Efficacy of fluoride varnish in treating orthodontically-induced white spot lesions: a systematic review and meta-analysis

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Objectives: To systematically review the effectiveness of 5% sodium fluoride varnish (FV) in the treatment of orthodontically-induced white spot lesions (WSLs).
Methods: A literature search of three independent databases (Medline, Cochrane Library and Web of Science) was performed from inception to November 2020. This systematic review included randomised/quasi-randomised clinical trials (RCTs) that used FV for patients who had at least one WSL as a result of fixed orthodontic treatment. Exclusion criteria were split-mouth study designs or studies that failed to report WSLs as the outcome variable or studies with less than 3 months follow-up. An Inverse-Variance fixed-effect method was performed for continuous variables. Changes in the mean difference (MD) for the DIAGNOdent (DD) scores following FV application were calculated at the 95% confidence interval (CI).
Results: Three of the four included studies showed significant improvement in the remineralisation of WSL after treatment with FV in comparison to control subjects. Three studies were conducted on patients after fixed orthodontic treatment and one study was conducted during treatment. The studies included a total of 284 participants with the majority in the age range of 10 to 25 years. The distribution of the participants was approximately equal in the FV and control group. When compared with the control group, there was a statistically significant reduction in the mean DD readings for the FV group at the 3-month (MD = -3.43; 95% CI: -4.72 to -2.15; p < 0.001) and at the 6-month (MD = -4.47; 95% CI: -4.72 to -2.15; p < 0.001) follow-up visit.
Conclusions: Although few studies have shown the effectiveness of FV application in the treatment of orthodontically-induced WSLs, the limited number of robust clinical trials, makes it difficult to draw a definitive conclusion.

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Background

Despite the rapid advances in science and nanotechnology, more than three billion people still suffer from untreated dental caries globally.¹ It has remained one of the two most prevalent human diseases alongside untreated periodontal disease. Dental caries occurs due to a dynamic interplay between the host, micro-organisms and the harsh oral environment.² The first indication of this complex interrelationship is the development of white spot lesions (WSLs) which are "subsurface enamel porosities from carious
demineralisation” that presents as “a milky white opacity” when located on smooth surfaces.\(^2,5\) During the first month after the placement of orthodontic appliances these enamel lesions appear as minor lines adjacent to attachments, whilst in some patients, they might progress to large decalcified areas without cavitation.\(^1\) Depending on the types of examination techniques, the estimates, prevalence and incidence of WSLs may vary. Earlier reports suggested a wide prevalence of 23.4 to 96%.\(^4,5\)

The use of fixed appliances for treating malocclusion has become an integral part of modern orthodontics. Of the appliances, brackets, bands and wires further create plaque retentive sites that interfere with a natural self-cleansing ability through the movement of oral musculature and saliva.\(^6\) Recently, the development of sensitive diagnostic techniques including quantitative light induced fluorescence (QLF) has further demonstrated a higher prevalence of WSLs than previously believed.\(^6\)

QLF, which is a visual light-based detection and quantification system, functions by quantifying the loss of fluorescence in a carious lesion in comparison with the fluorescence radiance level of sound enamel.\(^7\) This is indicative of the mineral alterations of incipient enamel lesions.\(^8\) The difference in fluorescent intensities aids in the degree of demineralisation to be quantified.\(^7\) Similarly, DIAGNOdent (DD) has been introduced because of its ability to detect dental caries by irradiating teeth using red light excitation at 655 nm. This system is based on the fact that carious lesions exhibit a stronger fluorescence signal compared with that of the surrounding healthy tooth structure. However, an increment in the readings of DD has sometimes been attributed to bacterial metabolites like protoporphyrin IX, the presence of intrinsic enamel stains and also irregular enamel structure without dental caries.\(^9\) Clinically, the role of visual, QLF and DD techniques have been investigated in a number of studies; however, a clinician cannot totally rely on a particular technique and rather assimilate all of the information and process it in the light of patient’s individual situation.\(^10\)

Dietary carbohydrate control and supplemental fluoride use could not only reduce the incidence but also prevents the progression of dental caries.\(^11\) Fluorides are specifically known to act by creating a remineralised layer resistant to acid and also by aiding the inhibition of microbial enzymes that produce the acid responsible for demineralization.\(^12\) Owing to its beneficial effect in reducing tooth decay, water containing regulated levels of fluoride has long been supplied in several countries as an effective community health intervention.\(^13\) An expert panel convened by the American Dental Association Council on Scientific Affairs and the Center for Evidence-Based Dentistry recommend the use of 5% sodium fluoride varnish (FV) to arrest or reverse non-cavitated carious lesions on the facial or lingual surfaces of permanent teeth.\(^14\) As recently reported in the network meta-analysis, FV showed a 2- to 3-times greater chance of arresting or reversing lesions in primary and permanent teeth compared with no treatment.\(^15\) The use of FV as an effective caries preventive measure is now advocated by several international clinical guidelines.\(^5,16–18\) The FV has also been demonstrated to be proficient in reducing the incidence of caries in both deciduous and permanent dentitions.\(^19\) The varnish with its high fluoride concentration (up to 22,600 ppm), could thereby provide enamel fluoride protection even in non-compliant patients who fail to maintain dietary advice and dental hygiene using fluoride supplements. Data support a sustained release pattern of fluoride in the first six months after application with the highest release seen during the initial three months.\(^20\)

Several systematic reviews and meta-analyses have analysed the effectiveness of remineralising agents in controlling WSLs.\(^5,18,21,22\) However, to date, there are only few studies that have assessed the efficacy of FV in treating orthodontically-induced WSLs. This systematic review aims to summarise the evidence from clinical trials on the efficacy of FV in the treatment of orthodontically-induced WSLs.

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**Methods**

The systematic review was conducted in accordance to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews).\(^23\) The PICO (P = Patient population; I = Intervention of interest; C = Comparative intervention; O = Outcome) question for this study was: “Among patients undergoing or having completed orthodontic treatment with fixed appliances (P), how effective is sodium FV (I) compared with no intervention (C) in the reversal of WSLs (O)?
**Inclusion and exclusion criteria**

The systematic review included randomised/quasi-randomised controlled clinical trials that used FV for patients who had at least one WSL as a result of fixed orthodontic treatment. Only studies that assessed WSLs using clinical, visual or photographic evaluation or used other equipment like DD or QLF were included. Exclusion criteria were: 1) non-English language studies; 2) studies that used a split-mouth study design and 3) studies with less than 3 months follow-up.

**Search strategy**

A total of three databases (Medline, Cochrane Library and Web of Science) were searched from inception to November 1st, 2020, to identify all relevant articles. The literature search used different combinations of the following Medical Subject Headings (MeSH) and other keywords: “tooth remineralisation”, “white spot lesion”, “dental caries”, “orthodontic appliance” and “fluoride varnish”. Filters applied were: 1) clinical trials and 2) studies in humans (Figure 1). Furthermore, the reference lists of the included studies and previous reviews were thoroughly searched to identify any potential article to be included in this review.

**Study selection**

The titles and abstracts were screened by two independent reviewers (AAR, AAS) to find relevant studies defined by the present inclusion/exclusion criteria. In cases of discrepancies in the results, a third reviewer (JKB) was consulted. Cohen’s kappa coefficient was calculated to ascertain the level of inter-rater reliability.

**Quality assessment**

The quality of the selected RCTs and the risk of bias were assessed using the Cochrane risk-of-bias tool. The composite assessment of the included RCTs
was comprised of different types of systematic errors including selection bias related to limitations during recruitment of study participants, performance bias related to the balance between the comparable groups with respect to non-intervention variables, detection bias related to an appropriate measurement of the study outcome, attrition bias related to retention of the study participants through the study duration, reporting bias related to study design that may influence the study outcome, and conflict of interest bias related to financial interest of the authors in effecting the reported results. Clearly, each of these biases could lead to over- or underestimation of the outcome with respect to the true outcome. RCTs had a low risk of bias when all bias domains were rated as low risk; the risk of bias was considered to be unclear when one or more bias domains had an uncertain result; the risk of bias was high when one or more bias domains were rated as high risk. Any discrepancy in the categorisation of different types of biases among the reviewers was further resolved by seeking the opinion of an additional reviewer (Figure 2). In addition, the included articles underwent a quality assessment using the Critical Appraisal Skills Program (CASP) checklist (Table I).

Data collection and process

Data on the diagnostic criteria, population characteristics, dental hygiene protocol adopted, treatment assigned to both intervention and control arm, study duration, frequency of treatment and the conclusions made by the authors were extracted from the included studies (Table II).

Summary measures and synthesis of results

Inverse-Variance (IV) fixed-effect method was performed for assessing the changes in the mean DD scores following FV application. Studies which used DD for assessment of WSLs were included in the forest plot. The difference in means and standard deviations (SD) were calculated at the 95% CI. Statistical heterogeneity was assessed by using Chi-square based Q-statistic method and I-squared measurement with significance indicated by \( p < 0.05 \). Statistical analyses were performed using the Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; 2014).

Results

Selection of studies

The initial search identified a total of 513 articles (Figure 1). A subsequent review of title and the abstract of the articles based on inclusion and exclusion criteria resulted in the shortlisting of 16 articles for full-text screening. After reviewing the selected full text articles, 12 were excluded for reasons detailed and presented in Figure 1. Finally, 4 articles (26–29) were included in this systematic review. The value of Cohen’s kappa (\( \kappa \)) for study selection was 0.84, thereby indicating a strong level of agreement.

Extraction of data

Descriptive characteristics

All the extracted data are listed in Table II. The four included studies (26–29) explored the effect of FV on lowering the severity of WSLs associated with the use of fixed orthodontic appliances. Three studies (26–28) were conducted on patients after fixed orthodontic treatment.
and 1 study was conducted during treatment. The studies included a total of 284 participants between the ages of 12 and 25 years. All the included studies except one, had a follow-up period of six months. The frequency of application of FV varied from once per month for six months to only once at the start of study. Restrepo et al. reported two applications of FV, with a one-week interval between applications. Three studies employed a DD score to examine the lesions and one study used QLF. Furthermore, two studies also employed the additional method of a visual score to assess lesion severity.

High concentration FV (22,600 ppm F) was used as the intervention in the included studies. FV showed significant caries-reducing effect in three of the four included studies. Quality assessment

The quality assessment revealed a low or unclear risk of bias for the majority of the elements in the included studies. Only one study exhibited a high risk of bias due to unclear reporting of the study outcome measures. Furthermore, the included studies were evaluated as having low reporting bias with no risk of results influenced by conflicts of interest (Figure 2).

Synthesis of meta-analysis

The mean difference (MD) in the DD score was calculated for two studies at three- and six-months follow-up. Two of the included studies were excluded from a meta-analysis due to high reporting bias and the use of a different diagnostic method (QLF). The result showed the mean difference in the DD score for the intervention group was significantly lower by 3.43 (95% CI: -4.72 to -2.15; \( p < 0.001 \)) compared with the control group at the third month follow-up visit. Only one of the two studies included for the meta-analysis had a follow-up period of six months. The group that received FV had a significantly lower DD score compared with the control group (MD = -4.47; 95% CI: -4.72 to -2.15; \( p < 0.001 \)) (Figure 3).

Discussion

The present systematic review evaluated the effectiveness of FV application in treating orthodontically-induced WSLs. Since the effectiveness of FV in preventing caries is well-documented, this review focused on the ability of FV to treat WSLs. Three of the included studies showed significant lesion reversal after FV application and one study reported non-significant results.

One of the most common adverse effects of fixed orthodontic treatment is the development of WSLs. A higher incidence of WSLs has been reported among

Table 1. Critical Appraisal Skills Program quality assessment of the included studies.

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<th>Authors</th>
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1. Did the trial address a clearly focused issue?
2. Was the assignment of patients to treatments randomised?
3. Were patients, health workers and study personnel blinded?
4. Were the groups similar at the start of the trial?
5. Aside from the experimental intervention, were the groups treated equally?
6. Were all of the patients who entered the trial properly accounted for at its conclusion?
7. How large was the treatment effect?
8. How precise was the estimate of the treatment effect?
9. Can the results be applied in your context?
10. Were all clinically important outcomes considered?
11. Are the benefits worth the harms and costs?
Table II. Characteristics of the included studies.

<table>
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<tr>
<th>Study</th>
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<td>Author, year</td>
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C, Control group; DD, DIAGNOdent; F, Fluoride; I, Intervention group; QLF, Quantitative light-induced fluorescence; WSL, White-spot lesions.
orthodontic patients compared with non-orthodontic patients. WSLs can develop around the attachments of fixed appliances often within one month after bracket placement, and can progress to frank cavitation within six months. Nearly one-third of orthodontic patients develop at least one WSL as a result of poor oral hygiene and the retention of plaque around orthodontic appliances. The inability to maintain adequate hygiene around brackets is the primary cause for enamel demineralisation and strategies to prevent and reverse WSLs are commonly applied during orthodontic treatment. The first line of treatment for WSLs is the application of remineralising agents. A recent meta-analysis reported that FV is the most effective treatment for arresting or reversing non-cavitated facial/lingual lesions on primary and permanent teeth. Professional topical fluoride application enhances remineralisation of active enamel carious lesions by replacing the depleted calcium and phosphate with fluorapatite. Individual studies have recommended that FV should be routinely used following orthodontic treatment, as it has been shown to reduce the DD values of WSLs. The frequency of fluoride varnish applications varied considerably between the included articles. Singh et al. applied FV once at baseline whereas Du et al. and He et al. had monthly application for six months. Singh et al. observed no supplementary advantage in the remineralisation of WSL after orthodontic therapy by using FV. In contrast, the three other included studies reported a reduction in the DD score after the application of FV. However, to date, no consensus has been reached regarding the appropriate duration and frequency of use of various remineralising agents for either the prevention or reversal of WSLs. However, based on current understanding regarding the mechanism of action of fluoride, it could be assumed that more frequent applications of FV would positively impact the remineralisation process. Studies that used four applications at weekly intervals and three applications at quarterly intervals were effective in reversing active enamel carious lesions in the permanent dentition. Visual methods can aid in assessing the severity of WSLs, but it may not be able to detect minor changes in the enamel structure. Most studies assessing demineralised enamel rely on techniques such as QLF and DD which are highly sensitive measures are used to quantitatively assess WSLs. Bader and Shugars, in their systematic review on DD concluded that DD is more sensitive than traditional diagnostic methods. The relatively high sensitivity of DD is accompanied by an increased likelihood of false-positive diagnoses. In addition, the presence of plaque, calculus, stains or saliva on the tooth surface would affect the DD readings. Additionally, there are only a limited number of studies that have assessed the performance of DD on the facial and lingual smooth surfaces. These factors limit the usefulness of DD as a principal diagnostic tool. In one of the included studies, Restrepo et al., combined two evaluation methods, visual and DD, but found significant outcomes only for the DD scores. It was therefore suggested that an evaluation of WSLs by the combined use of visual assessment and sensitive techniques could be the best method in future research studies.
A recent network meta-analysis comparing different remineralising agents for the prevention and treatment of orthodontically-induced WSLs concluded that FV was the best preventative agent. However, the present review could not make any firm conclusions on the ability of different remineralising agents to treat orthodontically-induced WSLs. Kim et al. assessed the role of additional factors associated with WSL treatment that might explain the difference in the effectiveness of the treatment between patients. The authors suggested that there was a significant relationship between age, the duration of orthodontic treatment, the type of tooth, the area of the lesion, and the frequency of toothbrushing. These findings highlight the importance of ensuring similar baseline characteristics between the intervention and control group.

The development of WSLs is determined by the dynamic balance between pathological factors that cause demineralisation and protective factors that facilitate remineralization. The progression or the reversal of WSLs is therefore dependent upon biological factors in plaque and saliva, the composition of enamel, oral hygiene, dietary habits and exposure to preventive agents. Biofilm control by maintaining good oral hygiene is the most effective method of arresting enamel caries. The effectiveness of interventions cannot be achieved without ensuring adequate daily oral hygiene. All of the included trials reported educating the participants on oral hygiene and recommended the use of fluoridated toothpaste.

A strength of this systematic review involves its adherence to the Cochrane Handbook for Systematic Reviews of Interventions and the assessment of the quality of individual studies using the CASP forms. The present quality assessment confirmed a low risk of bias in most of the reviewed articles. The current review included only RCT’s which are known to provide the best evidence without epidemiological biases. Several published systematic reviews had high heterogeneity values due to differences in the diagnostic criteria, the differences in the treatment time and review periods between the studies. Since the present meta-analysis included only two studies that had a similar diagnostic and reporting criteria, the data were relatively homogeneous. Due to a limited number of studies included in the review, publication bias could not be assessed using funnel plots. In addition, the risk of bias was found to be unclear for several items in the included studies and this may have influenced the results. Lastly, non-standardisation of the control groups and the small number of participants limited the generalisability of the results. The limitations affect the strength of the clinical evidence and make it difficult to draw any meaningful conclusion regarding the effectiveness of FV application in the treatment of WSLs.

Conclusion

Although few studies have shown the effectiveness of FV application in the treatment of orthodontically-induced WSLs, the limited number of robust clinical trials, makes it difficult to draw a definitive conclusion.

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Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors of this manuscript have no competing interests to declare.

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Authors’ contributions
DE, AAR, SBQ, AAL and AAS participated in the design, acquisition of literature and draft preparation. JKB assisted in checking the selected articles, performed and interpreted the statistical analysis and assisted in preparing the study draft. All authors read and approved the final manuscript.

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