Systematic Review
Cariology

Is professionally applied topical fluoride effective in treating incipient caries? A systematic review

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Abstract: The present systematic review aimed to investigate the effectiveness of professionally applied topical fluoride as therapeutic agent for incipient carious lesions in permanent teeth. Randomised clinical trials (RCTs) comparing the effectiveness of professionally applied topical fluoride (varnish or gel) with that of placebo, no intervention, and toothbrushing (control group) in the treatment of incipient carious lesions in permanent dentition were included. An electronic search was performed in the PubMed, Web of Science, Scopus, Virtual Health Library, Embase, and Cochrane databases, in the grey literature, and in clinical trials registered until January 2021. Two reviewers independently screened titles and abstracts and assessed the risk of bias using the Cochrane tool. The certainty of evidence was classified using GRADE. A total of 2,223 articles were screened using titles/abstracts. After full-text reading of the 22 selected studies, nine RCTs were included. Five RCTs found that topical fluoride may be effective in reversing incipient carious lesions in permanent teeth. Overall, five studies were classified as having a low risk of bias and four as having some concerns. Only descriptive analysis was performed because of the heterogeneity of the data. Studies comparing fluoride varnish with usual home care oral hygiene have demonstrated topical fluoride does not appear to be more effective in improving the appearance of incipient carious lesions. Therefore, usual home care oral hygiene with fluoride toothpaste may be sufficient to treat incipient carious lesions in permanent dentition. Further studies with greater methodological rigor are, however, required to reduce bias, to allow a meta-analysis, and to draw well-founded conclusions (CRD42019120406).

Keywords: Dental Caries; Fluorides, Topical; Acidulated Phosphate Fluoride; Fluorides, Topical.

Introduction

Dental caries is considered a major public health problem affecting individuals worldwide.[1] Even with a reduction in its prevalence in recent years, there are still 2.5 billion people around the world with untreated dental caries in permanent teeth.[1] The dynamic caries process involves alternating periods of tooth demineralisation and remineralisation, modulated by fluoride salivary levels and salivary buffering capacity. This process results in specific carious lesions when demineralisation

occurs for sufficient time because of an imbalance between periods.[2]

Carious lesions become clinically visible as white spot lesions (WSLs) when sufficient mineral amounts are lost.[2] WSLs are considered the initial stage of carious lesions, defined by demineralisation without any cavity formation.[3] The incidence and prevalence rates of WSLs during orthodontic treatment were evaluated by a meta-analysis, with significant rates of 45.8% and 68.4%, respectively.[4] This initial phase is clinically relevant in the carious process because it is the stage at which the lesion can be arrested or reversed by modifying causal factors or by adopting preventive measures.[2]

Incipient carious lesions can be managed using remineralisation therapies, involving behavioural changes (reviewing dietary habits and plaque control) and using fluoride-containing products.[5,6] The rate and magnitude of initial remineralisation can be increased with fluoride application (*e.g.*, use of toothpaste at home – which is the most widely used form of fluoride worldwide).[2,7-9] Fluoride dentifrices are effective against dental caries and the benefit of using them derives from frequent low-dose application, which delivers fluoride daily to the dental surface, thus contributing to dental remineralisation.[7,8,10,11]

One of the major mechanisms of action of topical fluoride for the arrest and reversal of a dynamic caries process initiates when fluoride adsorbs onto the dental surface and attracts calcium and phosphate ions, forming a fluorapatite-like remineralised veneer on the crystal surface, which is less soluble than the original hydroxyapatite and more difficult to be dissolved.[12] In addition, fluoride speeds up the remineralisation process.[12]

There are also some preventive strategies and minimally invasive approaches described in the literature that are performed by dentists for the treatment of WSLs, such as professionally applied topical fluoride, sealants, and silver diamine fluoride.[13] Professionally applied topical fluoride, which is widely used not only for prevention, but also for the treatment of incipient carious lesions, has a different mechanism of action, delivering fluoride at high concentrations to exposed tooth surfaces for a local effect and for a certain period.[14] Scientific evidence about the effect of topical fluoride products on the prevention of dental caries has been well documented and extensively reviewed, demonstrating the benefits of fluoride for caries arrest.[14-17] Nevertheless, evidence regarding fluoride treatment for dental caries in permanent dentition is still lacking.

Some findings on the remineralizing ability of fluoride have been published in the literature, but most of them were obtained from *in vitro*[18] and *in situ* studies.[19-23] Few randomised controlled clinical trials (RCTs) have evaluated the effectiveness of professionally applied topical fluoride (varnish or gel) in the treatment of incipient carious lesions in permanent dentition,[24-32] and their findings are contradictory. Additionally, a systematic review and meta-analysis aimed at reviewing the evidence on the effectiveness of topical fluorides (varnish or gel) for treating carious lesions, was published; however, both permanent and deciduous dentition were included in the same analysis.[33]

Given the lack of consensus about the effectiveness of topical fluoride application for the treatment of noncavitated incipient carious lesions in permanent dentition, summarising and discussing the available literature on this topic is of great relevance. This study aimed to perform a systematic review of the literature to find out whether professionally applied topical fluoride is effective in treating incipient carious lesions in permanent teeth when compared to a control group (placebo, no intervention, and toothbrushing).

Methodology

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[34,35].

Eligibility criteria

Only RCTs comparing the effectiveness of professionally applied topical fluoride with that of a control group treatment for incipient enamel carious lesions in permanent dentition were included in this review. The outcome was the remineralisation of noncavitated incipient carious lesions circumscribed to the enamel surface assessed through objective

measures and criteria. We did not include split-mouth studies because this study design posed the risk of a carryover effect (contamination across treatments) and was therefore unsuitable for topical fluoride studies. *In vitro* and *in situ* studies, abstracts, observational studies, protocols, studies without abstracts, and systematic reviews were also excluded.

Topical fluoride agents (varnish and gel) applied for the treatment of incipient enamel carious lesions were considered the intervention. To be included in this review, the study should have received one of the following treatments as a control group: placebo, toothbrushing and/or only follow-up without any intervention.

We excluded studies that reported no dental caries data or studies that only reported data of cavitated or noncavitated carious lesions at the dentine level.

Search strategy

The search strategy was based on MeSH terms related to our research question, following the PICO model.

a) P: adults and/or children with permanent teeth; b) I: professionally applied topical fluoride for the treatment of incipient carious lesions; c) C: toothbrushing, placebo and/or no intervention; and d) O: incipient carious lesion remineralisation.

No restrictions on language or publication date were applied to the electronic database search. The electronic search was performed in PubMed, Web of Science, Scopus, Virtual Health Library,

Table 1. Detailed search strategies used for specific databases.

PubMed	((((((((((((("Non-Randomized Controlled Trials as Topic"[MeSH Terms]) OR "Non-Randomized Controlled Trials") OR "Non-Randomized Clinical Trials") OR "Randomized Controlled Trial"[Publication Type]) OR "Randomized Controlled Trial") OR "Clinical Trials") OR "Clinical Trials as Topic"[MeSH Terms]) OR "Clinical Studies as Topic"[MeSH Terms]) OR "Clinical Studies") OR "Controlled Clinical Trials as Topic"[MeSH Terms]) OR "Controlled Clinical Trials"[MeSH Terms])) AND ((((((("dental caries") OR "dental caries"[MeSH Terms]) OR "Tooth Demineralization") OR "Tooth Demineralization"[MeSH Terms]) OR "incipient caries") OR "white spots")) AND ((((((((("Dental Care") OR "Dental Care"[MeSH Terms]) OR Therapeutics[MeSH Terms]) OR therapy[MeSH Subheading]) OR "Conservative Treatment"[MeSH Terms]) OR "Conservative Treatment") OR Therapeutics) OR therapy) OR "fluoride therapy") OR "treatment")) AND ((((((((((((((((((Fluorides) OR Fluorides[MeSH Terms]) OR "Fluorides, Topical"[MeSH Terms]) OR "Fluor Protector"[Supplementary Concept]) OR "Fluor Protector") OR "sodium fluoride topical preparation"[Supplementary Concept]) OR "sodium fluoride topical preparation") OR "Sodium Fluoride") OR "Sodium Fluoride"[MeSH Terms]) OR "Acidulated Phosphate Fluoride") OR "Acidulated Phosphate Fluoride"[MeSH Terms]) OR "All Solutions Fluoride Varnish"[Supplementary Concept]) OR "All Solutions Fluoride Varnish") OR "Fluoride varnishes") OR "Fluoride varnish") OR "Fluoride gels") OR "Fluoride gel") OR "Topical fluoride")
Web of Science	TS=(Fluoride OR Fluorides OR "Topical fluoride" OR "Topical fluorides" OR "Fluoride Varnish" OR "Fluoride Varnishes" OR "Fluoride gel" OR "Fluoride gels") AND TS=("Dental Caries" OR "Tooth Demineralization" OR "Incipient Caries" OR "White Spots" OR "Early Lesions Caries") AND TS=("Fluoride Therapy" OR Treatment) AND TS=("Non-Randomized Controlled Trials" OR "Randomized Controlled Trials" OR "Clinical Trial" OR "Clinical Trials")
Scopus	TITLE-ABS-KEY(Fluoride OR Fluorides OR "Topical fluoride" OR "Topical fluorides" OR "Fluoride Varnish" OR "Fluoride Varnishes" OR "Fluoride gel" OR "Fluoride gels") AND TITLE-ABS-KEY("Dental Caries" OR "Tooth Demineralization" OR "Incipient Caries" OR "White Spots" OR "Early Lesions Caries") AND TITLE-ABS-KEY("Fluoride Therapy" OR Treatment) AND TITLE-ABS-KEY("Non-Randomized Controlled Trials" OR "Randomized Controlled Trials" OR "Clinical Trial" OR "Clinical Trials")
BVS	(tw:(("Acidulated Phosphate Fluoride" OR Fluorides OR "Sodium Fluoride" OR "Fluorides, Topical" OR "Fluoride Varnishes" OR "Fluoride gel"))) AND (tw:((Therapeutics OR Therapy OR Treatment))) AND (tw:(("Dental Caries" OR "White Spot" OR "Incipient Caries" OR "Early Lesions Caries"))) AND (tw:(("Randomized Controlled Trials as Topic" OR "Non-Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial")))
Embase	('fluoride'/exp OR 'fluoride varnish'/exp OR 'sodium fluoride'/exp OR 'fluoride tray'/exp OR 'acidulated fluorophosphate'/exp) AND ('dental caries'/exp OR 'tooth disease'/exp) AND ('therapy effect'/exp OR 'dental procedure'/exp) AND ('randomized controlled trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'randomized controlled trial (topic)'/exp)
Cochrane	("Fluoride" OR "Fluorides" OR "Topical fluoride" OR "Topical fluorides" OR "Fluoride Varnish" OR "Fluoride Varnishes" OR "Fluoride gel" OR "Fluoride gels") AND ("Dental Caries" OR "Tooth Demineralization" OR "Incipient Caries" OR "White Spots" OR "Early Lesions Caries") AND ("Fluoride Therapy" OR "Treatment") AND ("Non-Randomized Controlled Trials" OR "Randomized Controlled Trials" OR "Clinical Trial" OR "Clinical Trials")

Embase, and Cochrane databases until January 2021. Search strategies used for each database are listed in Table 1. We also searched the grey literature on Google Scholar and protocol registrations on Clinical Trials to identify additional eligible references. Additionally, the reference lists of all the included studies were reviewed.

Selection process

The references were managed using EndNote X7.5 software 2016 for Windows & Mac (desktop) (Thomson Reuters, New York, USA), and duplicate references were automatically identified and excluded. Two authors independently screened titles and abstracts after an electronic search to identify potentially eligible studies. A third author moderated any disagreement between the other two reviewers. The full texts of articles were read by the same two reviewers to determine whether they met the inclusion criteria for this review.

Data collection process

A Microsoft Excel spreadsheet (2019) was created for data extraction (Microsoft Corporation, Redmond, USA). The two reviewers independently extracted the data from each study. The third reviewer moderated any discrepancies. If missing or additional data were necessary, the corresponding authors were contacted once by e-mail.

Data items

The outcome assessed in this review was the remineralisation of incipient carious lesions, measured by changes in lesion surface texture during follow-up assessments. Incipient carious lesions were considered noncavitated and circumscribed to the enamel surface, assessed through objective measures and criteria, such as clinical examination, quantitative light-induced fluorescence (QLF), laser fluorescence, and photographic assessment.

The other investigated variables were the first author's name, year of publication, country, aim of the study, sample characteristics, study design, type of intervention and comparison, outcomes reported, follow-up assessments, and statistical analyses (statistical methods and effect measures used, adjustments performed, and confounding factors).

Risk of bias assessment

Two reviewers (C.B.F.C. and C.S.S.) independently assessed the risk of bias of all included studies using the Cochrane recommended tool for RCTs (RoB 2).[36] Any disagreements were resolved by discussion or consensus involving a third reviewer (M.G.C.). This tool has a fixed set of five domains that aims to obtain relevant information for assessing risk of bias as follows: randomisation process, if participants or people delivering the interventions were aware of the assigned intervention, missing outcome data, measurement of the outcome, and selection of the reported findings.

Issues in each domain can be judged as "low" or "high" risk of bias or also as "some concerns" according to RoB 2 guidelines and to the study description of the relevant information for each domain. If the study did not report or reported insufficient details, the issues were judged as "not informed" for a given question, influencing the rating in that domain. The overall risk of bias for each study was based on the risk obtained in each of the five domains.

Synthesis methods

Quantitative and qualitative data (such as place of publication, population context, and study design) were collected from the included studies for data synthesis. Statistical analysis data (statistical methods and effect measures used, adjustments performed, and confounding factors) from all included studies were collected and described (when available). The studies were grouped by material (fluoride varnish and fluoride gel) and only descriptive analysis was performed considering individual results, as methods and outcomes varied considerably among studies.

Certainty assessment

The certainty of evidence for remineralisation of incipient carious lesions in permanent teeth was classified using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) by two independent reviewers (C.B.F.C. and C.S.S.). Any disagreements were resolved by discussion or consensus involving a third reviewer (M.G.C.). The assessment was performed considering the study's outcome stratified by intervention groups (fluoride

varnish and fluoride gel). The following aspects were considered to rate the certainty of evidence: risk of bias of the studies, inconsistency between trials, indirectness of evidence, and imprecision of results.

Results

Study selection

A total of 4,415 articles were selected after an electronic search to identify eligible references. After the removal of duplicates, 2,223 articles were screened by titles and abstracts and 22 were selected for full-text reading. Among these, 13 studies that did not fulfil the inclusion criteria were excluded. A list of excluded studies and reasons for exclusion are shown in Table 2. Therefore, nine RCTs were included in this systematic review. A flowchart summarises the process according to the PRISMA statement (Figure 1).

Study characteristics

The main characteristics of the included studies are summarised in Table 3. All studies were RCTs, totalling 636 participants. In addition, there was one study that was not included in this count because the adopted tooth was the experimental unit, comprising a total of 80 teeth. The sample was predominantly female, although three studies did not report the proportion between males and females, and one did not report this proportion by group. The ages of the participants ranged from 5 to 25 years. Five studies included only individuals under 16 years of age.[24,26,29,31,32]

Studies were developed after the 2000s in the following countries: Brazil (n = 2),[24,29] China (n = 2),[25,27] USA (n = 1),[28] Iran (n = 1),[26] India (n = 1),[30] Sweden (n = 1),[31], and the Netherlands (n = 1).[32]. Regarding the population context, the majority of studies were conducted in universities, and four studies performed the procedures after the individual had undergone orthodontic treatment.[25,27,28,30] The population caries activity was described in one study that evaluated WSLs in caries-active adolescents.[31] Two RCTs investigated active WSL,[24,29] whereas the others did not report information about caries activity.

Most studies performed dental prophylaxis prior to the professionally applied topical fluoride through professional toothbrushing[24,25,29,31,32] or polishing with pumice powder and rubber prophy cups.[26,30] Two studies did not report this information[27,28].

Five RCTs investigated the effect of fluoride varnishes on the treatment of active incipient carious lesions, of which four evaluated the effect of 5% sodium fluoride (NaF) varnish[25,27,28,30] and the other assessed the effect of 1.5% ammonium fluoride varnish.[31] Different

Table 2. Excluded studies and main reasons for exclusion.

Study	Setting	Reason for exclusion
Agrawal and Pushpanjali, 2011	India	Prevention study
Alavi and Yaraghi, 2018	Iran	Did not evaluate noncavitated incipient carious lesions separately
Aykut-Yetkiner et al., 2014	Turkey	Did not evaluate professionally applied fluoride
Ferrari et al., 2005	Brazil	No access to the full article
Goldenfum et al., 2021	Brazil	Did not evaluate permanent dentition separately
Gozetici et al., 2019	Turkey	Split-mouth design
Guçlu et al., 2016	Turkey	The control group used mouthrinse and xylitol gum
Gugwad et al., 2011	India	Prevention study
Kukleva, 2001	Bulgaria	No access to the full article
Llena-Puy et al., 2013	Spain	Review of an article
Restrepo et al., 2016	Brazil	Did not evaluate noncavitated incipient carious lesions separately
Salamara et al., 2020	Greece	Did not evaluate noncavitated incipient carious lesions separately
Vivaldi-Rodrigues et al., 2006	Brazil	Split-mouth design

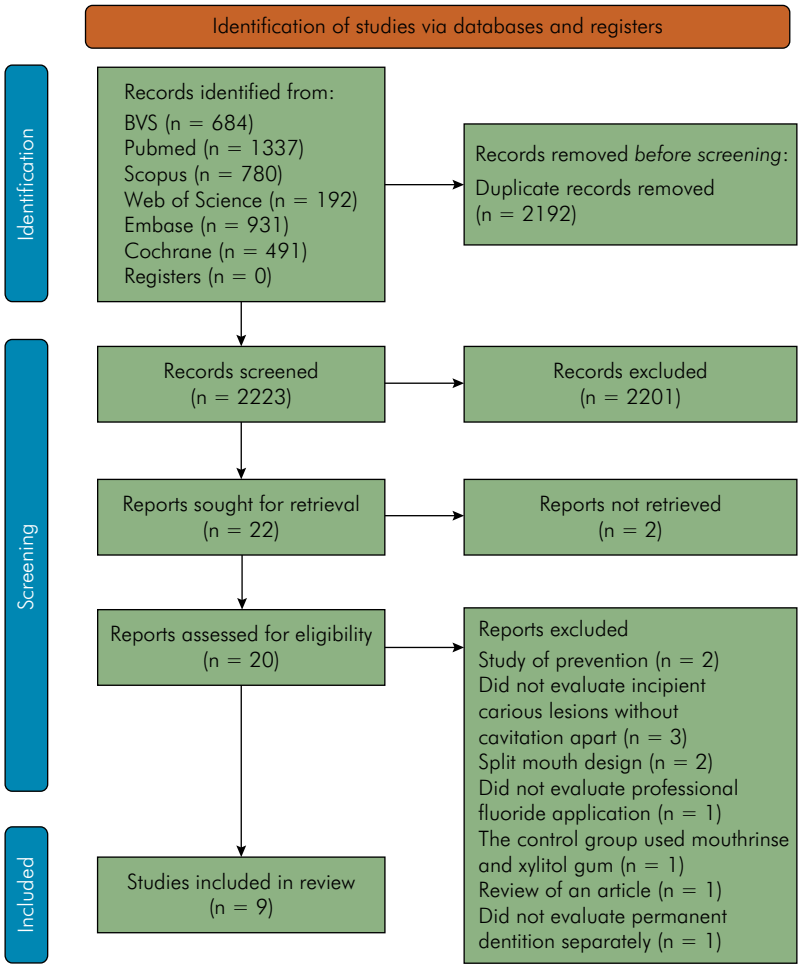

Figure 1. Flowchart showing the inclusion of studies according to the PRISMA statement.

application protocols were adopted in these studies. Ammonium fluoride varnish was applied six times (at the beginning of the study, after 1 week, and then 4 times once every 6 weeks for 6 months).[31] Regarding sodium fluoride varnish application, the protocols also varied as follows: a single application[28,30] once a month for 6 months.[25,27]

Considering the effect of fluoride gel, four articles addressed three different types of gel: 1.23% acidulated phosphate fluoride (APF),[24,29] 1% neutral NaF[32], and 2% neutral NaF.[26] The APF gel protocol varied between two applications at a one-week interval[29] and weekly applications for 8 weeks.[24] The 1% neutral NaF gel was professionally applied through eight semi-annual periods using a flexible tray for 4 min[32] and the 2% neutral NaF gel was applied in the same manner for 10 min, three times for 10 days.[26]

Different objective measures and devices have been used to detect caries and assess remineralisation of lesions, such as clinical examination,[24,32] quantitative light-induced fluorescence (QLF),[26,30] laser-induced fluorescence,[25,29,30] and photographic assessment.[26,27]

Heterogeneity was also observed in the follow-up periods between the included studies, from 10 days,[26] two months,[24,28] three months,[29] six months,[25,27,30,31] up to 48 months.[32]

Risk of bias assessment

The risk of bias assessment results are shown in Figure 2. Overall, five studies[24,25,27,29,32] were classified as having a low risk of bias and four[26,28,30,31] were rated as having some concerns. The main domains in which studies were rated as some concerns of risk of bias were deviations from intended

Table 3. Main characteristics of included studies.

Author, year/ Country	Study design	Population context	Intervention (n)	Application frequency	Control (n)	Usual home care oral hygiene	Outcome assessment method	Conclusions
Bonow et al., 2013/Brazil	Double-blind RCT	Public School; Pelotas, Brazil	1.23% APF gel; DFL, Brazil (n = 30)	Every week for 8 weeks	Placebo gel (n = 29)	Subjects were given toothbrushes and fluoridated dentifrice (1,100 ppm NaF)	Clinical: DMFS (RR)	The equivalence of treatments was shown. The use of the APF gel showed no additional benefits
Du et al., 2011/ China	RCT	After orthodontic treatment; Wuhan University	5% NaF varnish; Duraphat Colgate Oral Pharmaceutical, USA (n = 47)	Every month during the first 6 months after debonding	Placebo solution (Saline solution) (n = 49)	Standard tooth cleaning and oral hygiene instruction (toothbrushing twice a day with fluoride toothpaste)	DIAGNOdent (Mean ± SD)	Topical fluoride varnish application is effective in reversing WSLs after debonding
Ebrahimi et al., 2017/Iran	Single-blind RCT	School of Dentistry; Mashhad University of Medical Sciences	2% Neutral NaF gel; Sultan Healthcare Inc., USA (n = 20)	3 times over 10 days	No treatment (n = 20)	All subjects were instructed to brush twice daily using a soft-bristled toothbrush and fluoridated toothpaste (1100 ppmF)	Photographic assessment: Area mm^2 and Mineral content (Mean ± SD)	3 times NaF application over 10 days was effective in reducing area and increasing mineral content of WSLs in children, whereas the control group did not show any significant improvement
He et al., 2016/ China	Single-blind RCT	After orthodontic treatment; Sichuan University	5% NaF varnish; Duraphat Colgate Oral Pharmaceutical, USA (n = 69)	Once a month for 6 months	Placebo paste (fluoride-free deliquescent toothpaste) (n = 72)	Subjects were instructed to brush their teeth twice a day using the same commercial fluoride toothpaste and toothbrush	QLF: ΔQ mm^2x% (Mean ± SD)	Daily use of fluoride toothpaste and oral hygiene education can support enamel remineralization, and treatment with fluoride varnish can induce remineralization after orthodontic therapy
Huang et al., 2013/USA	Single-blind RCT	After orthodontic treatment; Private and general dentistry offices	5% NaF varnish; PreviDent Colgate Oral Pharmaceutical, USA (n = 40)	Single application at the beginning of the study	Usual home care oral hygiene (n = 41)	All subjects received oral hygiene instructions and a packet with fluoride toothpaste (1100 ppmF), toothbrush, and dental floss	Photographic assessment: Percentage of area affected (Mean ± SD)	Fluoride varnish does not appear to be more effective than normal home care for improving the appearance of WSL over 8 weeks
Mendes et al., 2018/Brazil	RCT	Municipal elementary Schools; Botucatu, Brazil	1.23% APF gel; DFL, Brazil; (n = 20)	Twice at a one-week interval	Placebo paste (n = 20)	Subjects received clinical examination once a month for 3 months, and oral hygiene instructions with use of fluoride toothpaste (1450 ppmF)	DIAGNOdent (Median (1^{st}; 3^{rd} quartiles))	Remineralization effect of WSL can be improved when casein phosphopeptide-amorphous calcium phosphate is applied in combination with fluoride

Continue

Continuation

Singh et al., 2016/India	RCT	After orthodontic treatment	5% NaF varnish; Fluoritop-SR ICPA Health Products Ltd., India (n = 13)	Single application	1.000 ppmF toothpaste; Colgate-Palmolive Company, USA (n = 14)	Subjects were advised to brush their teeth twice daily with fluoride toothpaste (1000 ppmF)	DIAGNOdent (Mean ± SD) and Clinical: Boyd score (Mean ± SD)	Use of 5% NaF varnish in addition to twice-daily use of 1000 ppmF toothpaste had no additional beneficial effect in remineralization of post-orthodontic WSLs
Tranaeus et al., 2001/Sweden	Single-blind RCT	Institute of Odontology; Karolinska Institutet	Fluoride varnish; Fluor Protector Ivoclar Vivadent, Liechtenstein (n = 13)	At study start, after 1 week and then four times, every 6 week for 6 months	Professional tooth cleaning (n = 18)	Subjects received oral hygiene instruction to brush for 2 min using Bass technique with fluoride dentifrice (1450 ppmF) twice a day, and counselling on dietary habits	QLF Changes in lesion area and average change in fluorescence (Mean ± SEM)	Measurements after 6 months showed that repeated fluoride applications had a favorable effect on remineralisation of WSL
Truin and van't Hof, 2007/ Netherlands	Double-blind RCT	Three dental clinics; The Netherlands	1% Neutral NaF gel (n = 161)	8 semiannual periods	Placebo gel (n = 161)	Regular preventive treatment included oral hygiene instruction, followed by supervised tooth brushing with fluoride toothpaste	Clinical: Marthaler criteria (Mean % ± SE)	Professionally applied fluoride gel showed no statistically significant caries-inhibiting effect on both enamel and dentin lesions in permanent dentition of low-caries children

RCT: randomised clinical trial; NaF: sodium fluoride; APF: acidulated phosphate fluoride; DMFS: decayed, missing, filled surface; WSLs: white spot lesions; QLF: quantitative light-induced fluorescence; RR: relative risk; SE: standard error; SEM: standard error of mean.

Figure 2. Risk of bias assessment using the recommended Cochrane tool for RCTs (RoB 2).

interventions[26,28,30,31]. These deviations arose because people who delivered the intervention were not blinded to it.

Results of individual studies

The results of individual studies are summarised in Table 4. From the studies that evaluated the effect of 5% sodium fluoride (NaF) varnish,[25,27,28,30] two addressed 5% NaF varnish in comparison to usual home care oral hygiene, revealing no additional benefits of varnish to the remineralisation of WSLs.[28,30] Others assessed the 5% NaF varnish effect compared to a placebo solution (saline solution)[25] or placebo paste (fluoride-free deliquescent toothpaste).[27] Although these studies had different types of comparison groups, they showed similar results. One found that 5% NaF varnish application was effective in reversing WSLs after orthodontic debonding[25] and the other concluded that 5% NaF varnish application compared to a fluoride-free deliquescent toothpaste might induce remineralisation after orthodontic therapy.[27] Similarly, repeated applications of 1.5% ammonium fluoride varnish compared to professional tooth cleaning had a favourable effect on the remineralisation of WSL.[31]

Four studies evaluated the effects of different types of fluoride gel.[24,26,29,32] Considering the 1.23% APF gel, studies compared its effect with a placebo gel[24] or paste[29] on lesion remineralisation. Although the articles evaluated the same type of fluoride gel, the first study showed no additional benefits of using APF gel in the arrest of carious lesions[24] and the second article revealed that the remineralisation effect may be improved with 1.23% APF fluoride gel application.[29]

A study assessed the efficacy of 1% neutral NaF gel compared to placebo gel and showed no additional benefit in the treatment of incipient carious lesions.[32] Conversely, a study that investigated the effect of 2% neutral NaF gel compared to no treatment concluded that the neutral NaF gel applied three times over 10 days was effective in reducing the area

Table 4. Results of individual studies.

Author, year/Country	Outcome assessment method	Follow-up	Intervention	Control
Bonow et al., 2013/Brazil	DMFS (RR)	2 months	2.18 (0.95-5.00); Adjusted 1.65 (0.69-3.96)	1.00
Du et al., 2011/China	DIAGNOdent (Mean ± SD)	Baseline	17.66 ± 5.36	16.19 ± 5.70
		3 months	11.88 ± 4.27	13.75 ± 4.76
		6 months	10.10 ± 4.86	13.10 ± 5.19
Ebrahimi et al., 2017/Iran	Photographic assessment: Area mm^2 (Mean ± SD)	Baseline	9.39 ± 0.59	9.35 ± 0.66
		10 days	8.54 ± 0.37	9.00 ± 0.45
	Mineral content (Mean ± SD)	Baseline	1.21 ± 0.038	1.19 ± 0.047
		10 days	1.14 ± 0.053	1.16 ± 0.042
He et al., 2016/China	QLF mm^2x% (Mean±SD)	Baseline	41.86 ± 45.29	34.12 ± 41.32
		3 months	25.03 ± 30.18	28.06 ± 35.00
		6 months	19.13 ± 23.77	26.21 ± 31.96
Huang et al., 2013/USA	Photographic assessment: Percentage of area affected (Mean±SD)	2 months	24.6 ± 24.3	17.2 ± 18.6
Mendes et al., 2018/Brazil	DIAGNOdent (Median (1^{st}; 3^{rd} quartiles))	Baseline	19 (16;25)	18 (15;29)
		8 days	11 (6;21)	22 (13;26)
		1 month	6 (4;11)	16 (12;26)
		3 months	14 (6;18)	14 (7;19)
Singh et al., 2016/India	DIAGNOdent (Mean ± SD)	Baseline	105.54 ± 25.20	131.43 ± 41.42
		1 month	107.67 ± 27.73	134.00 ± 45.14
		3 months	102.61 ± 34.90	121.93 ± 37.31
		6 months	88.85 ± 30.41	118.71 ± 46.46
	Boyd score (Mean ± SD)	Baseline	12.31 ± 6.45	15.71 ± 7.94
		1 month	8.85 ± 6.22	12.12 ± 8.41
		3 months	7.46 ± 5.47	10.57 ± 8.18
		6 months	5.00 ± 3.03	7.71 ± 7.66
Tranaeus et al., 2001/ Sweden	QLF Changes in lesion area (Mean ± SEM)	6 months	-0.152 ± 0.056	-0.006 ± 0.047
	QLF Average change in fluorescence (Mean ± SEM)	6 months	-0.107 ± 0.032	-0.008 ± 0.027
Truin and van't Hof, 2007/ Netherlands	Marthaler criteria (Mean % ± SE)	48 months	Regressed 51 ± 5%	50 ± 5%
			Unchanged 36 ± 5%	38 ± 5%
			Progressed 12 ± 3%	12 ± 3%

DMFS: decayed, missing, filled surface; QLF: quantitative light-induced fluorescence; SD: standard deviation; RR: relative risk; SE: standard error; SEM: standard error of mean.

and increasing the mineral content of permanent teeth WSLs in children.[26]

Certainty of evidence

According to GRADE (Table 5), the certainty of evidence from the evaluated studies was classified as low, considering the outcome for both materials. Three studies assessing fluoride varnish and one evaluating fluoride gel were rated as some concerns for risk of bias, and the results differed across all included studies, thus explaining the downgraded risk of bias and inconsistency.

Table 5. Quality of evidence assessment according to the Grade.

N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Importance
Remineralisation of incipient carious lesions in permanent teeth – Professionally applied topical fluoride varnish compared to usual home care control, placebo, or no intervention									
5	randomised trials	serious[a]	serious[b]	not serious	not serious	none[c]	Five studies assessed the therapeutic effect of fluoride varnish for incipient carious lesions, finding different results. Three studies observed that fluoride varnish was effective in the lesions remineralisation and the others found that the varnish does not appear to be more effective than usual home care.	⊕⊕◯◯ LOW	IMPORTANT[d]
Remineralisation of incipient carious lesions in permanent teeth – Professionally applied topical fluoride gel compared to usual home care control, placebo, or no intervention									
4	randomised trials	serious[e]	serious[f]	not serious	not serious	none[c]	Four studies assessed the therapeutic effect of fluoride gel for incipient carious lesions, finding different results. Two studies observed that fluoride gel was effective in the lesions remineralization and the others found that the gel does not appear to be more effective than the control group.	⊕⊕◯◯ LOW	IMPORTANT[d]

Discussion

This systematic review investigated the available evidence from RCTs on the effect of topical fluorides (gel/varnish) on the treatment of incipient carious lesions in permanent teeth. Based on the findings, we observed that the individual results of the included studies showed different trends, with some concerns or low risk of bias. Five RCTs concluded that topical fluoride application may be effective in reversing incipient enamel carious lesions in permanent teeth,[25-27,29,31] three of which investigated fluoride varnish use. Hence, fluoride varnish seems to be effective in caries therapy, corroborating the findings of a previous systematic review.[33] Although our results are similar to those of a previous review,[33] they included studies that evaluated primary dentition as well, unlike ours, which assessed only the permanent dentition.

Four included studies[24,28,30,32] did not show any additional benefits of professional fluoride use for the remineralisation of incipient lesions. However, these results should be interpreted cautiously. Different application protocols and types of control groups (placebo gel/paste/solution, toothbrushing with fluoride dentifrices, no intervention, professional tooth cleaning) were used in the included studies, which might explain the different findings among the articles. Furthermore, two studies were classified as low risk of bias and the others were rated as having some concerns.

Four studies assessed the effect of 5% NaF varnish and found different results, with some concerns or low risk of bias.[25,27,28,30] The studies in which fluoride varnish was considered effective in WSL remineralisation used a saline solution[25] and a fluoride-free deliquescent toothpaste[27] as controls and applied the varnish over a six-month period. On the other hand, studies that compared the single application of 5% NaF varnish with usual home care oral hygiene (with fluoride dentifrice) found that the varnish does not appear to be more

effective than normal home care in improving the appearance of WSL.[28,30]

Bonow et al.[24] evaluated the efficacy of 1.23% APF gel in comparison with a placebo gel, and both groups received toothbrushing instructions and fluoridated dentifrice, demonstrating the equivalence between the control and intervention groups. Even though different assessment methods have been used among studies, the results obtained by Bonow et al.[24] corroborate the findings of Huang et al.[28] and Singh et al.,[30] where no additional benefits were observed for professionally applied fluoride compared to usual home care oral hygiene.

Regarding the results of the included studies that demonstrated no additional benefits of topical fluoride use,[24,28,30,32] it is worth mentioning that they had applied some source of fluoride to the comparison group, such as toothbrushing with fluoridated dentifrice. Furthermore, other studies have demonstrated that toothbrushing with fluoridated dentifrices can arrest the development of WSLs.[20,37]

Remarkably, the mechanism of action of topical fluoride agents is different. The effect of fluoride dentifrices derives from frequent low-dose application, which delivers fluoride daily to the dental surface.[7,8,10,11] On the other hand, professionally applied fluoride gel or varnish delivers fluoride at high concentrations to exposed tooth surfaces, forming a fluoride reservoir for a local effect and for a certain period.[14]

This way, studies[24,28,30,32] in which some source of fluoride was applied to the comparison group probably showed no difference because the dentifrice provided dental surfaces with fluoride on a daily basis without the need for additional fluoride application to form a reservoir. By contrast, studies that used a saline solution[25] and a fluoride-free deliquescent toothpaste[27] as controls revealed fluoride varnish was effective in the remineralisation of WSLs.

In fact, as shown by previous studies, regular home care oral hygiene (toothbrushing with fluoride dentifrice) plays an important role in caries therapy and is sufficient to arrest noncavitated incipient carious lesions, avoiding fluoride overtreatment and reinforcing the relevance of toothbrushing with fluoride dentifrice for caries treatment.[24,28,30] Moreover, in our review, we observed that the studies[25,27] in which 5% NaF varnish was applied for a longer period (6 months), there were favourable outcomes, with low risk of bias. By contrast, some studies that used a single application of 5% NaF varnish demonstrated no additional benefits of topical fluoride use, with some concerns regarding the risk of bias[28,30]. Therefore, fluoride application protocols with a longer period may be more effective for the treatment of incipient carious lesions. However, there is no established fluoride varnish application protocol in the literature as a recommendation for the treatment of incipient carious lesions, and more RCTs on this topic are needed.

It seems that usual home care oral hygiene with fluoride toothpaste may be sufficient to treat incipient carious lesions in permanent dentition, without the need for professional topical fluoride application. Studies that compared fluoride varnish with usual home care oral hygiene (fluoride-containing dentifrice) found that the varnish does not appear to be more effective than normal home care in improving the appearance of WSLs.[28,30]

The main limitation of this systematic review was the considerable heterogeneity of the included studies, which did not allow us to conduct a meta-analysis and draw more compelling conclusions. Different assessment methods, criteria, and parameters were adopted to evaluate carious lesions, such as clinical and photographic assessments, laser-induced fluorescence, and QLF. No studies that used clinical parameters to assess the outcomes found statistical differences between the groups. Conversely, articles that assessed the outcome through QLF measurements revealed a favourable effect in the intervention group compared to the control group. Note that the use of parameters such as QLF to evaluate the remineralisation of lesions can eventually overestimate the effect of the treatment, showing outcomes that are not clinically perceptible. Thus, clinical examination with well-established and objective criteria should be prioritised for this type of outcome. Future research should also include patient-centred outcomes, such as the impact on quality of life, to assess the effectiveness of these therapies in the treatment of incipient caries.

Additionally, there was no consensus on how data were presented in the studies, given that mean and

standard deviation, mean percentage, median, and relative risk were reported. The evaluation methods and presentation of data in a study are a critical and fundamental part of the research; hence, studies must follow a standard for increasing the probability of quantitative comparison studies. Although our research question is simple, it is a relevant issue for clinical practice with a great impact on the routine of dentists; thus this issue should be further investigated through RCTs. Currently, many complex studies have been developed, and basic questions with great impact on clinical practice have been underexplored, making it difficult for clinicians to make a decision based on solid scientific evidence.

RCTs addressing the effectiveness of professionally applied topical fluoride in the treatment of incipient dental carious lesions in permanent dentition are scarce. Therefore, more studies with greater methodological rigor and standardization are required and should be developed with appropriate analysis to reduce bias and allow a meta-analysis.

Registration and protocol

This review has been registered on PROSPERO under protocol number CRD42019120406.

Conclusions

It seems that usual home care oral hygiene with fluoride toothpaste may be sufficient to treat incipient carious lesions in permanent dentition. However, few RCTs have addressed the effectiveness of professionally applied topical fluoride in the treatment of incipient carious lesions in permanent dentition. Therefore, more studies with greater methodological rigor and standardization are required to reduce bias, allow a meta-analysis, and gather more compelling evidence.

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