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Review article

Effectiveness of professional fluorides against enamel white spot lesions during fixed orthodontic treatment: A systematic review and meta-analysis

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ABSTRACT

Objectives: To systematically review the effectiveness of professionally applied topical fluorides in the prevention and reversal of Enamel White Spot Lesions (EWSLs) occurring during multi-bracketed fixed orthodontic treatment.
Data: Randomized/quasi-randomized controlled clinical trials.
Sources: Four electronic databases and grey literature (up to February, 2018).
Study selection: Two reviewers independently selected studies, extracted data and assessed risk of bias using the Cochrane Risk of bias tool 2.0. Only 11 studies fulfilled the inclusion criteria, seven assessing reversal and four assessing prevention of EWSLs. Six of the eleven studies were included for quantitative synthesis, three assessing prevention and three assessing reversal of EWSLs.
Conclusions: Using the Mantel-Haenszel fixed-effect method, the risk ratio was found to be 0.39 (95% C.I.: 0.26-0.59) in studies evaluating the prevention of EWSLs. On employing an inverse-variance fixed-effect method for mean DIAGNOdent scores, the standardized mean difference was found to be 0.57 less in the professional topical fluoride group than the control group (95% C.I.: 0.23 to -0.91) in studies evaluating reversal of EWSLs. Professional topical fluoride application brought 25–30% reduction in the incidence of EWSLs after debonding; however, the effect of professional topical fluoride application in a reversal of EWSLs was unclear due to the concerns in interpreting DIAGNOdent values to estimate EWSLs.
Clinical significance: Due to a limited number of clinical trials, further research is warranted to identify the type of professional fluoride agent, the concentration of fluoride and the frequency of applications in prevention or reversal of EWSLs in patients undergoing multi-bracketed fixed orthodontic treatment.

1. Introduction

Patients often seek orthodontic treatment primarily to improve their esthetics and functions. However, enamel demineralization, clinically manifesting as Enamel White Spot Lesion (EWSL), is an undesirable but frequent sequela of multi-bracketed fixed orthodontic treatment. These EWSLs can be esthetically unpleasing and unacceptable to the patient as well as treating orthodontist when they develop as a result of fixed orthodontic treatment. A meta-analysis encompassing 14 studies in 2041 patients reported a pooled prevalence of 68.4% and pooled incidence of 45.8% of EWSLs after orthodontic treatment [1]. The range of the prevalence of EWSLs was high but varied considerably (33.8–97%) [2,3] as was the incidence rate (23.4–75.6%) [4,5], thus highlighting the significance of this alarming problem. An increase in the physical plaque retention sites due to brackets, along with a corresponding alteration in the composition of oral microflora (an increase in *S. mutans* and *Lactobacillus* counts), favors the formation of EWSLs in orthodontic patients [6,7]. The presence of fixed orthodontic appliances is known to influence the quantity and quality of oral microflora within one month of fixed orthodontic treatment [6,8]. The enamel demineralization that occurs during treatment can be an extremely rapid process in the absence of any fluoride to the extent that appreciable lesions may develop as early as four weeks from the start of orthodontic treatment [9].

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Topical fluorides have remained the cornerstone in the prevention of dental caries in all populations, irrespective of age, gender, underlying medical conditions and the caries risk of an individual. Self-applied topical fluorides in the form of mouth rinses and dentifrices have been used widely, but these agents depend on the patient compliance with regards to their frequency and the amount used [10]. Despite the long-established use of fluoridated dentifrices and other standardized general prophylactic measures, new EWSLs still develop during fixed multi-bracketed orthodontic treatment, and this has led to the need to consider alternative and additional preventive strategies [10,11]. In contrast to self-applied fluorides, professional topical fluorides provide high concentrations of fluorides over a short time and need to be applied by the healthcare providers, hence the term *"professionally applied."* Professional topical fluorides are applied in the form of gels, foams, and varnishes with an aim to sustain higher concentrations of fluoride on enamel to prevent demineralization and aid in remineralization of already demineralized areas. Post-orthodontic EWSLs can self-improve over eight weeks after debonding depending on various patient-related and tooth-related factors [12], however, these lesions may persist for long-term if no intervention is provided [13]. Hence, the present review aimed to critically appraise the current evidence regarding the role of professional topical fluorides in prevention, as well as the reversal of EWSLs occurring during or after fixed multi-bracketed orthodontic treatment, respectively.

2. Materials and methods

2.1. Protocol and registration

The present review was devised *a priori* by following PRISMA guidelines [14] and the Cochrane handbook [15]. Subsequently, the protocol was registered in the PROSPERO database (CRD42018094782) which can be freely accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID = 94782.

2.2. Eligibility criteria

For the present systematic review, inclusion criteria for the studies were randomized/quasi-randomized controlled clinical trials, in which any form of professional topical fluoride applications have been done in patients undergoing multi-bracketed fixed orthodontic treatment to achieve prevention or reversal of EWSLs. Laboratory-based studies, as well as studies in languages other than English, were excluded from this review. Because of the possibility of a carry-over effect of fluoride in split-mouth study designs, it was decided to exclude such studies from the review. PICO schema (Population, Intervention, Control, and Outcome) for the individual studies were used to determine the eligibility criteria and is presented in Table 1.

Table 2
Literature search on Ovid Medline with the yield (number of hits per keyword) performed on 19th February 2018.

Serial no.	Search key word	Results
	exp ORTHODONTICS/	49391
	orthodontic$.mp.	51617
	(orthodontic and (therapy or treatment)).mp.	21076
	1 or 2 or 3	59575
	exp FLUORIDES/	34773
	exp Sodium Fluoride/	6639
	exp stannous fluoride/	846
	exp fluorides, topical/	4174
	fluoride$.mp.	53306
	(fluoride or APF or acidulated phosphate fluoride or sodium fluoride or fluoride gel or fluoride foam or fluoride varnish).mp.	42784
	5 or 6 or 7 or 8 or 9 or 10	56254
	exp tooth demineralization/	43469
	((dental or tooth or teeth or enamel or dentin$) and (decay$ or cavit$ or demineral$ or remineral$ or "white spot$" or lesion$)).mp.	55485
	12 or 13	85313
	4 and 11 and 14	**514**

2.3. Information sources and literature search

A total of four databases were searched systematically by two independent authors (SD and ZJ) up to February 20, 2018, using the broad keywords and MeSH terms. The four databases searched were: Medline (*via* Ovid), Embase (*via* Ovid), Cochrane library (all databases) and Scopus. No limits were applied to the search strategy regarding the year of publication or current stage of the trial (completed/ongoing). The complete search strategy with the yields is presented in *Appendix 1*. In addition to these four databases, hand-searching of orthodontic journals and other non-specialty scientific journals, which have been publishing studies about EWSLs in patients with multi-bracketed fixed orthodontic treatment was also performed. To identify grey literature, www.opengrey.com was searched to find any registered trial or unpublished material; as well as university databases for conference proceedings and thesis /dissertation. 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. Table 2 summarizes the search strategy used for the Ovid Medline.

2.4. Study selection

After the removal of duplicates, two authors (DS and ZJ) independently scrutinized the titles and their respective abstracts in a standardized manner to decide upon their inclusion/exclusion in the review as defined by the preset inclusion/exclusion criteria. In case, the abstract of an article was not available (as in most of the earlier studies), the full-text reading was performed to decide on its inclusion or exclusion from this review. If the title and abstract of the study were

Table 1
PICO schema to assess the role of professionally applied topical fluoride agents in prevention and reversal of EWSLs occurring during multi-bracketed fixed orthodontic therapy.

	Prevention of EWSLs in patients undergoing multi-bracketed fixed orthodontic therapy	Reversal of EWSLs in patients who underwent multi-bracketed fixed orthodontic therapy
Population	Patients undergoing multi-bracketed fixed orthodontic therapy	Patients having one or more EWSLs after completion of multi-bracketed fixed orthodontic therapy
Intervention	Professionally applied topical fluoride either in the form of gels, foams or varnishes	Professionally applied topical fluoride either in the form of gels, foams or varnishes
Control	Placebo controlled or no control	Placebo controlled or no control
Outcome	Changes in the incidence of EWSLs assessed through clinical evaluation (use of any index) or photographic evaluation or use of any dental caries diagnosis aids (DIAGNOdent, QLF etc.)	Decrease in prevalence of EWSLS; or Changes in the size of EWSLs or its mean fluorescence values obtained from DIAGNOdent, QLF etc.

ambiguous to allow for its exclusion, the study was planned for full-text reading and evaluation. Cohen's kappa coefficient (κ) was calculated to ascertain the level of inter-rater agreement. Any incongruity over the final inclusion was discussed among both authors and opinion from a third author (CY) was solicited if necessary.

2.5. Data collection process

The characteristics of individual studies and their respective statistical data were extracted individually by two authors (DS and ZJ) on a piloted *pro forma*. Disagreements, if any, were resolved by discussion and seeking an opinion from a third author (CY).

2.6. Data items

Information and data pertaining to the following parameters were extracted from each trial: demographic details of the study participants, sample size, type of professional topical fluoride agent used in the trial (gel, foam or varnish) along with its composition and fluoride concentration, type of control (any other fluoride agent, placebo or no treatment), frequency of application in all groups, type of outcome measure (prevention of EWSLs or reversal of EWSLs), methods of assessment of outcome [clinical or visual or photographic evaluation or use of any other equipment like DIAGNOdent or quantitative light-induced fluorescence (QLF)] and follow-up periods.

2.7. Risk of bias in individual studies

Cochrane risk of bias tool (RoB 2.0) [16] was used to contemplate the validity of clinical trials included in this review. This tool evaluates the risks across the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result and finally, the overall bias. A set of signaling questions and algorithm as suggested by the authors of RoB 2.0 tool was used to adjudge the risk of bias for individual domains as low risk, high risk or to be of some concerns. Separate risk of bias assessments was made for trials which evaluated the prevention of EWSLs and trials which evaluated the reversal of EWSLs. Quantitative synthesis was performed if 2 or more studies addressed the same outcome measured in the same way using the similar approach to analysis.

2.8. Summary measures

For binary outcomes (presence or absence of EWSLs or studies assessing the difference in incidence following professional topical fluoride applications), relative risks (RR) was computed and for continuous variables (change in mean QLF scores or mean DIAGNOdent scores following professional topical fluoride applications), difference in means was calculated at 95% confidence intervals.

2.9. Synthesis of results

Where appropriate, because of the expected inter-study heterogeneity, the planned analytical approach was frequentist Inverse-Variance (IV) random-effect meta-analysis. However, when data were sparse (such as the number of studies was less than four), Mantel-Haenszel fixed-effect method was performed for binary variables and IV fixed-effect method for continuous variables [17]. Statistical heterogeneity was assessed by using Chi-square based Q-statistic method and I-squared measurement with significance indicated by $p < 0.05$. Meta-analysis was performed using Stata Version 13.1 (StataCorp, College Station, TX, 2013).

2.10. Risk of bias across studies

Publication bias was planned to be investigated using funnel plot techniques, Begg's rank test and Egger's regression test, as appropriate given the known limitations of these methods [18]. Cochrane RoB tool 2.0 used in the present study also evaluates bias in the selection of reported data, which in turn may occur due to selective reporting from the multiple outcomes evaluated or the multiple analysis of the data. The authors of this review acknowledge that selective reporting is difficult to identify, however, the signaling questions with answers probably yes, yes, no information, probably no & no with the corresponding algorithm in RoB 2.0 tool was used to identify any selective reporting.

2.11. Additional analysis

Sensitivity analysis was performed if necessary based on the inclusion of trials with low risk of bias. Depending on the results, the subgroup analysis was planned by pooling the studies evaluating the same fluoride agent and also from studies having similar follow-up periods. Meta-regression analysis was used to compare the effect of different fluoride agents on EWSLs if a sufficient number of studies were available for pooling the data.

3. Results

3.1. Study selection

Fig. 1 provides an overview of the PRISMA flow diagram of the study selection process instituted in this systematic review. After identification and screening of titles and abstracts, 49 articles were subjected to full-text reading, out of which finally 12 articles [19–30] (equal to 11 studies) were included in the systematic review. The details of the reason for the exclusion of the studies after full-text reading is presented in *Appendix 2*. The value of Cohen's kappa (κ) for study selection was 0.875, thereby indicating a strong level of agreement. Out of the 11 included studies, four assessed the prevention of EWSLs during multi-bracketed fixed orthodontic treatment using professionally applied topical fluorides [19–22]. Remaining seven studies (equal to 8 articles [23–30], since one group of authors presented their study results in two different articles [23,24]), focused on the reversal of EWSLs after multi-bracketed fixed orthodontic treatment using professionally applied topical fluorides. Six studies (3 studies evaluating prevention [19–21] and three studies evaluating reversal of EWSLs [28–30] could be included for meta-analysis, since the outcome assessment of these studies were similar (difference in incidence and mean DIAGNOdent readings for studies $_{\text{PREVENTION}}$ and studies $_{\text{REVERSAL}}$, respectively).

3.2. Study characteristics

The type of professional topical fluoride agents with their respective frequency of applications in all the included studies and the methods of outcome assessments are presented in Table 3.

3.2.1. Studies $_{PREVENTION}$

All the four studies evaluating prevention of EWSLs included in the present review were randomized controlled trials; out of which three were published in scientific journals [19,20,22] and 1 was a thesis [21]. These four studies $_{\text{PREVENTION}}$ were conducted on 518 participants with at least 117 males and 123 females.

3.2.2. Studies $_{REVERSAL}$

The seven randomized trials [23–30] evaluating reversal of EWSLs included in the present review recruited a total of 693 patients with at least 222 males and 293 females. One trial presented its results in two parts of the paper [23,24], and hence the results are considered only

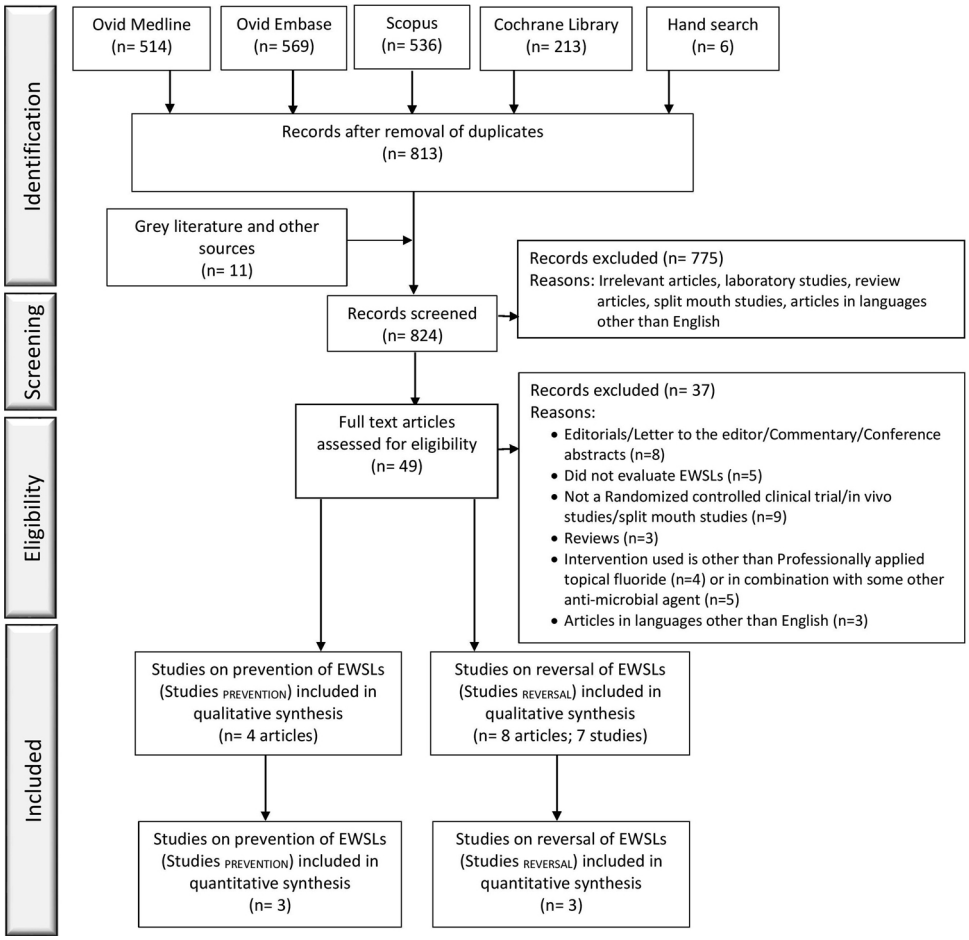

Fig. 1. PRISMA flow diagram of the study selection process.

once for analysis.

3.3. Risk of bias within studies

Risk of bias assessment for all the included clinical trials evaluating the role of professionally applied topical fluorides in the prevention or reversal of EWSLs during multi-bracketed fixed orthodontic treatment is shown in Table 4.

3.3.1. Studies PREVENTION

Only the study by Stecksén-Blicks et al. [19] was adjudged to be at low risk of overall bias using RoB 2.0 tool; whereas the study by Kirschneck et al. [22] was adjudged by review authors to be at high risk of overall bias, arising as a result of high risk of bias in the domain in "bias in measurement of outcome". The remaining two studies [20,21] were both adjudged to have "some concerns" overall due to "some concerns" in the domain of "bias arising from the randomization process." Thus, the most problematic domains of bias arising within the studies were "bias due to randomization process" (50%), followed by "bias in the measurement of outcome" (25%). The detailed risk of bias assessment along with the support for judgment and algorithm used to conclude overall bias for all the four studies is presented in Appendix 3.

3.3.2. Studies REVERSAL

Nearly 58% of the studies (N = 4 studies) [23–27] evaluating reversal of EWSLs using professional topical fluoride applications were adjudged to be of low overall risk according to RoB 2.0 tool, and another 29% (N = 2 studies) [28,30] were adjudged to have "some concerns." The remaining one study [29] was adjudged to be at high risk because of the high risk in the domain of "bias in the selection of reported result." "Bias due to randomization process" was the most problematic domain (nearly 43%), followed by "bias in the selection of reported result" (14.2%). The exhaustive risk of bias assessment along with the support for judgment and algorithm used to deduce overall bias for all the seven studies is presented in Appendix 3.

3.4. Results of individual studies

3.4.1. Studies PREVENTION

Table 3 outlines the outcome parameters used to assess the prevention and clinical diagnostic criteria used to measure the outcome. Two of the studies evaluated the outcomes of the prevention at the end of orthodontic treatment (after debonding) [19,20]; whereas one study evaluated the outcome at 6–8 months [21] and one study at 20 weeks [22].

3.4.2. Studies REVERSAL

The evaluation of the outcome i.e. reversal of EWSLs was assessed using DIAGNOdent (3 studies) [28–30], photographs (3 studies) [23–26], clinical criteria (3 studies) [23,24,30] and QLF images (1 study) [27]. The reversal was assessed from as low as ten days [26] to as high as six months [28] after application of professional topical fluoride agents.

3.5. Synthesis of results

3.5.1. Studies PREVENTION

Fig. 2 provides the results of the quantitative synthesis of studies

Table 3
Characteristics of the included trials.

	Study (Year, Country)	Sample size (baseline)	Age of participants (years)	Intervention group	Control group	Frequency	Method of assessment of Enamel white spot lesions	Maximum follow-up	Outcome
Studies PREVENTION	Stecksén-Blicks et al (2007, Sweden)	273	Mean age: 14.3 ± 1.6 years	Fluor Protector (Ivoclar Vivadent, Schaan, Liechtenstein), containing 0.1% F	Placebo varnish: identical composition to fluoride varnish but without fluoride	Every 6 weeks	Frontal and lateral digital photographs were evaluated using index by Gorelick et al. [1982].	Debonding	Incidence and progression of WSL on the upper incisors, cuspids and premolars
	Jiang et al (2013, China)	100	Mean age: 13.5 ± 2.2 years	APF foam group- Dentology (1.23 percent APF, Suntech Medical Appliances Co, Ltd, Beijing, China) applied through a sponge lined tray for four minutes	The placebo foam (fluoride-free foam, Suntech Medical Appliances Co, Ltd)- identical composition but lacked fluoride	Every 2 months	WSL index (Gorelick et al, 1982)	Debonding	Primary outcomes- incidence of WSLs (percent) and the increment of WSLs scores during orthodontic treatment Secondary outcomes- distribution of WSLs score (percent) in both the 1.23 percent APF foam and placebo groups after debonding
	Hutto Fretty (2014, USA)	55		Nupro 1.23% APF gel (Dentsply®) for one minute	Placebo gel was exactly the same composition, but lacked fluoride Placebo group received a gel treatment for one minute every 8 weeks.	Every 8 weeks	Photographs and Fluorecam® readings (Daraza, Indianapolis)	6 or 8 months depending on when their second set of brackets was placed	Incidence and progression of EWSLs; Severity of EWSLs (assessed by Øgaard score); size, intensity and impact of demineralization
	Kirschneck et al (2016, Germany)	90	Median 12 years in all groups (interquartile range in control grp- 11 to 13 years, Elmex fluid group- 11 to 14 years and Fluor Protector S group- 11 to 14 years)	One time application of Elmex® fluid varnish or Fluor Protector S varnish	One-time application of placebo varnish (70 % w/v ethanol), at the beginning of fixed orthodontic treatment	Once application at the beginning of fixed orthodontic treatment depending on the allocation group.	Visual examination- ICDAS index	20 weeks	Changes in ICDAS scores and Gingival index scores
Studies REVERSAL	Du et al (2012, China)	110	16.6 ± 3.2 years	Group 1: Duraphat application	Group 2: Saline solution applied similar to group 1	Every month	DIAGNOdent pen (DD)	6 months	Changes in mean DIAGNOdent values at 3 months and 6 months.
	Huang et al (2013, USA)	135	14.4 ± 1.5 years	MI Paste Plus group (intervention 1): 8-week supply of MI Paste Plus at the start of the study and instructed to apply a pea-sized amount to each arch twice daily. Fluoride varnish group (intervention 2): application of 0.4 ml of 5% sodium fluoride varnish (22,600 ppm of fluoride, PreviDent).	Home-care group (control): usual home-care oral hygiene instructions and a packet with nonprescription fluoride toothpaste (1100 ppm of fluoride), a manual toothbrush, and dental floss.	Once application before the start of the study	Intra-oral frontal photographs standardized for magnification, color, shade and angulation to limit the reflection from flash to incisal 1/3rd of the tooth.	8 weeks	Primary outcomes: mean percentages of improvement of the WSLs from entry to the 8-week follow-up with both subjective (visual analogue scale from 0 to 100 mm) and objective assessments (proportions of WSLs area relative to the total surface area of the 4 incisors)
	He et al (2016, China)	240	Median 16.0 years with IQR 3 in Fluoride varnish and control group. Median 17.0 and IQR 4 in fluoride film group	Fluoride varnish (Duraphat containing 5% NaF) or fluoride film (Sheer; containing 5% acidulated NaF) for 6 months	Placebo treatment. Oral hygiene education and fluoride toothpaste daily	Once a month	Quantitative light-induced fluorescence images	6 months	Primary outcome- decrease in the lesion volume of each patient after 6 months of treatment; Secondary outcome- fluorescence loss and area

(*continued on next page*)

Table 3 (*continued*)

Study (Year, Country)	Sample size (baseline)	Age of participants (years)	Intervention group	Control group	Frequency	Method of assessment of Enamel white spot lesions	Maximum follow-up	Outcome
			depending on group allocation.					
Restrepo et al (2016, Brazil)	35	17.2 ± 2.3	Fluoride varnish group- 5% NaF varnish CHX group: 2% Chlorhexidine gel-	Control group-saline solution was applied with the aid of a bendable micro applicator brush, in the same way as was done for the two intervention groups + Usual home care control – CO	Two applications F with one-week interval (for two weeks)	DIAGNOdent Pen 2190 – DDpen (KaVo, Biberach, Germany) Visual examination: using Nyvad criteria	3 months	Primary outcome- change in the lesions fluorescence measured with the DDPen after 3 months. Secondary outcomes- fluorescence analysis done 1 week, 1 month and 2 months after each application, the lesion activity (Nyvad criteria) and the S-OHI after three months were considered the secondary outcomes.
Singh et al (2016, India)	45	Group I- 18.93 ± 2.97, Group II-19.08 ± 3.57, and Group III-16.93 ± 3.24	Group II- fluoride varnish (5 % NaF, Fluoritop-SR® ICPA Health Products Ltd.) Group III- (CPP-ACP group) for home use	Group I - twice daily use of dentifrice containing 1000 ppm fluoride (Colgate total® Colgate-Palmolive Company) during the follow-up period. No other fluoride supplements were allowed for use.	1 month, 3 months and 6 months	Boyd criteria using visual examination, 1993 (subjective method) and DIAGNOdent readings (objective method)	3 months	Changes in mean visual scores and mean DIAGNOdent scores.
Bock et al (2017a,b; Germany)	48	15.3 (Test group-15.0 ± SD 2.3 and Placebo group15.5 ± SD1.6)	Professional fluoride (1.25 per cent fluoride including 1 per cent fluoride from sodium fluoride and 0.25 per cent fluoride from olaflur/dectaflur; approximately 0.5 g gel or 6.25 mg fluoride in line with usual recommendations) plus self-administered home application (weeks 3–24; T3 to T5) using a toothbrush for 2 minutes on all teeth once a week	Placebo gel (same formulation as high-dose fluoride gel except fluoride components but additional parabens as preservatives;	Application at baseline, week 1 and week 2 (T0 to T2) using a rotating rubber cup for 20 seconds per tooth	Photographs of upper front teeth in dark room without natural light Clinical examination	24 weeks	Photographic WSL assessment (dimension and luminance) of the upper front teeth (T0–T5). Clinical evaluation of WSL index, lesion activity (ICDAS II), plaque index, gingival bleeding index, and decayed, missing, and filled teeth index as well as saliva buffer capacity and stimulated salivary flow rate
Ebrahimi et al. (2017, Iran)	80		Group 1: 2% neutral sodium fluoride gel (Sultan Healthcare Inc., Englewood, New Jersey, USA). Group 2:remineralizing cream containing CPP-ACPF (MI Paste Plus; GC Corporation, Tokyo, Japan) Group 3: remineralizing cream containing fluoridated hydroxyapatite (Remin Pro, VOCO GmbH, Cuxhaven, Germany)	Group 4: No treatment	3 times over 10 days	Photographs (VistaCam iX (Dürr Dental, Bietigheim-Bissingen, Germany)	10 days	Difference in the area and mineral content of WSLs

Table 4
Risk of Bias assessment of included trial using Cochrane's risk of bias tool 2.0 (RoB 2.0).

	Study (year)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome	Bias in measurement of outcome	Bias in selection of reported result	Overall bias
Studies PREVENTION	Stecksén-Blicks et al. (2007)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Jiang et al. (2013)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
	Hutto Fretty (2014)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
	Kirschneck et al. (2016)	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Studies REVERSAL	Du et al. (2012)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
	Huang et al. (2013)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	He et al. (2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Restrepo et al. (2016)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
	Singh et al. (2016)	Some concerns	Low risk	Low risk	Low risk	High risk	High risk
	Bock et al. (2017a,b)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Ebrahimi et al. (2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

PREVENTION (the difference in incidence rates of the intervention group and control group).. From the four included trials in systematic review evaluating the prevention of EWSLs in orthodontic patients, data from 3 trials [19–21] could be pooled for meta-analysis because of the similar outcome measurement (i.e., the incidence of EWSLs). Using a Mantel-Haenszel fixed-effect method, the risk ratio (RR) was 0.39 with a 95% confidence interval of 0.26 and 0.59, which could be interpreted as that professional topical fluoride agents can decrease the risk of EWSLs in patients undergoing multi-bracketed fixed orthodontic treatment by 41–74%. The value of I^2 was calculated to be 81.2, which reveals that around 81% of the observed variance was due to real differences between the studies and could be potentially explained by study-level covariates. The calculated Z-value was 4.52 (at $p < .001$), which favors the effect of professional topical fluorides in the prevention of EWSLs.

3.5.2. Studies REVERSAL

Fig. 3 provides the results of the quantitative synthesis of studies REVERSAL (the change in mean DIAGNOdent scores). Seven trials [23–30] were included in the qualitative synthesis out of which three trials [28–30] evaluated the change in mean DIAGNOdent scores at three months, and hence, the outcome could be pooled for quantitative synthesis. Due to studies fewer than 4, random effect meta-analysis could not be used, and IV fixed-effect method was used to determine the standardized mean difference (SMD). The SMD of DIAGNOdent values was less by a value of 0.57 in the professional topical fluoride varnish group than the control group (95% C.I. of -0.23 to -0.91; p = 0.071).

3.6. Additional analysis

Sensitivity analysis was performed by excluding "high risk" trials and trials with "some concerns" from the quantitative synthesis of (both Studies PREVENTION and Studies REVERSAL), although it did not alter the overall result significantly. Further sub-group analysis was attempted, the detailed results of which are presented in Appendix 4 and should be interpreted with caution because of the fewer number of included trials. The highlights of these analyses are as follows:

3.6.1. Studies PREVENTION

Additional analysis evaluating the results of professional topical fluoride at different follow-ups (debonding vs. 6–8 months) was performed. Two studies [19,20] evaluated their results at debonding and had a combined weight of 86.75% whereas the one study [21] weighted 13.25% on quantitative synthesis. Thus, no significant change in overall result was found on adding the results of the latter study.

Meta-regression analysis comparing different agents (1.23% APF vs. fluoride varnish) was performed, and the detailed result of the analysis is presented in *Appendix 4*. The percentage weight of two studies [20,21] evaluating 1.23% APF and one study [19] evaluating fluoride varnish was found to be approximately equivalent (50.08% and 49.92% respectively). However, the result was not statistically significant (p = 0.732), thereby the superiority of one fluoride agent over the other remains inconclusive. `

3.6.2. Studies REVERSAL

The weighted mean difference (WMD) score was calculated for two studies [28,30] at three months follow-up since both studies evaluated mean DIAGNOdent scores of the individual tooth. The result showed the mean score in the intervention group was lesser by 2.68 value than the score in the control group, but this decrease could not achieve statistical significance (p = 0. 244). The SMD of reversal at six months using mean DIAGNOdent scores of the 2 studies [28,29] as well as the WMD and SMD scores at three months of two similar studies [28,30] are also presented in Appendix 4.

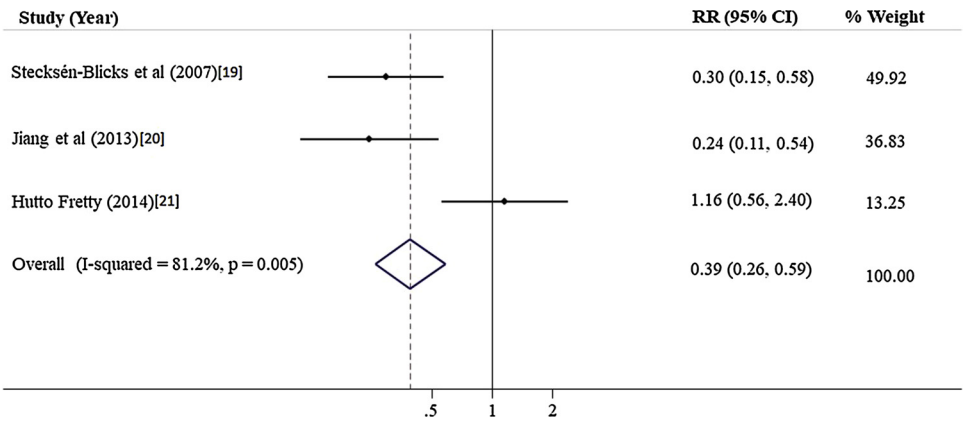

Fig. 2. Effect of professional topical fluoride applications on the incidence of Enamel White Spot Lesions during orthodontic treatment (Studies $_{PREVENTION}$) [19–21]. The horizontal line depicts the 95% confidence intervals (CI) whereas the diamond shape signifies the meta-analysis pooled effect estimate and it's CI. A dotted vertical line shows the location of the meta-analysis pooled effect estimate. RR, relative risk.

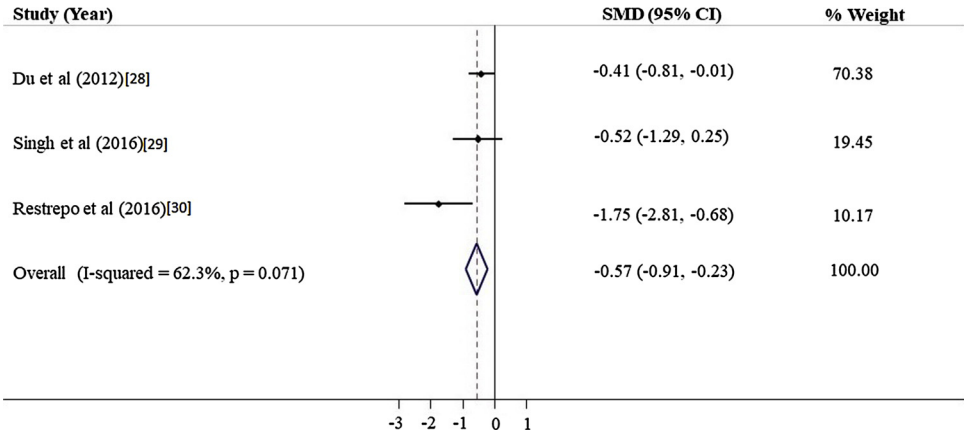

Fig. 3. Effect of professional topical fluoride applications on mean DIAGNOdent scores of Enamel White Spot Lesions occurring after orthodontic treatment (Studies $_{REVERSAL}$) [28–30]. The horizontal line depicts the 95% confidence intervals (CI) whereas the diamond shape signifies the meta-analysis pooled effect estimate and it's CI. A dotted vertical line shows the location of the meta-analysis pooled effect estimate. SMD, standardized mean difference.

4. Discussion

The present systematic review analyzed the role of professional topical fluorides against EWSLs occurring during or after multi-bracketed fixed orthodontic treatment. The main strengths of this review were the inclusion of studies evaluating the effect of professional topical fluorides in the prevention of EWSLs as well as in the reversal of EWSLs occurring after multi-bracketed fixed orthodontic treatment. The other salient features of this review are it's *a priory* registration on PROSPERO database, extensive unconstrained search of the published and unpublished literature, utilization of sensitivity analysis and subgroup analysis wherever possible and finally the use of robust approach in the synthesis of results both qualitatively and quantitatively. Use of recently introduced Cochrane risk of Bias tool 2.0 [16] in this review is an added advantage, as this tool evaluates the *"overall risk"* of the trial and is more sensitive than an original tool because of the use of signaling questions & suggested algorithm which was adopted in the present study.

Despite the sound methodology of the present review coupled with the strengths mentioned above, this review has some limitations. One such limitation was the inclusion of only English literature for the review. The exclusion of studies published in languages other than English has little or no summary effect estimates and hence might not result in systematic bias [31,32]. Due to a limited number of studies included in the review, publication bias could not be assessed by plotting funnel technique. However, a sensitivity analysis was still done by excluding the studies with high overall risk and studies with some concerns. The control and intervention group patients of nearly all the included studies were either advised to use or provided with fluoridated toothpaste. Hence the synergistic effect of self-applied fluoride on professional fluoride applications cannot be ruled out completely. Nonetheless, since both the groups in all trials were matched for the use of fluoridated toothpaste, the effect of self-applied fluorides would have been evident in both the treatment and control groups and hence would not have impacted the conclusion of the trials significantly.

A similar systematic review regarding professional topical fluoride application has made recommendations for further research in development of standard methodologies for well-designed trials with standardized reporting and trial registration [33]. However, the systematic review did not address the efficacy of professional topical fluorides in patients undergoing multi-bracketed fixed orthodontic treatment. The Cochrane systematic review [34] on a similar topic has evaluated the effects of different fluoride therapies (in the form of professional, self-applied and even sustained release devices) in only the prevention of EWSLs in patients undergoing multi-bracketed fixed orthodontic treatment. However, our review differs from it because of the evaluation of the role of professional topical fluorides exclusively not only in prevention but also in reversal of EWSLs. Although the number of included studies was quite limited in the Cochrane review [34] as in the present review, the process of systematic review and meta-analysis has practical advantages to the stakeholders (*viz.* clinicians, researchers, patients, and the companies). The systematic review provides an unbiased summary of the clinical trials and evidence to assist clinicians in choosing a particular intervention as the decision could have been biased if the clinicians relied on just one or few trials. Statistically, a meta-analysis combines the effects of individual studies and provides a more reliable estimate of pooled effect with narrower confidence intervals, because of larger sample size and higher statistical power [35].

4.1. Studies $_{PREVENTION}$

Only four studies [19–22] could be included to evaluate the prevention of EWSLs using professional topical fluoride, out of which only one was adjudged to be of low overall risk [19]. This judgment is in

accordance with the Cochrane systematic review [34], wherein the review authors evaluated all forms of fluorides against EWSLs and gave low risk to the same study. Two of the other studies PREVENTION [21,22] included in this review were adjudged to be of "some concerns"; one of them being an unpublished data [21], probably because of short follow-up of 6–8 months and not evaluating the incidence after debonding of the brackets. Moreover, the unpublished study did not find any significant effect of 1.23% APF gel in prevention of EWSLs during orthodontic treatment which might have resulted in publication bias. However, sensitivity analysis by excluding this unpublished study from the quantitative synthesis did not change the overall result remarkably, and professional topical fluorides could still achieve a relative risk reduction from 25% to 30% based on the pooled results of the other two studies. Despite the relative risk reduction, it is difficult to give clinical recommendations regarding the frequency of applications and the type of fluoride to be used based on just these two trials; only one of which was adjudged to be of low overall risk. Even though randomization was performed by the study authors, there were some concerns in the actual randomization process of the above two studies [21,22], because the authors did not mention the methods of allocation or concealment. Sequentially numbered opaque sealed envelopes, sequentially numbered containers and external control of the randomization process are additional stringent steps that can be used to reduce bias due to randomization in future trials [36]. Lastly, the only study [22] adjudged to be of high risk of overall bias was assigned so because of the bias in the measurement of outcome; assessors were not blinded. If the outcome assessment involves some judgment (e.g., use of any EWSL index or subjective criteria), training and calibration are a prerequisite. Standardized clinical photographs can be used as a guide to assist criterion validity in EWSL assessment. Alternatively, if blinding is not feasible, the potential of 'objective' measures can be considered (e.g., QLF or DIAGNOdent).

4.2. Studies REVERSAL

Nearly 58% of the studies (N = 4 studies) [23–27] were adjudged to be of low risk of overall bias when reversal of post-orthodontic EWSLs was assessed. However, the reversal of EWSLs is clinically challenging to assess because of the difficulty in the estimation of mineral content with the current tools available. The data from only three studies [28–30] could be pooled for quantitative synthesis of the change in mean DIAGNOdent scores at three months to evaluate the remineralization of the EWSLs. Surprisingly, one of the three studies [29] used the total mean DIAGNOdent score of all the included teeth of the patient rather than the mean DIAGNOdent score of an individual tooth; hence the standardized mean difference (SMD) was calculated rather than the weighted mean difference (WMD). The study [29] was adjudged to be of high risk of bias due to bias in selective reporting as the mean DIAGNOdent values were presented at a patient level rather than tooth level. The SMD is used as a summary statistic in a meta-analysis when all the studies assess the same outcome but measure it on a different scale [17]. In the present review, it was necessary to standardize the results of the studies to a uniform scale before they could be combined. The SMD value of 0.2, 0.5, and 0.8 are widely used, corresponding to small, medium, and large effects [37]. In our meta-analysis, the combined SMD of −0.57 was obtained which corresponds to a medium effect (p = 0.071). In contrast, WMD is on the same scale of measurement as the clinical trial and hence is easy to interpret as the results of the clinical trial itself. The results of the WMD of the two studies, which have used mean DIAGNOdent scores of the individual tooth (i.e., same scale) are present in Appendix 4. Furthermore, the sensitivity analysis was done by excluding the study [29], which used the different scale as the review authors adjudged it to be of high overall risk, because of high risk in the domain of "selective outcome reporting." The results of the included trials that assessed reversal of post-orthodontic EWSLs should be interpreted with caution, because of the concern in the use of DIAGNOdent and debatable effect of plaque, calculus or stains and the degree of hydration of the concerned tooth on its readings [38,39]. A systematic review on DIAGNOdent has suggested that the DIAGNOdent offers an additional advantage of improved diagnostic sensitivity in detection of enamel and dentinal caries on occlusal surfaces [39]. However, this improved sensitivity comes at the cost of a decrease in specificity values. The review further suggested that clinicians should not rely only on DIAGNOdent as their primary diagnostic method because of the uncertainty regarding diagnostic threshold value in diagnosing incipient caries. The follow-up periods of the included studies REVERSAL were quite varied as was the use of different fluoride agents with different frequencies. One study [26] adjudged to be at low risk of overall bias, followed the reversal of EWSLs for ten days only, but was still not excluded from the present review as the duration it takes to remineralize is not precisely known. Due to the limited number of studies, different fluoride agents and their application frequencies as well as the use of different diagnostic aids to assess remineralization, specific guidelines are difficult to establish based on the present review and further studies with better diagnostic aids are necessary.

Finally, the issue of bias in selective outcome reporting underscores the importance of the registration of the protocol of the trials at appropriate platforms, since the *"the registration of all interventional trials is a scientific, ethical and moral responsibility* [40]." A useful practice to minimize the bias of selective outcome reporting is to adhere to reporting guidelines and statements such as CONSORT [41].

5. Conclusions

Based on the present review and meta-analysis, it can be concluded that professional topical fluoride application brought about a 25–30% reduction in the incidence of EWSLs after debonding. Due to a limited number of clinical trials, further research is warranted to identify the type of fluoride agent (varnish, gel or foam), the concentration of fluoride and the frequency of applications in patients undergoing multibracketed fixed orthodontic treatment. Because of the difficulties in assessing the reversal of EWSLs and mineral content, it is still unclear that whether professional topical fluorides are effective in reversing EWSLs after orthodontic treatment. However, based on the present systematic review and pooling data from the readings of DIAGNOdent scores, it appears that the professional topical fluoride application reduces the mean DIAGNOdent scores compared to the control group. Further research should focus on correlating changes in DIAGNOdent scores with the severity of EWSLs as assessed by subjective and clinical parameters and with the change in the mineral content of the teeth. Also, due to wide variations in the application frequencies, type, concentrations of fluoride and different follow-ups to judge remineralization of EWSLs used in the included trials, recommendations are difficult to make and research in this context is the need of an hour.

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Conflicts of interest

None to be declared.

Declarations of interest

None

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdent.2018.12.006.

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