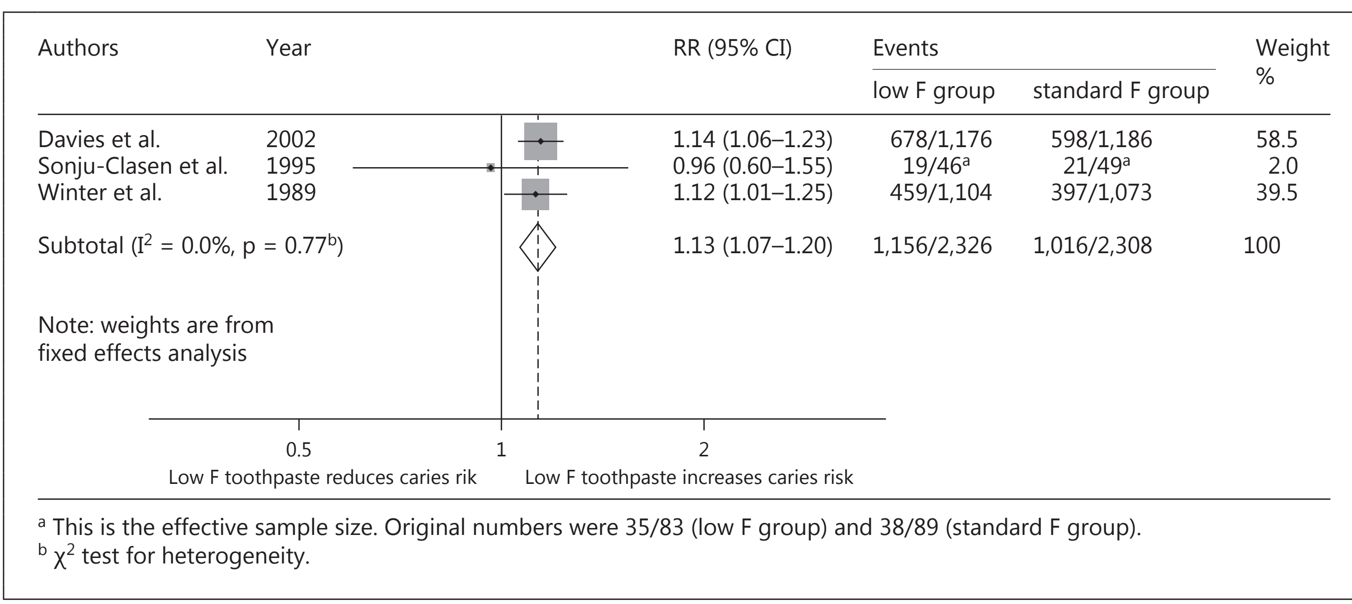

Fig. 3. Comparison between low and standard F toothpaste regarding the proportion of children developing caries in the primary dentition.

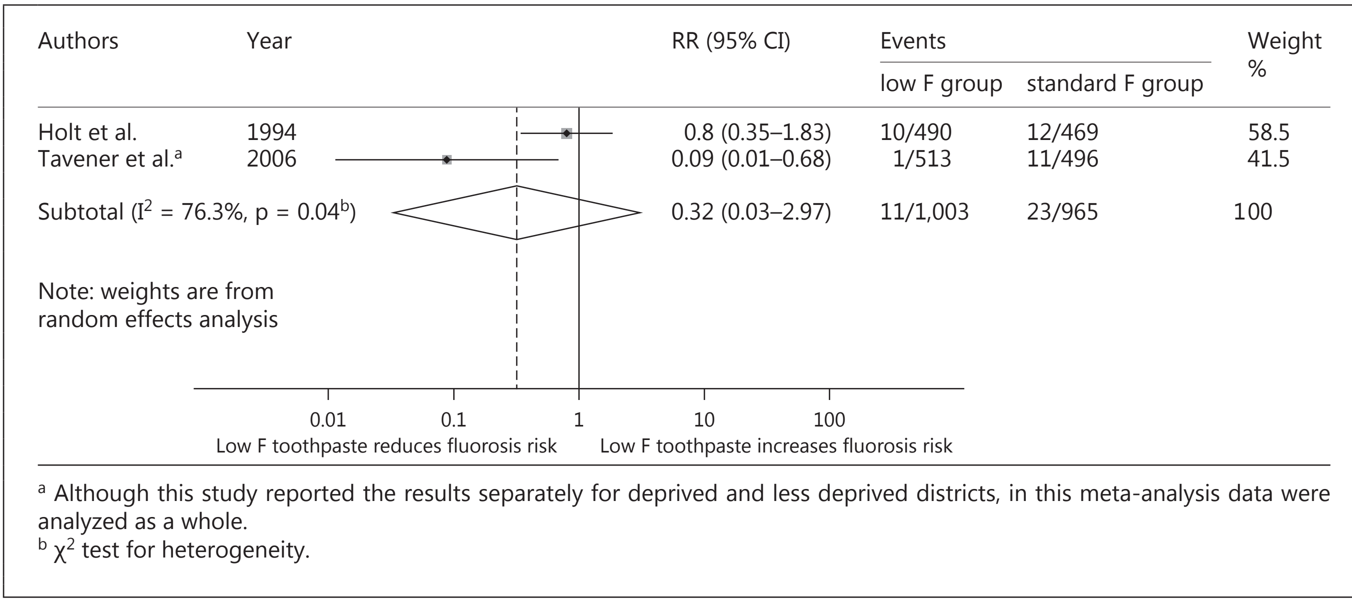

Fig. 4. Comparison between low and standard F toothpaste regarding the proportion of children developing moderate to severe fluorosis in upper permanent anterior teeth.

dentition also provided data on fluorosis in the upper permanent anterior teeth [Holt et al., 1994; Tavener et al., 2006]. Both studies were carried out in non-fluoridated or non-optimally fluoridated areas of England. Dental fluorosis was assessed by the Thylstrup-Fejerskov fluorosis index (TF) and the comparison consisted of children who developed no fluorosis or mild fluorosis (TF = 0, 1 or 2) and children who developed aesthetically objectionable fluorosis (TF ≥3). Figure 4 shows the pooled RR of 0.32 (0.03–2.97).

Discussion

Low F toothpastes have been marketed to young children in many countries such as Australia, Brazil, Switzerland and the UK, among others, and there is considerable support to the use of this type of toothpaste [Steiner et al., 2004; Do and Spencer, 2007b] even in countries where they are not easily purchased, such as the USA [Horowitz, 2000].

Two Cochrane systematic reviews have contributed information regarding the benefits and risks of F toothpastes for children of all ages, including specific information for primary teeth [Walsh et al., 2010; Wong et al., 2010]. However, to the best of our knowledge, ours is the first systematic review that focuses on the effects of F toothpastes on the prevention of caries in primary teeth of children at risk of developing aesthetically objectionable fluorosis, i.e. not older than 7 years of age. Therefore, it provides the information needed as to the type of toothpaste that should be recommended to children belonging to this age group. The rationale behind the advocacy of low F toothpastes to young children is to reduce the risk of fluorosis. Thus, evidence accrued from trials that assessed the effectiveness of low F toothpastes in primary or permanent teeth of schoolchildren does not help decision making as these children are no longer at risk of developing aesthetically objectionable fluorosis and can benefit from the well-established anti-caries effects of standard F toothpastes. Furthermore, although it has been reported that standard F toothpastes are associated with an increased risk of developing fluorosis [Wong et al., 2010], our review has specifically addressed the effects of F toothpastes on the occurrence of aesthetically objectionable fluorosis.

Our results showed that children who brushed their teeth with low F toothpastes had an increased risk of developing caries at dentine level in the primary teeth. In populations with high 5-year caries incidence (e.g. 70%), 11 preschool children need to use low F toothpaste (as opposed to standard F toothpaste) in order to harm 1 preschooler (i.e. for 1 preschooler to develop at least 1 dentine caries lesion). In populations with medium (e.g. 50%) and low (e.g. 20%) 5-year caries incidence, NNTHs would be 15 and 38, respectively.

Among the trials that assessed caries incidence at surface and tooth level, two tested low F toothpastes with acidic pH. At surface level, no significant differences were observed when trials compared low and standard F toothpastes with neutral pH or low F toothpastes with acidic pH and standard F toothpastes with neutral pH. Reducing the pH of a topical F agent increases the formation of calcium F-like material (CaF_2), which acts like an F reservoir to be released during cariogenic challenges [Ogaard, 2001]. On the other hand, a dose-response effect between the CaF_2 concentration on enamel and reduction of demineralization has only been shown for acidic high F concentration treatments, such as an acidulated sodium F solution (pH 3.5 and 9,500 ppm F) [Tenuta et al., 2008]. The extent to which this dose-response effect can be extrapolated to acidic toothpastes is unknown. Also, the lack of a statistical difference when low F toothpastes with acidic pH were compared with standard F toothpastes with neutral pH does not imply an equivalence of effects; this should be properly tested in an equivalence clinical trial [Jones et al., 1996].

Some aspects related to potential of bias in the included studies that might have influenced their results should be noted. Firstly, most studies had more than 20% losses to follow-up. Secondly, it was not possible to evaluate the baseline balance regarding caries levels, age, gender and socioeconomic status. Thirdly, two studies lasted less than 2 years [Sonju-Clasen et al., 1995; Vilhena et al., 2010], despite the recommendation that trials should last at least 2 years in order to allow a significant number of lesions to develop at the cavitation level [Chesters et al., 2004]. Finally, one trial was quasi-randomized as the interventions were allocated according to the children's month of birth [Gerdin, 1974]. Non-random methods of allocation presumably yield biased results due to the inability to conceal the allocation scheme adequately [Moher et al., 2010].

Although we sought information on the increment of caries at enamel and dentine levels, all the included studies assessed caries at the dentine level. We identified one trial evaluating both active and inactive enamel and dentine lesions, which showed that, in children with active caries, low F toothpaste was less effective than standard F toothpaste [Lima et al., 2008]. However, this study could not be included in our review as the increment of enamel and dentine lesions were not recorded separately. Enamel or initial lesions, also called white spot lesions, are the first clinical manifestation of caries and many spontaneously arrest or reverse. However, once caries develops into the dentine, restoration is necessary [Pitts, 2004; Gordan et al., 2010]. Besides, only after reaching the dentine can caries affect patients' daily lives. Therefore, dentine caries, but not enamel caries, can be regarded as a true endpoint. Another reason for the importance of recording enamel and dentine lesions separately is the role of F in controlling the rate of caries progression; F does not prevent caries initiation, rather it delays or avoids the progression of caries from enamel through the dentine. Therefore, when both enamel and dentine lesions are considered together, there may be virtually no difference in caries incidence between groups exposed and unexposed to F, whereas when only dentine lesions are considered there is a marked reduction in caries incidence [Groeneveld et al., 1990; Ellwood et al., 2008].

Very few cases of aesthetically objectionable fluorosis were reported in the two trials included and therefore the pooled RR was very imprecise. One trial recruited 2-year-old children, lasted 3 years and compared 500 and 1,000 ppm F toothpastes [Holt et al., 1994], whereas the other recruited 12-month-old children, lasted 5 years and compared 440 and 1,450 ppm F toothpastes [Tavener et al., 2006]. It should be noted that the F agent of the 1,450-ppm toothpaste is a combination of sodium monofluorophosphate (Na_2FPO_3) and sodium F in a calcium-based abrasive system. It has already been shown that Na_2FPO_3/$CaCO_3$ formulations containing 1,400–1,500 ppm F of total F present approximately 1,000 ppm F in a soluble form [Falcão et al., 2013]. Therefore, it is possible that part of the toothpaste used in the study by Tavener et al. [2006] was not bioavailable. Our results showed that, in non-fluoridated or non-optimally fluoridated areas, the use of low F toothpastes did not protect preschoolers from developing moderate to severe forms of fluorosis in upper permanent anterior teeth. There is no information regarding the effects in optimally fluoridated areas.

We found no evidence to support the use of low F toothpastes by preschoolers as they increased the risk of caries in the primary dentition and did not decrease the risk of aesthetically objectionable fluorosis in upper permanent anterior teeth. However, as preschool children do swallow a significant amount of toothpaste during toothbrushing [Bentley et al., 1999; Cochran et al., 2004b; Franco et al., 2005; Moraes et al., 2007] and the ingestion is greatest in the youngest children [Cochran et al., 2004b], care should be taken to guarantee a safe use of standard F toothpastes. Thus, a small amount of standard F toothpaste should be used under parental supervision [Ellwood and Cury, 2009] and toothbrushing should be performed after meals in order to decrease the bioavailability of F [Cury et al., 2005].

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Disclosure Statement

The authors declare no potential conflicts of interest.

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