ADA CE Program ARTICLE 1

COVER STORY

Are topical fluorides effective for treating incipient carious lesions?

A systematic review and meta-analysis

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Early caries detection and the use of noninvasive interventions are important approaches for controlling caries progression.[1] It has long been known that not all lesions progress to cavitation.[2] Thus, the challenge has been to determine which white-spot lesions will progress to cavitation. Therefore, the proper assessment of lesion activity is crucial to provide appropriate clinical decisions.[3-5]

In this sense, diet and dental biofilm control are sufficient for monitoring inactive enamel lesions. Conversely, topical fluorides, such as gels and varnishes, have been used as adjuvants for the treatment of active white-spot lesions.[1,6]

The evidence on the effect of topical fluorides on the prevention of dental caries has been extensively reported,[7-12] presenting a clear benefit to fluoride varnish application at least twice per year for caries prevention in children and adults.[9,11] Likewise, professional acidulated phosphate fluoride (APF) gel applications 3 times per year are effective for caries inhibition.[10,11]

However, the protocol for the use of fluorides as a therapeutic intent is not clear. When gels or varnishes are used for therapeutic purposes, some authors have recommended 4 to 8 weekly or biweekly sessions[13] or even daily applications.[14]

Xtra Supplemental material is available online.

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

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ABSTRACT

Background. This systematic review and meta-analysis evaluated the effectiveness of professional topical fluoride application (gels or varnishes) on the reversal treatment of incipient enamel carious lesions in primary or permanent dentition.

Methods. Literature searching was carried out by the authors in PubMed (MEDLINE), Cochrane Central Register of Controlled Trials, Turning Research Into Practice, and ClinicalTrials.gov to verify the clinical trials available about the outcome. From 754 potentially eligible studies, 21 were selected for full-text analysis, 5 were included for review, and 3 for meta-analysis. The statistical analysis was performed only for studies assessing fluoride varnish; there were insufficient data to perform it for fluoride gel studies. Two reviewers independently selected the studies, extracted the data, and assessed the risk of bias. Pooled-effect estimates were expressed as the weighted mean difference between groups.

Results. The therapeutic methods ranged considerably regarding the fluoride application protocols. There was a significant trend of effectiveness of fluoride varnish on the reversal of incipient enamel carious lesions ($P < .05$). High heterogeneity was found in the meta-analysis.

Conclusions. Fluoride varnish seems to be an effective treatment for the reversal of incipient carious lesions in primary and permanent dentition; however, further clinical trials concerning efficacy of topical fluorides for treating those lesions are still required, mainly regarding the fluoride gel.

Practical Implications. Considering the scientific evidence on topical fluorides, pediatric dentists can use fluoride varnishes as an adjuvant for the treatment of active white-spot lesions in primary or permanent dentition.

Key Words. Enamel caries; topical fluorides; noncavitated carious lesions; remineralization; systematic review.

JADA 2016:147(2):84-91

http://dx.doi.org/10.1016/j.adaj.2015.06.018

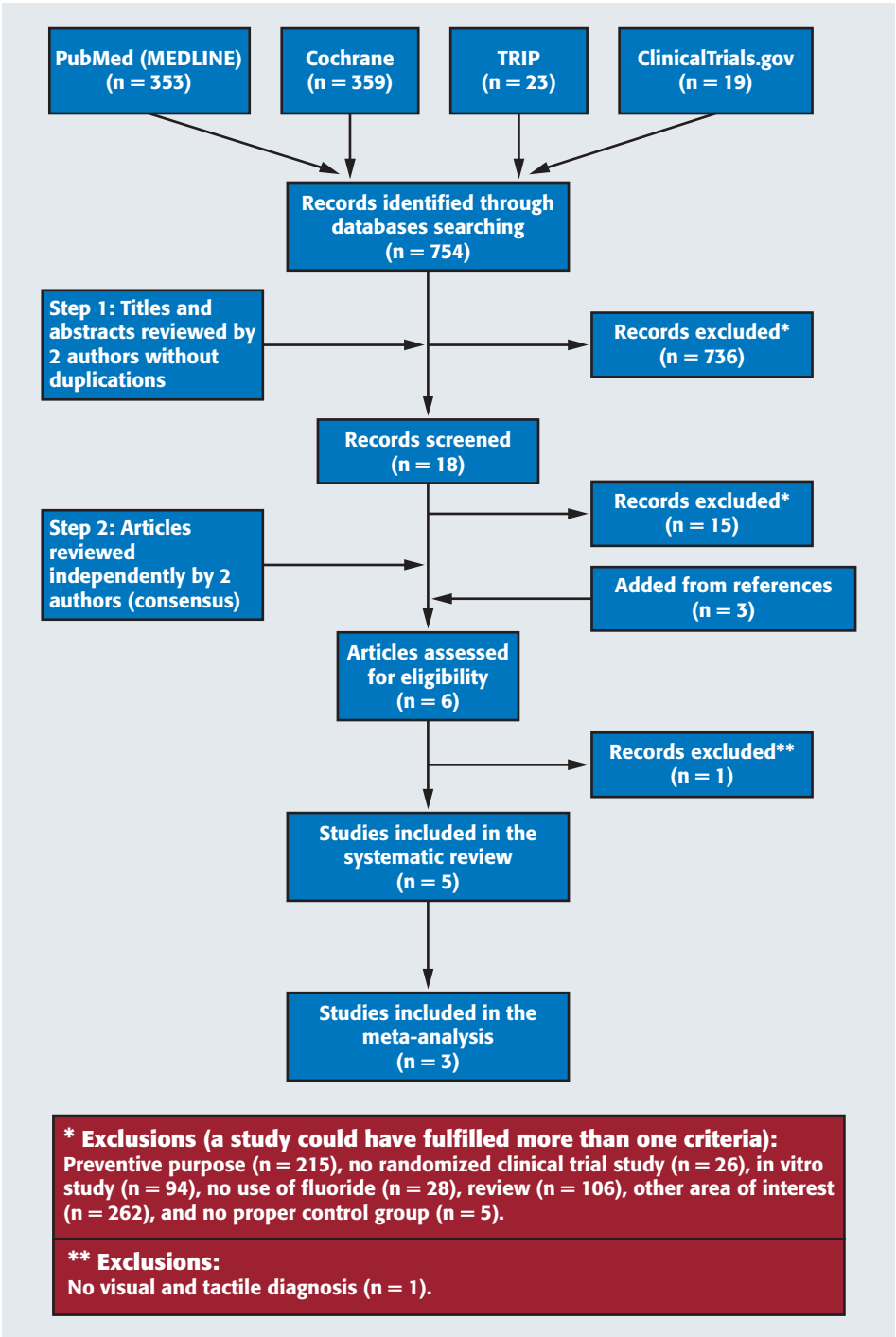

Figure 1. Flow diagram of the study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21] TRIP: Turning Research Into Practice.

Professional topical fluoride application enhances remineralization of active enamel carious lesions because the quantities of calcium and phosphate lost by the dental structure can be replaced by the enamel in fluorapatite form.[15] The action of topical fluoride has been verified in in vitro[16] and in situ studies[14,17-20] regarding the formation of fluoride and its remineralizing ability; however, there is limited clinical evidence on its actual effectiveness. To the best of our knowledge, a systematic quantitative evaluation of the available evidence on the therapeutic effect of the main modalities of topically applied fluoride has never been undertaken. Moreover, comparisons of regimens and agents for remineralization of incipient carious lesions may provide more useful information for clinical evidence-based decision making.

Therefore, the aim of this study was to systematically and quantitatively evaluate the effectiveness of professional topical fluoride applications (gels or varnishes) on arresting the progression of early enamel carious lesions in primary or permanent teeth.

METHODS

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Search strategy and selection criteria. We performed a comprehensive literature search

ABBREVIATION KEY. **APF:** Acidulated phosphate fluoride. **D_ES:** Decayed surfaces with initial enamel lesions. **NA:** Not applicable. **NR:** Not reported. **TRIP:** Turning Research Into Practice.

TABLE 1

Main characteristics of data sets from randomized selected studies for systematic review for fluoride varnish.

STUDY	COUNTRY	PARTICIPANT AGE (MEAN YEARS)	TYPE OF TOOTH, SURFACE, OR DENTITION	TOPICAL FLUORIDE AGENT	APPLICATION PROTOCOL
Autio-Gold and Colleagues,[26] 2001	United States	3-5	All primary tooth surfaces	Duraphat (Colgate Palmolive)	2 applications (at baseline and after 4 mo)
de Amorim and Colleauges,[25] 2008	Brazil	3.4	All primary tooth surfaces	Fluorniz (SS White)	4 applications at weekly intervals
Xhemnica and Colleagues,[27] 2008	Albania	11.7	All permanent tooth surfaces	Fluoridin (Voco)	3 applications at quarterly intervals

* D_ES: Decayed surfaces with initial enamel lesions.
† SD: Standard deviation.
‡ Significant difference ($P < .05$).

through the PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (Central), and Turning Research Into Practice (TRIP) databases to identify literature up to March 20, 2015, that evaluated fluoride gels or varnishes for treating incipient carious lesions in primary and permanent teeth. To retrieve all relevant articles, 2 reviewers (A.F.M. and T.L.L.) screened the reference lists of the included articles and their related reviews. They conducted the search with no publication year or language limits. For the subject search, they used a combination of controlled vocabulary and text words based on the search strategy for the PubMed (MEDLINE) database. The search parameters are provided in the supplemental Appendix (available online at the end of this article). A sensitive search strategy was adapted for the Central and TRIP databases. To reduce publication bias, they pursued unpublished documents through the ClinicalTrials.gov database. They cross-checked the results of searches of various databases to locate and eliminate duplicates.

The same reviewers (A.F.M. and T.L.L.) independently assessed the identified publications and selected them by title and abstract on the basis of the following inclusion criteria: parallel-group randomized clinical trials reporting the therapeutic effect of fluoride gels or varnishes on enamel carious lesions. They did not include studies performed in specific groups (for example, irradiated or special patients and teeth with amelogenesis). When only a relevant title without a listed abstract was available, they assessed a full copy of the article for evaluation. The references of the included articles were also cross-checked for additional studies

TABLE 2

Main characteristics of data sets from randomized selected studies for systematic review for fluoride gel.

STUDY	COUNTRY	PARTICIPANT AGE (MEAN YEARS)	TYPE OF TOOTH, SURFACE, OR DENTITION	TOPICAL FLUORIDE AGENT	APPLICATION PROTOCOL
Ferreira and Colleagues,[23] 2005	Brazil	7-12	Buccal surfaces of maxillary permanent incisors	1.23% APF†	7 or 8 applications at weekly intervals
Bonow and Colleauges,[24] 2013	Brazil	7-12	Buccal surfaces of maxillary permanent incisors or of mandibular permanent first molars	1.23% APF (manufactured by DFL)	8 applications at weekly intervals

* Significant differences ($P < .05$). Regression analysis was used to estimate relative risks of presence of active white-spot lesions.
† APF: Acidulated phosphate fluoride.
‡ NA: Not applicable. This group did not exist in the study.
§ NR: Not reported.

TABLE 1 (CONTINUED)

NO. PER GROUP		CARIES PREVALENCE (D_ES*), MEAN (SD†) AT BASELINE		DROPOUT (%)	FOLLOW-UP (MO)	CARIES PREVALENCE (D_ES), MEAN (SD) AFTER FOLLOW-UP		DIFFERENCE‡
Fluoride Group	Control Group/ No Treatment	Fluoride Group	Control Group/ No Treatment			Fluoride Group	Control Group/ No Treatment	
59	83	7.00 (5.72)	5.21 (3.96)	22.4	9	1.20 (1.96)	3.05 (2.99)	$P < .0001$
20	20	3.45 (2.31)	3.25 (2.00)	5	1	2.98 (1.33)	3.04 (1.28)	$P = .691$
					3	2.40 (0.53)	3.62 (1.10)	$P = .004$
40	52	3.12 (1.93)	3.05 (1.7)	0	7	0.87 (1.18)	3.90 (1.14)	$P < .05$

suitable for inclusion. The reviewers were previously trained and calibrated for article selection ($\kappa = 0.95$). Any discrepancies were solved through discussion and consensus with a third reviewer (R.O.R.).

A final decision about inclusion was made by the reviewers on the basis of the full-text article of the potentially relevant studies in accordance with exclusion criteria: first, it did not present a proper control group (placebo or no treatment); second, it had a dropout rate higher than 30%; third, it did not perform activity assessment of enamel carious lesions with visual and tactile criteria; and finally, it did not evaluate arresting or reversal of incipient carious lesions in primary or permanent teeth as a clinical outcome. In case of studies reporting the same sample, we included those that presented more information.

Data extraction. We defined a protocol for data extraction. Two reviewers (A.F.M. and T.L.L.) independently collected the data of the eligible studies. For each article, they systematically extracted the following data: publication details (title, authors, year), sample characteristics (age of participants, number of participants, mean number of initial active enamel carious lesions), study methodology (topical fluoride agent, application protocol, tooth type, surface, dentition), and outcome information (mean number of enamel carious lesions reversed or arrested in both groups, follow-up, dropout).

Statistical methods for meta-analysis. For the meta-analysis, we only included the data from the studies that evaluated the effect of fluoride varnish on the reversal of incipient carious lesions. It was not possible to perform the meta-analysis on studies assessing fluoride gels because there was insufficient information about the factors in the studies to be included in the pooling.

TABLE 2 (CONTINUED)

NO. PER GROUP			PERCENTAGE OF ARRESTED LESIONS AFTER FOLLOW-UP			DROPOUT (%)	FOLLOW-UP (MO)	DIFFERENCE*
Fluoride Group	Control Group		Fluoride Group	Control Group				
	No treatment	Placebo		No treatment	Placebo			
126	146	132	57.9	43.2	56.8	14	3	$P = .95$ treatment versus placebo; $P = .02$ treatment and placebo versus no treatment
30	NA‡	30	NR§	NR	NR	1.7	2	$P = .26$

The analysis was carried out with fluoride varnish (experimental) versus no treatment (control) at follow-up periods. For the study that reported more than 1 follow-up period, we only considered the data from the longer follow-up. We conducted the meta-analysis using Review Manager Software 5.1 (Nordic Cochrane Centre, Cochrane Collaboration) considering the random-effect model. Pooled-effect estimates were obtained by comparing the caries prevalence means using the decayed surfaces with initial enamel lesions (D_ES) and were expressed as the raw mean difference between the fluoride varnish and control groups. A P value of .05 or less was considered statistically significant (Z test). Statistical heterogeneity of the treatment effect (fluoride versus control) among studies was assessed by the Cochran Q test, with a threshold P value of .1, and the inconsistency I^2 test, in which values greater than 50% were considered indicative of high heterogeneity. Subgroup analysis was not possible as a result of the differences among the characteristics of each study, such as application protocol and follow-up.

Quality and bias risk assessment. We assessed the quality and risk of bias of studies included ($\kappa = 0.90$) in the meta-analysis using published specific study design–related risk of bias assessment forms.[22] We divided the criteria into 7 main domains related to randomization, masking, outcome data, and characteristics of the sample at baseline. We performed the evaluation of the studies by rating each of the study criteria as yes (low risk of bias), no (high risk of bias), or unclear (no information or uncertainty over the potential for bias). For the final classification of risk of bias, disagreements between the reviewers were solved by consensus.

RESULTS

Study selection. The search strategy identified 754 potentially relevant records. After screening titles and abstracts, we retrieved 21 full-text articles for more detailed information. Another 3 studies were identified in reference lists of related reviews. A high percentage of excluded studies were not related to the scope of our review (33.4%). Finally, 5 articles met the eligibility criteria and were included in the systematic review, and 3 of those were included in meta-analysis (fluoride varnish data). The flow diagram summarizes the process of study selection and the reasons for exclusion (Figure 1).

Study characteristics. The main characteristics of the articles included in the systematic review are summarized in Table 1 for fluoride varnish and in Table 2 for fluoride gel. Three of the 5 studies were performed on permanent teeth. Considering the type of tooth surface, articles that used fluoride gel included only buccal surfaces of maxillary permanent incisors[23,24] or of mandibular permanent first molars.[24] For fluoride varnish, all surfaces were considered.

Three articles evaluated the effect of fluoride varnish application on enamel carious lesions compared with no intervention.[25-27] Two studies investigated the efficacy of 1.23% professional APF on incipient carious lesions compared with a placebo application[23,24] or no treatment.[23] In both types of investigation, children received supervised or professional toothbrushing before fluoride gel or placebo applications. The follow-up periods varied from 1 to 9 months.

Regarding application protocols, 7 or 8 applications at weekly intervals were used for fluoride gel,[23,24] whereas the number and time frequency of fluoride varnish applications[25-27] varied considerably among the 3 included articles.

Quality and risk bias of the studies. The final assessment of the quality and risk of bias, considering only the studies included in the meta-analysis, is shown in Table 3. Although the participants were randomly assigned to experimental groups in 2 studies,[25,26] a clear statement of the randomization method was not observed. A lack of information about the allocation concealment and masking of participants was verified in the studies. Only 1 study reported a sample characteristics imbalance at baseline.[27]

Meta-analysis results. The values of the Cochran Q and the Z test were less than .05, showing statistically significant differences between groups, favoring the experimental group (fluoride varnish), which showed a higher decrease in D_ES caries prevalence compared with the control group (no treatment), and the I^2 test was 92%. The meta-analysis results are presented in Figure 2.

DISCUSSION

In active incipient carious lesions, fluoride is accumulated on bacterial plaque and saliva as calcium fluoride as a result of topical fluoride application, such as varnishes and gels. The acidic environment will react with the enamel surface by stimulating available calcium fluoride dissolution to inhibit the demineralization and enhance the remineralization.[28] This systematic review evaluated the available evidence on the ability of topical fluorides to arrest incipient carious lesions in primary or permanent teeth.

The meta-analysis showed that fluoride varnish is an effective approach for arresting the progression of enamel carious lesions in primary and permanent teeth. Nevertheless, the included studies presented different protocols for the treatment of white-spot lesions, using diverse application times and intervals as well as different commercial brands. The duration of the clinical trials testing the effectiveness of fluoride varnish products also ranged considerably.

Both 4 applications at weekly intervals[25] or 2 applications of fluoride varnish over 4 months[26] were effective in reversing active enamel caries lesions in primary dentition. In the last study, 81.2% of lesions became

TABLE 3

Ascertainment of risk of bias in studies included in meta-analysis (fluoride varnish data).

STUDY	ADEQUATE RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	MASKING OF PARTICIPANTS AND PERSONNEL	MASKING OF OUTCOME ASSESSMENT	FREE OF INCOMPLETE OUTCOME DATA	FREE FROM BASELINE IMBALANCE	ADEQUATE RELIABILITY
Autio-Gold and Colleagues,[26] 2001	−*	−	?†	+‡	+	+	+
de Amorim and Colleagues,[25] 2008	−	−	?	?	+	+	+
Xhemnica and Colleagues,[27] 2008	−	−	?	?	+	−	?

* −: No (high risk of bias).
† ?: Uncertain (no information or uncertainty over the potential for bias).
‡ +: Yes (low risk of bias).

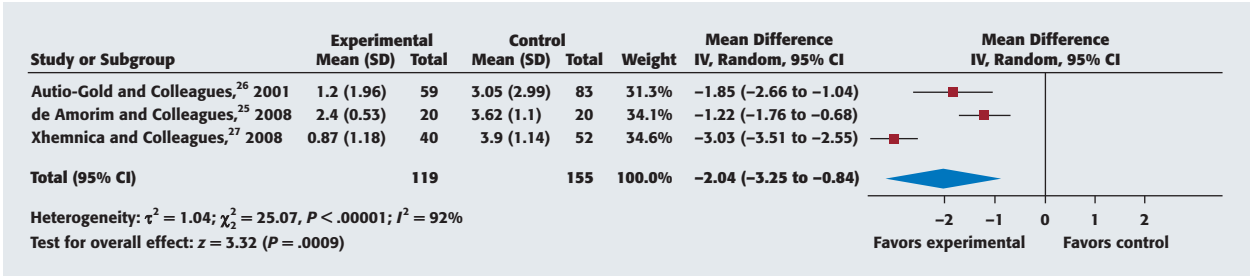

Figure 2. Forest plot for meta-analysis of experimental group (varnish fluoride) and control group (no treatment). CI: Confidence interval. IV: Inverse-variance. SD: Standard deviation.

inactive when using fluoride varnish, whereas only 37.8% were arrested in the control group (no treatment) at 9 months' follow-up.[26] Similarly, 3 applications with quarterly intervals[27] on permanent teeth lead to a significant decrease in caries prevalence compared with the control group at the 7-month interval. We found no evidence that this relative effect was dependent on baseline caries level (all studies included children with a high caries risk factor) or exposure to other fluoride sources, although this result should be interpreted with caution. Further clinical trials are encouraged to determine a standardized protocol (number and interval of applications) for therapeutic use of fluoride varnish in clinical practice. However, the protocol application based on 4 applications at weekly intervals seems to be more adequate for treatment of incipient lesions associated with biofilm control in clinical practice.

It is important to highlight that biofilm control itself is an effective way to arrest enamel carious lesions[17] because it promotes mechanical abrasion of the enamel surface[29,30] and clinically leads to a change in the appearance of white spots, from chalky and rough (active) to bright and smooth (inactive). Therefore, the regression of lesions could be mainly be the result of surface abrasion and not from repair (remineralization) of the enamel's mineral loss.

The presence of active lesions indicates that the reservoir of fluoride formed as a result of the use of fluoride toothpaste or fluoridated water (high frequency and low concentration) has not been enough to positively affect the demineralization–remineralization process. In this sense, the association of fluoride with a low frequency and high concentration through professional topical application, such as varnish and gel, is suggested. Thus, we do not consider a bias risk with the inclusion of studies in which participants had access to fluoridated toothpaste or water.

Furthermore, it was not possible to perform quantitative analysis on fluoride gel data as a result of the small number of trials screened for review and a lack of information in those studies. Fluoride varnishes have been widely used as standard practice for professional application of topical fluoride because of their safety, ease of use, patient acceptance, and convenience of application procedure.[31] This might explain the small number of studies evaluating the therapeutic effect of fluoride gel.

Only 2 clinical trials investigated the effect of regular gel application on incipient carious lesions compared with a placebo application[23,24] or no intervention.[23] The trials failed to demonstrate clear evidence of additional benefits of fluoride gel on reversal of active

enamel carious lesions subjected to weekly supervised toothbrushing. It is noteworthy that the evaluation of fluoride gel use was short term, enabling intense supervision and adequate biofilm control. It is expected that better results could be achieved with a longer period of follow-up or that significant differences between 1.23% APF gel and placebo gel groups could still be verified. An association between the number of active lesions at baseline and the number of gel applications has been reported.[24] Incipient carious lesions in patients with many lesions would require a longer period to become inactive compared with fewer white-spot lesions. Future research regarding the effectiveness of fluoride gel on reversal of early carious lesions should be carried out.

Studies on fluoride gels included only buccal surfaces of maxillary permanent incisors or of mandibular permanent first molars. Conversely, fluoride varnish studies considered all tooth surfaces. Perhaps lesions that have not arrested are those in occlusal surfaces. Carious lesions in less susceptible surfaces (smooth surfaces) reduce in higher proportion than lesions in more susceptible surfaces (occlusal surfaces), irrespective of topical fluoride application.[32]

A systematic review has evidenced that sealants are more effective than fluoride varnish in caries prevention on occlusal surfaces.[33] Therefore, sealants may be a better option to arrest occlusal carious lesions. Further studies should address this question.

The literature search was not conducted in the Embase database. Although Embase resulted in a higher number of studies identified,[34] this difference from PubMed (MEDLINE) seemed unimportant for the inclusion of relevant biomedical studies. Embase showed in its search many studies that did not meet the inclusion and exclusion criteria of systematic reviews; thus, this broad search did not always result in higher-quality citations.[34] Several other databases were used in this study, including unpublished data.

The results of this review should be considered carefully because few studies addressing the desired outcome were found, even with a proper and broad search. Most studies in the scientific literature have investigated the preventive effect of topical fluorides[7-12] and have not focused on therapeutic management. It is likely that the findings may have been influenced by the publication bias, as negative or similar results were probably not published or were published in low-impact-factor journals. A lack of reliable studies investigating the outcome of interest can also explain the absence of evidence concerning this topic. However, it is not possible to ensure which hypothesis is more related to our findings, or neither if a combination of them occurred.

The meta-analysis showed a high heterogeneity, probably because of the small number of articles included and also because of the differences in the studies' protocols (fluoride varnish). The heterogeneity could also be explained by the medium and high risk of bias of the included studies, which limits the meta-analytic approach.

The quality and risk bias assessments showed that most of the studies did not report important data to clinical trials, as suggested by the Consolidated Standards of Reporting Trials guidelines,[35] which could interfere with the quality analyses of those studies. The lack of proper randomization methods poses a threat to the validity of the studies, as they are susceptible to selection bias. In all trials on fluoride varnish, the control group received no treatment instead of a placebo. Clinical trials with no intervention groups may overestimate the effect measure. Moreover, there is no information about the calculation of the sample size, which may not be representative, thus limiting the extrapolation of results.

CONCLUSIONS

Fluoride varnish seems to be an effective treatment on the reversal of incipient carious lesions in primary and permanent dentition; however, the protocol of fluoride varnish application is not well established yet. Because of the few clinical data and the limitations of the included studies, further research is required to investigate the efficacy of professional fluoride topical applications on active enamel carious lesions, mainly assessing fluoride gel. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: http://dx.doi.org/10.1016/j.adaj.2015.06.018.

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Disclosure. None of the authors reported any disclosures.

The authors thank Programa Nacional de Pós-Doutorado (PNPD)/Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for financial support.

1. Stahl J, Zandona AF. Rationale and protocol for the treatment of non-cavitated smooth surface carious lesions. *Gen Dent*. 2007;55(2):105-111.

2. Dirks OB. Posteruptive changes in dental enamel. *J Dent Res*. 1966; 45(3):503-511.

3. Nyvad B, Fejerskov O. Assessing the stage of caries lesion activity on the basis of clinical and microbiological examination. *Community Dent Oral Epidemiol*. 1997;25(1):69-75.

4. Basting RT, Serra MC. Occlusal caries: diagnosis and noninvasive treatments. *Quintessence Int*. 1999;30(3):174-178.

5. Nyvad B. Diagnosis versus detection of caries. *Caries Res*. 2004;38(3): 192-198.

6. Kidd E. The implications of the new paradigm of dental caries. *J Dent*. 2011;39(suppl 2):S3-S8.

7. Marinho VC. Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries. *Eur Arch Paediatr Dent*. 2009;10(3):183-191.

8. Ijaz S, Croucher RE, Marinho VC. Systematic reviews of topical fluorides for dental caries: a review of reporting practice. *Caries Res*. 2010;44(6):579-592.

9. Marinho VC, Worthington HV, Walsh T, Clarkson JE. Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*. 2013;7:CD002279.

10. Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev*. 2002;(2):CD002280.

11. Weyant RJ, Tracy SL, Anselmo TT, et al. Topical fluoride for caries prevention: executive summary of the updated clinical recommendations and supporting systematic review. *JADA*. 2013;144(11):1279-1291.

12. Marinho VC. Evidence-based effectiveness of topical fluorides. *Adv Dent Res*. 2008;20(1):3-7.

13. Clarkson B, Fejerskov O, Silverstone LN. Rational use of fluorides in caries prevention and treatment. In: Clarkson B, Fejerskov O, Silverstone LN, eds. *Fluoride in Dentistry*. Copenhagen: Munksgaard; 1988:276-388.

14. Lagerweij MD, ten Cate JM. Remineralisation of enamel lesions with daily applications of a high-concentration fluoride gel and a fluoridated toothpaste: an in situ study. *Caries Res*. 2002;36(4):270-274.

15. Lambrou D, Larsen MJ, Fejerskov O, Tachos B. The effect of fluoride in saliva on remineralization of dental enamel in humans. *Caries Res*. 1981;15(5):341-345.

16. Takagi S, Liao H, Chow LC. Effect of tooth-bound fluoride on enamel demineralization/remineralization in vitro. *Caries Res*. 2000;34(4):281-288.

17. Paes Leme AF, Dalcico R, Tabchoury CP, Del Bel Cury AA, Rosalen PL, Cury JA. In situ effect of frequent sucrose exposure on enamel demineralization and on plaque composition after APF application and F dentifrice use. *J Dent Res*. 2004;83(1):71-75.

18. Calvo AF, Tabchoury CP, Del Bel Cury AA, Tenuta LM, da Silva WJ, Cury JA. Effect of acidulated phosphate fluoride gel application time on enamel demineralization of deciduous and permanent teeth. *Caries Res*. 2012;46(1):31-37.

19. Jardim JJ, Pagot MA, Maltz M. Artificial enamel dental caries treated with different topical fluoride regimes: an in situ study. *J Dent*. 2008;36(6):396-401.

20. Lee YE, Baek HJ, Choi YH, Jeong SH, Park YD, Song KB. Comparison of remineralization effect of three topical fluoride regimens on enamel initial carious lesions. *J Dent*. 2010;38(2):166-171.

21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.

22. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.0.1 Available at: http://www.cochrane-handbook.org/. Accessed June 29, 2015.

23. Ferreira MA, Latorre Mdo R, Rodrigues CS, Lima KC. Effect of regular fluoride gel application on incipient carious lesions. *Oral Health Prev Dent*. 2005;3(3):141-149.

24. Bonow ML, Azevedo MS, Goettems ML, Rodrigues CR. Efficacy of 1.23% APF gel applications on incipient carious lesions: a double-blind randomized clinical trial. *Braz Oral Res*. 2013;27(3):279-285.

25. de Amorim RG, Leal SC, Bezerra AC, de Amorim FP, de Toledo OA. Association of chlorhexidine and fluoride for plaque control and white spot lesion remineralization in primary dentition. *Int J Paediatr Dent*. 2008;18(6):446-451.

26. Autio-Gold JT, Courts F. Assessing the effect of fluoride varnish on early enamel carious lesions in the primary dentition. *JADA*. 2001;132(9):1247-1253.

27. Xhemnica L, Sulo D, Rroco R, Hysi D. Fluoride varnish application: a new prophylactic method in Albania. Effect on enamel carious lesions in permanent dentition. *Eur J Paediatr Dent*. 2008;9(2):93-96.

28. Clinical aspects of de/remineralization of teeth. Paper presented at: Proceedings of Models Conference; June 11-14, 1994; Rochester, NY. *Adv Dent Res*. 1995;9(3):169-340.

29. Artun J, Thylstrup A. Clinical and scanning electron microscopic study of surface changes of incipient caries lesions after debonding. *Scand J Dent Res*. 1986;94(3):193-201.

30. Holmen L, Thylstrup A, Artun J. Surface changes during the arrest of active enamel carious lesions in vivo. A scanning electron microscope study. *Acta Odontol Scand*. 1987;45(6):383-890.

31. Ogard B, Seppa L, Rolla G. Professional topical fluoride applications—clinical efficacy and mechanism of action. *Adv Dent Res*. 1994;8(2):190-201.

32. McDonald SP, Sheiham A. The distribution of caries on different tooth surfaces at varying levels of caries—a compilation of data from 18 previous studies. *Community Dent Health*. 1992;9(1):39-48.

33. Hiiri A, Ahovuo-Saloranta A, Nordblad A, Makela M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. *Cochrane Database Syst Rev*. 2010;(3):CD003067.

34. Wilkins T, Gillies RA, Davies K. Embase versus Medline for family medicine searches: can Medline searches find the forest or a tree? *Can Fam Physician*. 2005;51:848-849.

35. Rennie D. CONSORT revised—improving the reporting of randomized trials. *JAMA*. 2001;285(15):2006-2007.

APPENDIX: SEARCH STRATEGY FOR PUBMED (MEDLINE) DATABASE

((((((((((((((((((((dental enamel) OR dental enamel [MeSH Terms]) OR enamel) OR white spot lesion*) OR cavitated carious lesion*) OR non-cavitated carious lesion*) OR incipient carious lesion*) OR dental caries) OR dental caries[MeSH Terms]) AND Tooth, deciduous [MeSH Terms]) OR deciduous tooth) OR primary dentition[MeSH Terms]) OR primary dentition) OR primary tooth) OR Dentition, permanent[MeSH Terms]) OR Permanent dentition) OR Permanent tooth)) AND (((((((((fluoride gel) OR acidulated phosphate fluoride gel) OR acidulated fluoride gel) OR neutral fluoride gel) OR sodium fluoride gel) OR topical fluoride) OR Fluorides, topical[MeSH Terms]) OR fluoride varnish*) OR varnish*)) AND (((placebo) OR placebo control) OR no treatment)) AND ((((clinical [Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random[Title/Abstract] OR random allocation [MeSH Terms] OR therapeutic use[MeSH Subheading])))).