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Review

Preventive Effect of Professional Fluoride Supplements on Enamel Demineralization in Patients Undergoing Fixed Orthodontic Treatment: A Systematic Review and Meta-Analysis

Elham Babadi Oregani[1], Alireza Jafari[2], Seyed Masoud Sajedi[3], Saeed Reza Motamedian[4]

[1]Under graduate student, Student Research Committee, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Prosthodontics, School of Dentistry, Bushehr University of Medical Sciences, Bushehr, Iran
[3]Department of Oral and Maxillofacial Medicine, School of Dentistry, Shahed University, Tehran, Iran
[4]Department of Orthodontics, Dentofacial Deformities Research Center, Research Institute of Dental Sciences, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Main Points

- Following evaluation of a total of 615 articles, 7 articles were included in this systematic review and 3 of them were analyzed quantitatively.
- Application of fluoride varnish with at most 3 months interval or daily use of mouthwash or high-fluoride toothpaste reduces the number of white spot lesions (WSLs) in patients undergoing orthodontic treatment.
- One study reported that one-time use of fluoride varnish has no significant effect on WSLs, and orthodontists should apply fluoride varnish multiple times (4-20 times, at least every 12 weeks) during treatment.

ABSTRACT

Objective: The current study aimed to systematically review the randomized clinical trials assessing the preventive effect of professional fluoride interventions on enamel demineralization in patients undergoing fixed orthodontic treatment.

Methods: The electronic search was performed in PubMed and Cochrane library in September 2021. No restriction was set on the publication date. Randomized clinical trials assessing the preventive effect of fluoride varnish, gel, mouthwash, and high-fluoride toothpaste on white spot lesions compared to the control group by clinical or radiographic methods in more than 10 patients were included.

Results: A total of 7 articles consisting of 1418 participants were included. In 4 articles, fluoride varnish (contained a range of 1000-50 000 ppm fluoride) was applied multiple times (4-20 times) in test groups. Their results indicated that the test groups significantly had lesser new white spot lesions or advanced white spot lesions. One study used fluoride varnish only once at the beginning of treatment and reported no significant difference in white spot lesions compared to the control group. Application of high-fluoride toothpaste as well as fluoride mouthwash, also, showed significantly lower white spot lesions. Three studies were included in the meta-analysis and revealed that the relative risk of white spot lesions was 0.64 (95% CI = 0.40 to 0.89; $P < .01$) in favor of fluoride varnish.

Conclusion: Multiple applications (4-20 times) of fluoride varnish or daily use of fluoride mouthwash or high-fluoride toothpaste seem to reduce white spot lesions in patients undergoing orthodontic treatment. However, single use of fluoride varnish was not effective. Further research is needed to establish the required number of fluoride applications for the prevention of white spot lesions during orthodontic treatment.

Keywords: Fluorides, fluoride varnish, orthodontics, white spot lesion, systematic review

Corresponding author: Saeed Reza Motamedian, e-mail: drmotamedian@gmail.com

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INTRODUCTION

Orthodontic treatments are performed not only to correct the jaw and teeth malpositions but also to improve the aesthetic aspects of patients.[1] However, its potential disadvantages such as tooth demineralization must be considered because it harms the esthetic outcome of orthodontic treatment and untreated white spot lesions (WSLs) may progress to tooth caries. Orthodontic brackets affect the oral cavity and microbial variables and also provide a large area for cariogenic bacteria to adhere to the teeth and make oral hygiene more difficult.[2,3] So, enamel demineralization or WSLs formation is one of the most common adverse effects of orthodontic treatments including fixed appliances.[4] A meta-analysis reviewing 14 articles reported a total of 68.4% for prevalence and a total of 45.8% for incidence of WSLs after orthodontic treatment.[5] Tufekci et al.[6] revealed that WSLs had occurred rapidly during the first 6 months of treatment that continued to rise at a slower rate to 12 months (prevalence of WSLs before, at 6 months, and 12 months were 11%, 38%, and 46%, respectively). Similar findings were reported in the studies of Lucchese et al.[7] Farishta et al.[8] and Kawsar et al.[9] Although several methods have been proposed to remineralize the enamel (e.g., topical fluoride, amorphous calcium phosphate, or self-assembling peptides) or to mask and improve the esthetic appearance of these lesions (e.g., bleaching, micro-abrasion, or resin infiltration), there is little reliable scientific evidence of the efficacy of remineralization methods,[10] hence, it would be better to prevent tooth demineralization during orthodontic treatment.

There are different methods to prevent or reduce the development of tooth demineralization, including improvement of oral hygiene,[11] casein phosphopeptide-amorphous calcium phosphate application,[12] toothpaste or gel with a high concentration of fluoride,[13,14] different sealants,[15] using bioactive resin adhesive,[16] as well as fluoride mouthwash and varnish.[17-22] Fluoride supplements such as varnish release fluoride ions during the treatment period.[23] Fluoride ions substitute some hydroxyl ions of hydroxyapatite in the tooth structure and create fluorohydroxyapatite. The solubility product constant (K_{sp}) for fluorapatite is lower because of its more compact crystal structure, and therefore, it resists acid attack better.[24] Also, fluoride has cariostatic mechanisms that improve oral hygiene and prevent enamel demineralization.[25] Ekenback et al.[26] revealed that fluorides could reduce lactic acid formation in associated growing biofilms of *Streptococcus mutans*.[26] Amine fluorides in enough concentration could reduce the number of *Streptococcus sobrinus* and inhibit glucosyltransferase activity in the biofilm system.[27] Also, fluoride agents could lead to mineral crystallite growth with preferential calcium uptake.[28]

There is a controversy regarding the effectiveness of fluoride supplements on WSL prevention during orthodontic treatment. Some studies revealed that fluorides can reduce enamel demineralization,[18,19] whereas some others reported that the fluorides have no significant effect on WSLs formation.[17,22] In addition, a recent study[17] that had opposite results compared to previous reviews necessitated updating previous systematic reviews. The current study aimed to systematically review articles assessing the preventive effect of professional fluoride interventions on the prevention of enamel demineralization in patients undergoing fixed orthodontic treatment.

METHODS

Eligibility Criteria

The title of the current systematic review was according to the Participants-Intervention-Comparison-Outcome-Study design framework as follows: (I) Preventive effect of professional fluoride supplements (C) compared to placebo or control group on (O) enamel demineralization in (P) patients undergoing fixed orthodontic treatment. Preferred reporting items for systematic review and meta-analysis (PRISMA[29]) reporting guidelines were followed to conduct this study. The inclusion and exclusion criteria for articles are presented in Table 1.

Information Sources

The electronic search was performed in Medline via PubMed and Cochrane library in November 2020 and updated in September 2021. The references of included studies and previous systematic reviews were also reviewed to identify any potential study to be included in this study.

Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
P = fixed orthodontic patient	More than 10 orthodontic patients with fixed appliances. No restriction on sex, age, or systematic condition.	Assessing the effects of fluorides after debonding on the treatment of WSLs
I = professional fluoride supplements	Fluoride varnish, mouthwash or gel, and toothpaste with a high concentration of fluoride.	Combination of fluoride with other agents
C = control group	No treatment or placebo	
O = enamel demineralization	Prevention of orthodontically induced white spot lesion formation Clinical visual assessment or radiographic methods should be performed to assess the amount of enamel demineralization.	Treatment of orthodontically induced WSLs Evaluation of tooth demineralization by sectioning methods
S	Randomized clinical trials	

WSLs, white spot lesions.

Search
Table 2 presents the search queries, including the combination of keywords. The search was restricted to the English Language. No restriction was set on the publication date.

Study Selection
After the electronic search, the lists of obtained studies were entered into Endnote20 software and duplicate papers were excluded. Then, one of the authors (E.B.) screened the titles and abstracts of the remaining studies according to inclusion and exclusion criteria. Full texts of the selected studies were assessed for eligibility to include in the current study. Any uncertainty over the final inclusion was resolved through discussion with the second author (S.R.M.).

Data Collection Process
The characteristics and data from included studies were extracted by one of the authors (E.B.) and checked independently by the second author (S.R.M.).

Data Items
The data extraction includes items as follows: author and year of publication, study design, sample size, demographic details of the study participants, type of intervention (fluoride varnish, mouthwash, or toothpaste), type of control (placebo or no treatment), frequency of application, duration of follow-up, type of outcome assessment, and results. For the meta-analysis, the number of patients without WSLs and who had at least 1 WSL in both test and control groups were also extracted.

Risk of Bias in Individual Studies
The included articles were assessed according to the Cochrane risk of bias tool. The following domains were used to evaluate the risk of bias: random sequence generation and allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome, selective reporting, and other bias. The articles were considered in the low risk of bias (if it was a low risk of bias for all key domains) or unclear risk of bias (if it was low or unclear risk of bias for all key domains) or high risk of bias (if it was high risk of bias for one or more key domains).[30]

Summary Measures
To evaluate the preventive effect of fluoride varnish on WSLs, relative risks (RR) were computed. In collecting information, where data were missing, they were calculated based on data presented in tables or graphs in the articles.

SYNTHESIS OF RESULTS

Meta-analysis was performed by STATA 16 software on RR and its 95% CI. The impact of between-study heterogeneity was assessed by interpreting the forest plot by calculating the I^2 statistics and Cochrane Q statistics. As heterogeneity was detected among included studies, a random model following maximum likelihood was used.

RESULTS

Study Selection
Figure 1 shows the PRISMA flowchart of study selection. A total of 615 articles were obtained in search, and after the screening, the full texts of 34 articles were assessed for eligibility and quality. Ultimately, 7 articles were included in this systematic review, and 3 of them were entered into quantitative analysis.

Study Characteristics
The study characteristics are presented in Table 3. A total of 1418 participants were included;188 participants were in the high-fluoride toothpaste group, 36 participants were in the fluoride mouthwash group, 418 participants were in the varnish fluoride groups, and 636 participants were in the control groups. Also, 140 participants were in other test groups whose interventions were not considered in the current study.

The design of all articles was parallel-group RCTs.[14,17-22] In 5 of them,[17,18,20-22] the effect of varnish fluoride, in one of them,[19] the effect of fluoride mouthwash, and in another one,[14] and the effect of high-fluoride toothpaste were assessed.

In 4 varnish fluoride studies, participants in test groups received fluoride varnish several times (4-20 times) during their treatment, whereas, those in control groups received placebo varnish or no treatment.[17,18,20,21] Kirschneck et al.[22] applied 2 types of fluoride varnish for patients in the test groups just once at the beginning of the treatment and used placebo varnish for patients in the control group. In the study of van der Kaaij et al.[19], participants used fluoride and placebo mouthwash in test and control groups at home, respectively. In the study of Sonesson et al.[14], participants in the test group had to brush twice a day with high-fluoride toothpaste (contains 5000 ppm fluoride), whereas

Table 2. Search query

Database	Search Query
PubMed	("Orthodontic appliances, Fixed"[MeSH] OR "Orthodontic bracket"[MeSH] OR "Orthodontics"[MeSH] OR "Orthodontic treatment") AND ("Dental cavity lining"[MeSH] OR "Allsolution fluoride varnish"[MeSH] OR "Bifluoride 12"[MeSH] OR "Fluorides"[MeSH] OR "Mouthwashes"[MeSH] OR "Paint"[MeSH] OR "Fluorides, Topical"[MeSH] OR "amine fluoride solution"[MeSH] OR "amine fluoride gel"[MeSH] OR "toothpastes"[MeSH] OR "dentifrices"[MeSH] OR "Varnish fluoride" OR "fluoride gel" OR "gel" OR "amine fluoride") AND ("Tooth demineralization"[MeSH] OR "early enamel lesion" OR "White spot lesion")
Cochrane	("Orthodontic appliances, Fixed" OR "Orthodontic bracket" OR "Orthodontics" OR "Orthodontic treatment") AND ("Dental cavity lining" OR "Allsolution fluoride varnish" OR "Bifluoride 12" OR "Fluorides" OR "Mouthwashes" OR "Paint" OR "Fluorides, Topical" OR "amine fluoride solution" OR "amine fluoride gel" OR "toothpastes" OR "dentifrices" OR "Varnish fluoride" OR "fluoride gel" OR "gel" OR "amine fluoride") AND ("Tooth demineralization" OR "early enamel lesion" OR "White spot lesion")

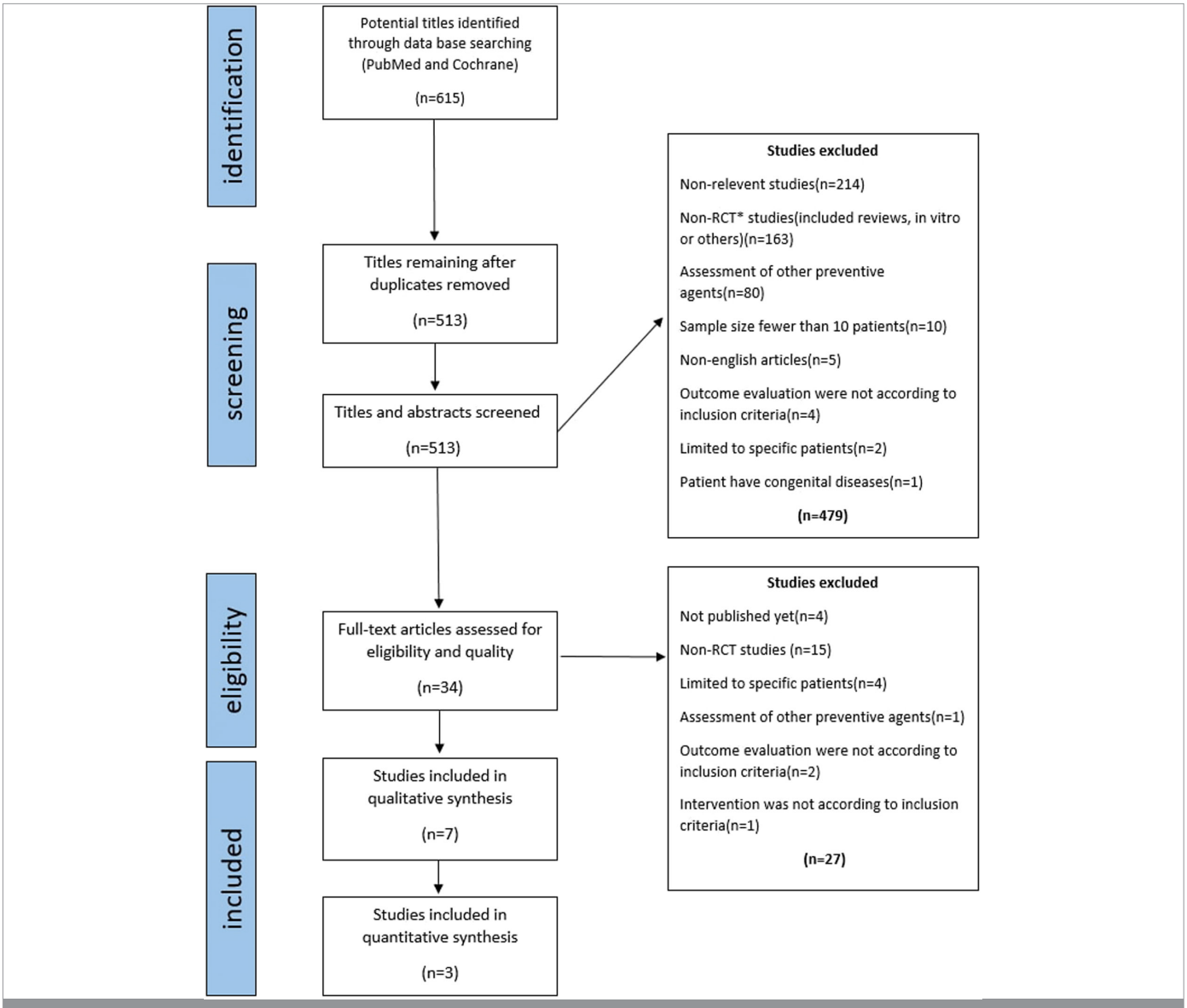

Figure 1. Preferred reporting items for systematic review and meta-analysis flowchart

participants in the control group had to use a toothpaste containing 1450 ppm fluoride for brushing.

In order to evaluate the numbers of WSLs, digital photographs,[14,17,18,20] quantitative light-induced fluorescence images,[19] clinical examinations,[21] as well as the ICAD index[22] were used.

Risk of Bias Within Studies

Figure 2 shows the risk of bias assessment of 7 included articles. Five out of 7 articles were low risk of bias and others were high risk of bias.

RESULTS OF INDIVIDUAL STUDIES

Results of 5 out of 7 studies[14,17-21] in which participants received varnish fluoride multiple times or they used fluoride mouthwash or high-fluoride toothpaste daily indicated significant differences between test and control groups; the number of WSLs or advanced WSLs or ICAD index value was lesser in the fluoride groups. In the study of Kirschneck et al.[22] in which the fluoride varnish was applied only once, there was no significant effect on WSLs compared to the control group.

SYNTHESIS OF RESULTS

The meta-analytical overall estimate of 3 studies with multiple applications of fluoride varnish is demonstrated in Figure 3. Meta-analysis indicated the studies were heterogeneous (I^2 = 63.63%; P = .01). The results of the meta-analysis revealed the data were in favor of using fluoride varnish and the RR was 0.64 (95% CI = 0.40 to 0.89; $P < .01$).

DISCUSSION

Summary of Evidence

Early enamel demineralization usually occurs during orthodontic treatment with fixed appliances. There are different methods to prevent this event. The current systematic review summarized

Table 3. Data extraction

Study	Design	Sample Size; Number of Arms	Age; Sex	Intervention	Control Group	Dose, Frequency, and duration	Duration of Follow-Up	Outcome Assessment	Result
Sonesson et al.[20]	Parallel group RCT	142 2 arms T* = 71 C* = 71	12-18 years F = 58% M = 42 %	Varnish contained 7700 ppm fluoride as ammonium fluoride	Varnish contained no fluoride	A thin layer every sixth week 13.2 times	1.7 years SD = 0.45	Digital photos	WSLs: test < control
Sonesson et al.[17]	Parallel group RCT	148 2 arms T = 75 C = 73	12-18 years F = 58% M = 42 %	Varnish contained 7700 ppm as ammonium fluoride	Varnish contained no fluoride	A thin layer every sixth week	1.7 years SD = 0.5	Digital photos	Advanced WSLs: test < control
Kirschneck et al.[22]	Parallel group RCT	90 3 arms T1 = T2 = C = 30	10-17 years	T1 = elmax fluid varnish (10 000 ppm fluoride as amine fluoride) T2 = fluor protector S varnish (7700/29 000 (dried) ppm fluoride as ammonium fluoride)	Placebo varnish	One time; a thin layer (0.2-0.3 mL) varnish	20 weeks	Assessment of ICADS index	ICADS index: No difference between groups
Van der Kaaij et al.[19]	Parallel group RCT	81 2 arms T = 36 C = 45	10-16 years M = 35 F = 46	Mouth rinse contained 250 ppm fluoride	Fluoride-free placebo rinse	Daily; 100 ppm amine fluoride and 150 ppm sodium fluoride	24.5 ± 5.5 months	Assessment of DMFT and ICDAS, QLF images for assessment of WSLs	WSLs: test < control
Sonesson et al.[14]	Parallel group RCT	380 2 arms T = 188 C = 192	11-16 years	T: high fluoride toothpaste (containing 5000 ppm sodium fluoride)	Regular fluoride toothpaste (containing 1450 ppm sodium fluoride)	Brushing twice a day; 2 cm (approximately 1 g) on brush	1.8 years SD = 0.53	Digital photos	WSLs: test < control
Stecksen Blicks et al.[18]	Parallel group RCT	257	12-15 years	Fluoride varnish	Placebo	Every check-up visit;	When the	Digital photos	WSLs:

(*Continued*)

Table 3. Data extraction (continued)

Study	Design	Sample Size; Number of Arms	Age; Sex	Intervention	Control Group	Dose, Frequency, and duration	Duration of Follow-Up	Outcome Assessment	Result
Stecksen Blicks et al.[18]		T = 132 C = 125		contained 1000 ppm fluoride as difluorosilane	varnish	0.2-0.3 mL 4-20 times	treatment ended		test < control
Ogaard et al.[21]	Parallel group RCT	320 3 arms T1 = 110 T2 = 110 C = 100	12-15 years	T1 = antimicrobial chlorhexidine and fluoride varnishes (50 000 ppm fluoride as difluorosilane) T2 = fluoride varnish (50 000 ppm fluoride as difluorosilane)	No treatment	Every 12 weeks	When the treatment ended	Clinical examination	WSLs: test2 < control

RCT, randomized clinical trials; T, test group; C, control group; F, female; M, male; SD, standard deviation; WSLs, white spot lesions; ICADS, International Caries Detection and Assessment System; DMFT, decayed, missing, and filled teeth; QLF, quantitative light-induced fluorescence.

evidence from RCTs on the preventive effect of professional fluoride supplements on enamel demineralization in undergoing fixed orthodontic patients. Results were favoring the multiple uses of fluoride varnish, toothpaste, and mouthwash to prevent WSLs. However, it seems that one-time use of varnish fluoride does not have a significant preventive effect.[22] Similarly, Rosin-Grget et al.[25] revealed that the use of topical fluoride agents only one-time has no more caries-protective effect, whereas a constant supply of low levels of fluoride in biofilm, saliva and toothpaste is considered the most beneficial in preventing dental caries.

Varnishes with different concentrations of fluoride are available. Since the current study included studies that had different protocols and frequencies for applying fluoride, and it was not feasible to compare the effect of fluoride concentration on the prevention of WSLs. Yongmei et al.[31] compared 4 varnishes with various concentrations (22 000, 10 000, 5000, and 2200 ppm) and concluded that acid resistance of enamel between 22 000 or 10 000 treatment groups was not significantly different, while both high-dose groups had significantly more acid resistance. Therefore, increasing the concentration of fluoride supplements to some level enhances the preventive effect. Further research is needed to compare the effect of varnishes containing different fluoride concentrations in the patients undergoing orthodontic treatments.

Although the current study included more articles compared to the previous systematic reviews, it was in line with their results. In meta-analysis of Sardana et al.[32] RR was 0.39 (95% CI = 0.26 to 0.59; *P* = .005), and in Tasios et al.[33] it was 0.46 (95% CI = 0.18 to 1.15).

Among 7 articles, 5 were adjudged to be of low overall risk.[14,17,19,20,22] The result of these articles had a controversy about the preventive effect of fluorides. Sonesson et al.[17,20] stated in their studies that the effect of fluoride supplements is only on advanced WSLs. Advanced WSLs are defined as the WSLs with scores 3 and 4 according to the 4-step index of Gorelick et al.[34] In this index, lesions with score 2 are named slight WSLs, and score 1 is associated with patients with no lesions. Kirschneck et al.[22] stated that there was no significant reduction in WSLs formation by using fluorides; however, it seems to be due to the use of varnish only in the initial treatment session and not repeated in subsequent sessions. Another 2 articles[18,21] were adjudged to be of high overall risk. These articles had similar results, using fluoride varnish reduces WSLs formation. Consequently, it is needed to perform studies with better design and pay attention to the risk of bias tools, particularly, blinding and allocation concealment.

The electronic search was performed in 2 search engines (PubMed and Cochrane) and was also limited to the English literature.

CONCLUSION

Evidence from included studies presented that the use of varnish fluoride multiple times (4-20 times) or daily use of high-fluoride

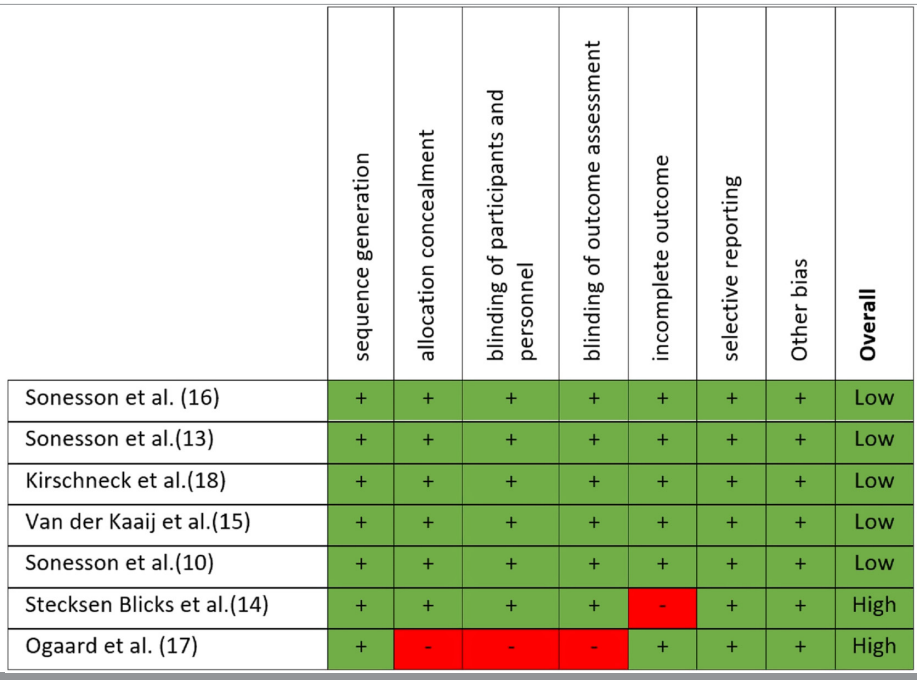

Figure 2. Risk of bias summary

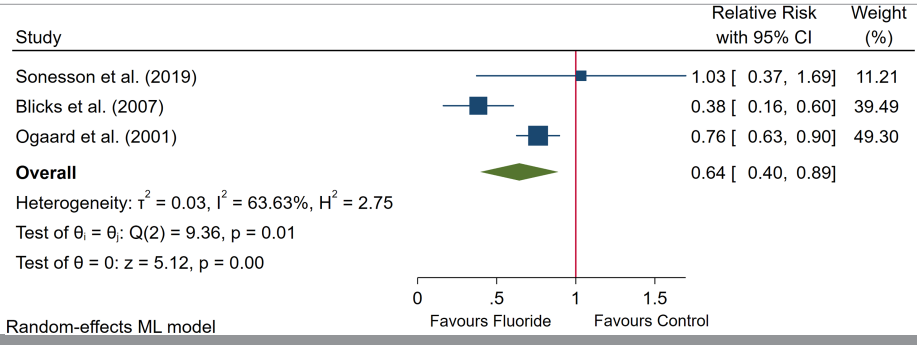

Figure 3. Forest plot comparing the relative risk of fluoride varnish and placebo on white spot lesions in patients undergoing fixed orthodontic treatment

toothpaste or fluoride mouthwash reduces the risk of enamel demineralization during fixed orthodontic treatment. However, a single application of fluoride varnish did not have a significant effect. Further research is needed to establish the most favorable interval of fluoride applications and dose (fluoride varnish, mouthwash, gel, or toothpaste) to prevent WSL formation in orthodontic patients.

Peer-review: Externally peer-reviewed.

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