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5th Year,
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Comparison the effectiveness of common topical fluoride application and CPP-ACP application on preventing white spot lesions in orthodontic – A systematic review

Master's Thesis

Supervisor

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EVALUATION TABLE OF THE MASTER'S THESIS OF THE TYPE OF SYSTEMATIC REVIEW OF SCIENTIFIC LITERATURE

Evaluation: .....

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No.	MT parts	MT evaluation aspects	Compliance with MT requirements and evaluation		
			Yes	**Partially**	**No**
1	**Summary (0.5 point)**	Is summary informative and in compliance with the thesis content and requirements?	0.3	0.1	0
2		Are keywords in compliance with the thesis essence?	0.2	0.1	0
3	**Introduction, aim and tasks (1 point)**	Are the novelty, relevance and significance of the work justified in the introduction of the thesis?	0.4	0.2	0
4		Are the problem, hypothesis, aim and tasks formed clearly and properly?	0.4	0.2	0
5		Are the aim and tasks interrelated?	0.2	0.1	0
6	**Selection criteria of the studies, search methods and strategy (3.4 points)**	Is the protocol of systemic review present?	0.6	0.3	0
7		Were the eligibility criteria of articles for the selected protocol determined (e.g., year, language, publication condition, etc.)	0.4	0.2	0
8		Are all the information sources (databases with dates of coverage, contact with study authors to identify additional studies) described and is the last search day indicated?	0.2	0.1	0
9		Is the electronic search strategy described in such a way that it could be repeated (year of search, the last search day; keywords and their combinations; number of found and selected articles according to the combinations of keywords)?	0.4	0.1	0
10		Is the selection process of studies (screening, eligibility, included in systemic review or, if applicable, included in the meta-analysis) described?	0.4	0.2	0
11		Is the data extraction method from the articles (types of investigations, participants, interventions, analyzed factors, indexes) described?	0.4	0.2	0
12		Are all the variables (for which data were sought and any assumptions and simplifications made) listed and defined?	0.4	0.2	0

13		Are the methods, which were used to evaluate the risk of bias of individual studies and how this information is to be used in data synthesis, described?	0.2	0.1	0
14		Were the principal summary measures (risk ratio, difference in means) stated?	0.4	0.2	0
15	Systemization and analysis of data (2.2 points)	Is the number of studies screened: included upon assessment for eligibility and excluded upon giving the reasons in each stage of exclusion presented?	0.6	0.3	0
16		Are the characteristics of studies presented in the included articles, according to which the data were extracted (e.g., study size, follow-up period, type of respondents) presented?	0.6	0.3	0
17		Are the evaluations of beneficial or harmful outcomes for each study presented? (a) simple summary data for each intervention group; b) effect estimates and confidence intervals)	0.4	0.2	0
18		Are the extracted and systemized data from studies presented in the tables according to individual tasks?	0.6	0.3	0
19	Discussion (1.4 points)	Are the main findings summarized and is their relevance indicated?	0.4	0.2	0
20		Are the limitations of the performed systemic review discussed?	0.4	0.2	0
21		Does author present the interpretation of the results?	0.4	0.2	0

22	Conclusions (0.5 points)	Do the conclusions reflect the topic, aim and tasks of the Master's thesis?	0.2	0.1	0
23		Are the conclusions based on the analyzed material?	0.2	0.1	0
24		Are the conclusions clear and laconic?	0.1	0.1	0
25	References (1 point)	Is the references list formed according to the requirements?	0.4	0.2	0
26		Are the links of the references to the text correct? Are the literature sources cited correctly and precisely?	0.2	0.1	0
27		Is the scientific level of references suitable for Master's thesis?	0.2	0.1	0
28		Do the cited sources not older than 10 years old form at least 70% of sources, and the not older than 5 years – at least 40%?	0.2	0.1	0
Additional sections, which may increase the collected number of points					
29	**Annexes**	Do the presented annexes help to understand the analyzed topic?	+0.2	+0.1	0
30	**Practical**	Are the practical recommendations suggested and are they related to the received results?	+0.4	+0.2	0
	Recommendations				
31		Were additional methods of data analysis and their results used and described (sensitivity analyses, meta-regression)?	+1	+0.5	0
32		Was meta-analysis applied? Are the selected statistical methods indicated? Are the results of each meta-analysis presented?	+2	+1	0

General requirements, non-compliance with which reduce the number of points					
33	**General requirements**	Is the thesis volume sufficient (excluding annexes)?		15-20 pages (-2 points)	<15 pages (-5 points)
34		Is the thesis volume increased artificially?	-2 points	-1 point	
35		Does the thesis structure satisfy the requirements of Master's thesis?		-1 point	-2 points
36		Is the thesis written in correct language, scientifically, logically and laconically?		-0.5 point	-1 points
37		Are there any grammatical, style or computer literacy-related mistakes?	-2 points	-1 points	
38		Is text consistent, integral, and are the volumes of its structural parts balanced?		-0.2 point	-0.5 points
39		Amount of plagiarism in the thesis.	>20% (not evaluated)		
40		Is the content (names of sections and sub-sections and enumeration of pages) in compliance with the thesis structure and aims?		-0.2 point	-0.5 points
41		Are the names of the thesis parts in compliance with the text? Are the titles of sections and sub-sections distinguished logically and correctly?		-0.2 point	-0.5 points
42		Are there explanations of the key terms and abbreviations (if needed)?		-0.2 point	-0.5 points
43		Is the quality of the thesis typography (quality of printing, visual aids, binding) good?		-0.2 point	-0.5 points
***In total (maximum 10 points):**					

***Remark:** the amount of collected points may exceed 10 points.*

Reviewer's comments:

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Abbreviations

WSLs ------ White spot lesions

CPP-ACP ------ Casein phosphopeptide–amorphous calcium phosphate

PICO ------ Population, Intervention, Comparison, Outcome

RoB ------ Cochrane Randomized Bias Risk Assessment Tool

ROBINS-I ------ Risk of Bias in Non-randomized Studies

Abstracts

Introduction:

The aim of the study is to evaluate the effectiveness of common topical fluoride application and casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) application on preventing White Spot Lesions (WSLs) in orthodontics. And compare the effectiveness of these two applications on preventing WSLs in orthodontics.

Material and Method:

Study was conducted from databases such as Pubmed, Embase (ScienceDirect). Articles included studies on humans, in vivo, clinical trials, published in English during the year in 2009 – 2019.

Result:

By screening titles and abstracts, we identified the total of 316 articles from databases, 7 clinical trial studies were included, 361 participants were evaluated during the study. It shows that both applications have effectiveness on preventing WSLs, but there is no significant statistical difference between common topical application and CPP-ACP contained application on prevent WSLs during or after orthodontic treatment.

Conclusions:

During these 7 clinical studies, the conclusion of effectiveness of common topical fluoride application on preventing WSLs in orthodontic treatment is positive. Meanwhile, during the studies made significantly positive conclusions about effectiveness on preventing WSLs in orthodontic treatment by CPP-ACP contained applications. However, there is no significant difference between two applications with common topical fluoride and CPP-ACP containing on prevent WSLs during or after orthodontic treatment. Thus, the conclusion of hypothesis will be rejected about that the agent content CPP-ACP have better effectiveness than common topical fluoride application on preventing WSLs during or after orthodontic treatment.

Keywords: Topical fluoride application, Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP), white spot lesions, orthodontic.

1. Introduction

Nowadays, people consider the esthetic as a significant problem for their personal life. They seek the method to improve their esthetic and function of tooth by orthodontic treatment. Meanwhile during the orthodontic treatment, it is difficult to apply precise oral hygiene, potentially will cause accumulation of bacterial biofilms on the dental surface [1, 2, 3]. And those bacteria will release acid from food debris, leading the demineralization of hydroxyapatite of dental enamel [4, 5, 6]. And then, resulting the enamel demineralization clinical symptoms as White Spot lesions (Picture 1) during orthodontic treatment. They are usually present on buccal surface of the maxillary lateral incisors firstly, and then will be on maxillary canines, maxillary premolars, and maxillary central incisors [8, 9]. These WSLs will interrupt the final esthetic result and future dental health for the patients. Thus, WSLs are a significant problem during orthodontics treatment [1, 7].

Saliva can remineralize WSLs during the first few months, and it slows down the rate continually [10], but only in the surface layer of WSLs [12]. WSLs will be hard to remove or even become unremovable after orthodontic treatment [11]. Because of the saliva can't involve remineralize in the deeper part of WSLs, then we can't achieve the best result of esthetic goal for the patients and untreated WSLs can result in the cavities and increase risk of the further dental problems.

By the evidence, the initial rate of remineralization can be increased by fluoride [13, 14]. It has been recommended during and after orthodontics treatment for decalcification and preventing WSLs from progressing to carious lesions in all gender and ages, although underlying conditions during medication [15]. It will improve the remineralization of the outer enamel and reducing demineralization of the inner enamel [16, 17]. The fluoride rinse and toothpaste are commonly used in personal life as a self-application method of topical fluoride, but at the same time it depends on personal compliance in the frequency and the amount to use regularly [18, 20]. Compare with self-application of topical fluoride, the professional topical fluoride application is mostly given as gel foams, varnish by high concertation of fluorides over a short time and applied by professional dental care. After debonding in post-orthodontic treatment in 8 weeks, the WSLs can increase on the enamel surface [19]. If no caring for these WSLs, they will remain on the dental surface for very long term [14]. Thus, the prevention of WSLs for the patients is a significant consideration by orthodontists [22]. And necessary to apply remineralization agents to repair the deeper parts of WSLs [21].

In recent year, new type of agents for preventing demineralization and improving the remineralization of enamel and dentine have been developed to reduce the risk of caries. These new agents are including casein phosphopeptide - amorphous calcium phosphate (CPP-ACP). In the 1980s, the first time it was concluded that casein phosphopeptide and amorphous calcium phosphate (CPP-ACP) was able to absorb through enamel surface and effect the carious process [19]. CPP-ACP is able to remain the free calcium, fluoride, and phosphate attached on the surface of enamel and reform into calcium phosphate, which can keep a supersaturated medium, to prevent the damage of the

dental biofilm formation and microorganism adhesion [22, 23]. Thus, the consideration of beneficial effect of CPP-ACP, it may increase the salivary buffering effect which in preventing demineralization and improving remineralization in the same time.

Figure 1: White Spot Lesions in orthodontics

1.1 Aim

The aim of the study is to evaluate the effectiveness of common topical fluoride application and casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) application on preventing White Spot Lesions (WSLs) in orthodontics. And compare the effectiveness of these two applications on preventing WSLs in orthodontics.

1.2 Tasks

- Evaluate the effectiveness of common topical fluoride application on preventing WSLs during or after orthodontic treatment
- Evaluate the effectiveness of CPP-ACP application on preventing WSLs during or after orthodontic treatment
- Compare the effectiveness of common topical fluoride application and CPP-ACP application on preventing WSLs

1.3 Hypothesis:

The agent content casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) have better effectiveness than common topical fluoride application on preventing WSLs during or after orthodontic treatment.

2. Selection criteria of the studies. Search methods and Strategy

2.1 Focus question

The focus question was developed according to the population, intervention, comparison, and the outcome study design. (PICO) is presented in Table 1.

Table 1: Population, Intervention, Comparison, Outcome study design. (PICO)

Population	Patients with WSLs presenting on tooth surface during or after orthodontic treatment
Intervention	CPP-ACP application
Comparison	Compare the effectiveness with other fluoride application
Outcome	Evaluate the prevention or treatment effectiveness on WSLs in orthodontics treatment

2.2 Types of publication

The systematic review included studies on human and published in English language.

2.3 Types of studies

The systematic review included all human prospective cohort studies and a randomized controlled clinical trial published between 2009-2019, that reported a comparison of common topical fluoride application and CPP-ACP application on preventing WSLs in orthodontics.

2.4 Population

Patients who are applied standard topical fluoride application or CPP-ACP application for preventing WSLs during or after orthodontic treatment.

2.5 Data collection

The information and articles are gathered from Pubmed, ScienceDirect databases

2.6 Literature search and screening

The systematic literature review was carried out through electronic search according to PRISMA guidelines [24] within Pubmed, ScienceDirect using the following MeSH terms and word combinations as principle search terms: “Topical fluoride application”[All Fields], OR “Fluoride varnish” [All Fields], AND “Casein phosphopeptide - amorphous calcium phosphate” [All Fields], OR “CPP-ACP application” [All Fields], OR “MI Paste Plus” [All Fields], OR “Tooth mousse GC” [All Fields] , AND “White spots lesion” [All Fields], OR “Caries prevention” [All Fields], OR “Enamel demineralization” [All Fields], AND “orthodontic treatment” [All Fields], OR “Post-orthodontic” [All Fields], OR “Orthodontic brackets” [All Fields], OR “Fixed appliance” [All Fields]. Also, a manual search was performed to find additional relevant articles and references.

2.7 Selection of studies

According to inclusion and exclusion criteria, the article title and abstracts were obtained for our study as consideration is enough for the inclusion in this systematic review. (Figure 1)

2.8 Inclusion and Exclusion criteria

Inclusion criteria:

- Randomized controlled trial (RCT) or Clinical controlled trial (CCT) which compared the effectiveness of prevention on WSLs during or after orthodontic treatment by standard topical fluoride application or
- The articles are written in English language
- The articles are published during 2009-2019
- The article of these clinical studies performed on humans

Exclusion criteria:

- Non-RCT trials, review articles
- Clinical in vitro
- Non orthodontic treatment
- Title not relevant
- Content of article not relevant (not include common topical fluoride, CPP-ACP)

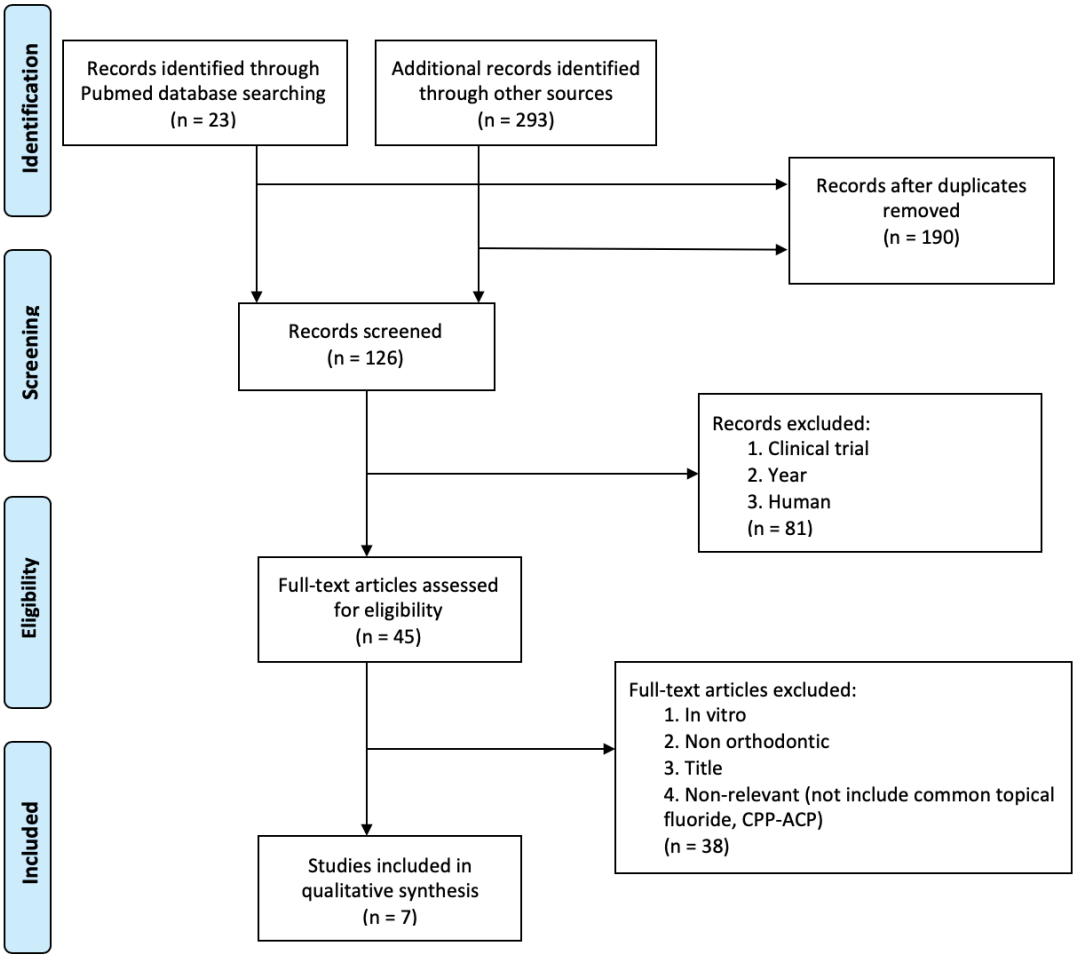

Figure 2: PRISMA flow diagram

2.9 Assessment of bias risk

All the studies were evaluated by the revised version of the Cohrane Randomized Bias Risk Assessment Tool (RoB) [32] (table 2) and by the Risk of Bias In Non-randomized Studies (ROBINS-I) [33] (table 3).

Table 2: Result of bias risk assessment of randomized controlled clinical trials by the RoB 2.0 tool

Risk by domains						
Authors	Randomization	Deviations from intervention	Incomplete outcomes	Measurement of results	Selective reporting of outcome	Risk of bias
Ann Bröchner et al. 2011	Low	Low	Low	Low	Low	Low
Huang et al. 2013	Low	Low	Low	Low	Low	Low
Uysal et al. 2010	Low	Moderate	Low	Low	Low	Moderate
Sombir Singh et al. 2016	Low	Low	Low	Low	Low	Low
Said Karabeklroglu et al. 2017	Low	Low	Low	Low	Low	Low

Table 3: Result of bias risk assessment of Non-randomized clinical controlled trials by the Risk of Bias in Non-randomized studies tool

Risk by domains								
Authors	confusion	Selection of participants	Classification of interventions	Deviation from interventions	Data hiding	Measurement of results	Reported results	Risk of bias
Mehmet Akin et al. 2012	Low	Low	Low	Low	Low	Low	Low	Low
Bora Korkut et al. 2017	Low	Low	Low	Low	Low	Low	Low	Low

3. Systemization and Analysis of data

3.1 Study selection

Identify the total of 316 articles from databases. Firstly, screened of 126 articles after removing duplicated of 190 articles. Secondary, excluded of 81 articles by exclusion criteria “clinical trials”, “published year during 2009-2019”, “experiment on human”, 45 articles remained. Then, the full-text articles assessed for eligibility, excluded of 38 articles due to “in vitro”, “non-relevant”, “not include common topical application, CPP-ACP application”, “non-orthodontic treatment”. Finally, 7 qualified studies are selected for this systematic review [25, 26, 27, 28, 29, 30, 31].
In 4 randomized controlled clinical trials and 2 clinical controlled trials were included, included 1 study in vivo in controlled clinical trials as well.

3.2 Systemization of data and characteristics of studies

Relevant data of interest on the previously stated variables and main characteristics of studies were collected and organized into Table 4

Table 4: Systemization of data and characteristics of studies

Reference	Type of study	Population of sample size	Gender	Mean of age	characteristics	Interventions	Period of study	Evaluation method
1. Ann Bröchner et al. 2011	Randomized controlled clinical trial	size: 50 22 CPP-ACP (Tooth Mousse, GC Europe), 28 fluoride toothpaste	27 boys 33 girls *10 drop out by study period and unreadable QLF images	15.2 years old	Minimal present 1 clinical WSL after orthodontic treatment	G1-CPP-ACP cream (night) +fluoride toothpaste (morning) G2-Standard fluoride toothpaste 2 times a day	4 weeks	Visual inspection Digital photos Quantitative light-induced fluorescence
2. Mehmet Akin et al. 2012	Clinical controlled trial	Size: 80, 966 affected tooth 20 Regular brushing tooth 20 Sodium fluoride (mouth rinse, NaF) 20 CPP-ACP (GC Tooth Mousse) 20 Microabrasion treatment	46 females 34 males		1. After fixed appliance therapy, Started after debonding 2. No smoking 3. No history of bleaching treatment 4. No plaque accumulation and gingival inflammation 5. No dental caries, prosthetic restoration, discoloration, deviation of tooth 6. No systemic disease	G1-Regular brushing tooth G2-Fluoride rinse 2 times a day G3-CPP-ACP 2 times a day G4-Microabrasion treatment		Digital photos

3. Bora Korkut et al. 2017	Clinical controlled trial	Size: 20 5 regular toothpaste 5 CPP-ACP (MI Paste Plus) 5 Remin Pro (Voco) 5 Experimental remineralizing cream		30 years old	Orthodontic treatment for 6-8 months with moderate risk of caries	G1-Standard toothpaste G2-CPP-ACP (MI Paste Plus) + Standard toothpaste G3-Remin Pro (Voco) + Standard toothpaste G4-Experimental cream + Standard toothpaste	3 weeks	Fluorescence enamel imaging (FluoreCam)
4. Huang et al. 2013	Randomized controlled clinical trial	Size: 115 41 control fluoride toothpaste 34 MI Paste Plus (CPP-ACP) + 40 PreviDent fluoride varnish (NaF)		14.4+/-1.5 years old	1. After orthodontic treatment with fixed appliance 2. At least 1 WSL on vestibular surface of maxillary incisor	G1-Fluoride toothpaste (1100ppm of fluoride) G2-MI Pasete Plus (CPP-ACP) 2 times a day + fluoride toothpaste (1100ppm of fluoride) G3-PreviDent fluoride varnish (NaF, 22600ppm of fluoride a single application at start of study, after applied fluoride toothpaste (1100ppm of fluoride)	8 weeks	Visual inspection Digital photos -Evaluation by analogue visual scale
5. Uysal et al. 2010	Controlled clinical trial in vivo	Size: 21 7 control fluoride toothpaste 7 CPP-ACP (Tooth Mousse, GC) 7 Fluoridin N5 (NaF topical gel)	12 females 9 males	15.05 years old	Orthodontic treatment with 4 premolar extraction	G1-Brushing with non-fluoride toothpaste G2-Brushing with non-fluoride toothpaste + CPP-ACP agent on enamel surface for 5 min G3-Brushing with non-fluoride toothpaste + NaF topical gel on enamel surface for 5 min	60 days	Microhardness DIAGNOdent

6. Sombir Singh et al. 2016	Randomized controlled clinical trial	Size: 41 14 Fluoride toothpaste only 13 Toothpaste + Fluoride varnish (5% NaF, Fluortop-SR) 14 Toothpaste + CPP-ACP (GC Tooth Mousse)	18 males 23 females	20.5 years old	After orthodontic treatment with at least 1 WSL	G1-Brushing 2 times a day with 1000ppm fluoride toothpaste G2-Once applied 1ml fluoride varnish + Brushing 2 times a day with 1000ppm fluoride toothpaste G3-CPP-ACP application (Tooth Mousse GC) 2 times a day + Brushing 2 times a day with 1000ppm fluoride toothpaste	6 month	Visual Score DIAGNOdent
7. Said Karabeklroglu et al. 2017	Randomized controlled clinical trial	Size: 34 178 teeth 18 subjects/89 teeth Controlled group 16 subjects/89 teeth CPP-ACP group		17 years old	After orthodontic treatment, in de-bonding time with at least 4 WSLs presented	G1-Brushing with fluoride toothpaste 1450ppm (Colgate total) G2-Brushing with fluoride toothpaste 1450ppm (Colgate) + CPP-ACP application (Tooth Mousse GC) 2 times a day	36 months	Visual inspection DIAGNOdent

3.3 Evaluation of data

The included studies were compared according to the result by evaluation method (visual inspection, QLF, FluoreCam, DIAGNOdent). Table 5

Table 5: Evaluation of data from the studies

Reference	Evaluation method	Result	Conclusion
1. Ann Bröchner et al. 2011	Visual inspection Digital photos QLF	G1: Fluorescence (QLF): T_0: 7.04 ± 1.65%, T_1: 4.51 ± 2.46%* Injury area (Visual inspection): T_0: 0.19 ± 0.43 mm2, T_1: 0.14 ± 0.31 mm2 G2: Fluorescence (QLF): T_0: 6.68 ± 0.58%, T_1: 4.45 ± 1.82%* Injury area (Visual inspection): T_0: 0.12 ± 0.16 mm2, T_1: 0.05 ± 0.09 mm2* *$P < 0.05$ compared to baseline values (T_0)	Standard fluoride toothpaste and CPP-ACP application both have effectiveness on reducing WSLs after orthodontic treatment, but there is not significant difference between two agents. So the result can't prove that CPP-ACP have better effectiveness than standard fluoride application on preventing WSLs in orthodontic treatment.
2. Mehmet Akin et al. 2012	Digital photos	G1: T0 – 0.46 ± 0.07%, T1 – 0.26 ± 0.05% G2: T0 – 0.54 ± 0.10%, T1 – 0.27 ± 0.05% G3: T0 – 0.46 ± 0.09%, T1 – 0.22 ± 0.07% G4: T0 – 0.52 ± 0.07%, T1 – 0.02 ± 0.02% Sign. P< 0.01	The result showed that the best treatment is micro-abrasion. But the CPP-ACP application can't provide better effectiveness than standard fluoride application on preventing WSLs.
3. Bora Korkut et al. 2017	FluoreCam	FluoreCam size score: G1: T0 – 2.11 ± 0.93, T1 – 3.80 ± 0.93, T2 – 4.69 ± 0.82, T3 – 6.46 ± 0.82 G2: T0 – 3.22 ± 1.29, T1 – 2.90 ±0.99, T2 – 2.16 ± 0.90, T3 – 1.31 ± 1.06 G3: T0 – 4.43 ±1.41, T1 – 4.01 ± 1.83, T2 – 3.67 ± 0.55, T3 – 2.93 ± 1.71 G4: T0 – 3.83 ±1.11, T1 – 3.75 ± 0.77, T2 – 3.52 ± 1.93, T3 – 3.35 ± 0.44 FluoreCam intensity score: G1: T0- -8.96 ± 2.04, T1 – 14.11 ± 5.29, T2 - -16.59 ± 4.08, T3 - -21.42 ± 3.69 G2: T0 - -12.13 ± 3.92, T1 - -11.61 ± 6.19, T2 - -10.73 ± 3.65, T3 - -9.32 ± 3.26 G3: T0 - -32.13 ± 5.62, T1 - -30.33 ± 7.83, T2 - -29.78 ± 2.81, T3 - -27.57 ± 9.01 G4: T0 - -28.63 ± 2.87, T1 - -28.43 ± 3.53, T2 - -28.12 ± 0.11, T3 - -27.98 ± 4.41 Sign. P<0.01	The CPP-ACP application and Remin Pro have almost equal effectiveness on preventing and reversing on WSLs around orthodontic brackets. But no adequate evidence to demonstrate that CPP-ACP have greater effectiveness on preventing and reversing on WSLs.

4. Huang et al. 2013	Visual inspection Digital photos: evaluation by analogue visual scale	Reduction scores in the lesion area: Expert evaluators: G1: 27.3%, G2: 21.2%, G3: 28.5% Appraisers: G1: 25.4%, G2: 29.4%, G3: 31 Goals: G1: 17.2%, G2: 15.7%, G3: 24.6% Self-assessment: G1, G2, G3: 37%	No difference were found the effectiveness of CPP-ACP or varnish compared to the control group for 8 weeks.
5. Uysal et al. 2010	Microhardness DIAGNOdent	Use of CPP-ACP and fluoridated gel were more efficient than the control group ($P < 0.001$). No significant differences between groups with CPP-ACP and fluoride	CPP-ACP with the effectiveness on preventing WSLs. But no significant difference compare with standard fluoride application
6. Sombir Singh et al. 2016	Visual inspection DIAGNOdent	G1: No significant effects on WSL remineralization G2: significant decrease in the severity of WSL ($p<0.01$) G3: significant remineralization of WSL ($p<0.05$) No statistically significant differences between groups ($p>0.05$) for visual inspection	Use of fluoride varnish and CPP-ACP cream concomitantly with fluoridated brushing twice daily does not present additional benefits in the remineralization of WSL
7. Said Karabeklroglu et al. 2017	Visual inspection DIAGNOdent	DD result – G1: T1 – 12.45 ± 6.52, T2 – 8.20 ± 4.38, G2: T1 – 13.06 ± 5.90, T2 – 4.76 ± 2.48 Severity of lesion decrease– G1 – 67.4%, G2 – 57.3% Use of CPP-ACP and fluoridated gel were more efficient than the control group ($P < 0.001$).	CPP-ACP with the effectiveness on preventing WSLs. But no significant difference compare with standard fluoride application

3.4 Result of individual studies

In total of the studies, 361 participants in these 7 studies. 118 participants are applied with CPP-ACP application for intervention groups. In these 118 participants, thereinto 57 participants applied with CPP-ACP application and fluoride included toothpaste, (7 participants applied with CPP-ACP application and non-fluoride include toothpaste). 133 participants are applied only standard tooth brushing, thereinto 126 applied with fluoride toothpaste, (7 applied with non-fluoride toothpaste). 110 participants are applied with other content application, 23 of the them applied fluoride included toothpaste, (7 applied with other content application with non-fluoride toothpaste).

From the study of Ann Bröchner et al. [25], the QLF measurement results showed that the changes of fluorescence (ΔF) and lesion area (A). It was similar in the intervention and control group for the baseline ΔF values, and statistically significant ($p<0.05$) reductions of about 30-35% after the 4 weeks study period in both of groups. The intervention group has smaller lesion area (A, mm^2) than controlled group in the baseline, but wasn't statistically significant in the difference. After 4 weeks study, the intervention group have average 58% decreasing of lesion area, it was significantly different to baseline ($P<0.05$), and it the controlled group have 26% was not significant difference. The difference between the two groups of the lesion area was close to reaching statistical significance ($p=0.06$). the clinical score showed the prevalence of WSL (score>1) was 84.6% in intervention group and 85.1% in the controlled group in the baseline. After 4 weeks treatment, it shows 52.3% and 47.3% in two groups. That is not statistically significant differences between two groups.

By evaluating he study of Mehmet Akin et al. [26], the mean of controlled group is 0.46% before treatment, and result in 0.26% after treatment. And compare with fluoride group 0.54% (pretreatment) to 0.27%(posttreatment) and CPP-ACP group 0.46% (pretreatment) to 0.22% (posttreatment). And in micro-abrasion group showed 0.52% (pretreatment) to 0.02% (posttreatment). The difference was statistically significant at $p< 0.01$ for all groups. With the results, we consider that micro-abrasion method has best effectiveness on preventing WSLs.

In the study of Bora Korkut et al. [27], the scores of all groups are different in the all evaluation including baseline. The all result between groups are statistically significant ($p<0.01$). The increase and decrease score of size and the increase and decrease score of intensity of controlled groups are statistically significant in each measurement period ($p<0.01$). But there is no evidence to demonstrate that CPP-ACP contained application have greater effectiveness on preventing WSLs.

During the study of Huang et al. [28], The score is assessed by professional panel is 27% for the fluoride toothpaste group, 21% for the MI Paste Plus group, and 29% for the fluoride vanish group. And by lay panel the results are 25%, 29%, and 31%, respectively. Goals of improvements in the surface affected are 17%, 16%, and 25%, respectively. And Self-assessment of improvement are 37% for all three groups. No assessments indicated significant differences between subjects in the active arms compared with the control arm.

From the study of Uysal et al. [29], the comparison of test presented that the use of CPP-ACP and fluoride containing topical gels were more significantly efficient than the non-fluoride toothpaste group ($p < 0.001$). But no significant differences were showed between CPP-ACP and the fluoride groups against demineralization.

By the study of Sombir Singh et al. [30], there is no significant effect on remineralization of WSLs in the group with only fluoride toothpaste used 2 times a day ($P=0.078$), but significant effect on remineralization of WSLs in both group with using fluoride varnish ($P<0.01$)and CPP-ACP application ($P<0.05$) for 6 months. Between the group comparison showed that the mean visual and DIAGNOdent scores at various time intervals of observations were decreased more when fluoride varnish and CPP-ACP application were used in addition to daily use of fluoride toothpaste, but the differences were not statistically significant ($P > 0.05$)

In the last study of Said Karabeklroglu et al. [31], total of 41 subjects, 7 of participants dropped out during the study, 3 from control group and 4 from CPP-ACP group. Thus 34 subjects with 178 teeth for this study. The WSL evaluating by the result of DD at baseline of 12.45 ± 6.52 in control group and 13.06 ± 5.90 in CPP-ACP group, and after 36 months evaluation of result at 8.20 ± 4.38 in the control group and 4.76 ± 2.48 in the CPP-ACP group. The mean of results are similar in two groups, and there was statistically significant differences between the two groups results after 36 months evaluation.

4. Discussion

During our study, we realized that WSLs are significant problems and common symptoms in orthodontic treatment. As orthodontist, we need to consider for the health of patients and final result of treatment. Based on some studies, we realized the most common method for preventing WSLs are applying a good hygiene with some agents (the most common use is topical application of fluoride agents) [36, 28, 37], Their remineralization action is based on fluorhydroxyapatite formation on the dental surface [39]. At the same time intaking with low carbohydrate in diet is also a significant factor [38].

By some researches, we find out that CPP-ACP products may in different forms like rinses, toothpaste, milk, lozenges, chewing gums based on xylitol or sorbitol [34, 35]. These products based on CPP-ACP, they have ability to against tooth decay, promoting the remineralization of carious lesion as we described previously. CPP-ACP products act on the demineralization from the release of phosphate and calcium ions when applied on the dental surface or biofilm, they are leading to the saturation of the oral pH reestablishment, at the same time delayed biofilm formation and impaired adhesion of the microorganisms.

Some studies presenting effectiveness of CPP-ACP for non-orthodontic patients. Azarpazhooh and Limeback, they find out that effectiveness on preventing of caries formation [40], and Yengopal and Mickenautsch mentioned high values for remineralization in patients who used CPP-ACP containing tablets compared to tablets without CPP-ACP or other substances containing [41]. However, it shows insufficient evidence of effectiveness of CPP-ACP for preventing WSLs development.

CPP-ACP does not cause cytotoxicity or sensitivity reaction, with the exception of casein-allergic individuals, and has good biodegradability. Doctors can apply small amount of CPP-ACP containing products to the mucosa to observe if the patient will present allergy reaction or not [42].

For comparing the effectiveness of different agent on preventing WSLs, firstly we need to find out methods to evaluating the WSLs development. From our study, some methods were like the QLF measurement, visual inspection, FluoreCam, Microharness, DIAGNOdent be used to demonstrate the lesions on the tooth surfaces. These measurements are based on fluorescence changes for evaluating the following loss of enamel demineralization.

Based on our study that CPP-ACP containing products have been used in orthodontic patients with the aim of promoting remineralization, we received a good result of their effectiveness on preventing WSLs. And with easy daily application method for the patient and non-toxic properties. It is highly recommended for the patient during or after orthodontic treatment as prevention agent for WSLs, to obtain the best result of esthetics. In same time, we also obtain the good result of common topical fluoride applications' effectiveness on preventing WSLs, they are more common during the daily use. However, both of these applications we strongly to prove that they have great effectiveness for preventing WSLs during or after orthodontic treatment. And both can

be suggested to the patients to prevent WSLs. However, based on comparing the results of these two agents during our study, we can't obtain the significant difference between the CPP-ACP containing products and fluoride products (rinse, varnishes, topical gel, toothpaste) effectiveness on preventing WSLs during or after orthodontic treatment.
In summary of our study, we can highly recommend that both two agents (CPP-ACP application and common fluoride application) for patient to prevent WSLs during or after orthodontic treatment. They both presented great effectiveness on preventing WSLs. But due to statistical result, our hypothesis that CPP-ACP can perform greater effectiveness than common fluoride agents on preventing WSLs during or after orthodontic treatment will be rejected.

Limitation:
Due to lack of high-quality clinical studies or systematic reviews about preventing of WSLs on orthodontic patients or follow up of patients after orthodontic treatment with CPP-ACP agents. And some studies with various inclusion criteria, insufficient size of the sample during the clinical studies, unreliable statistical analyses that unsuccessful to evaluating for effectiveness, small amount of studies in vivo, un-accurate investigate method like only examination by visual and so on. These all factors result that difficult to determine accurately which type agent can perform better effectiveness on preventing WSLs during or after orthodontic treatment for the patients.
And as orthodontist, we also need to consider that highly concentrated fluoride may lead to fluorosis. It will cause the tooth with tiny white specks or streaks that may be unnoticeable to dark brown stains and rough, pitted enamel that is difficult to clean [45]. It is a common complication that we know of overtaking by fluoride. Due to that insufficient clinical studies trails can prove or reject this question, so we need more and new high-quality studies for supporting to confirm this question [46, 47]. Thus, for preventing WSLs during our treatment, the amount of intaking is significant consideration for orthodontist as well.
It is also significant that consider if we can evaluate before WSLs improvement, such as during orthodontic treatment or after removing braces, or the level of these WSLs [28]. By this we realized that we need more accurately and high-quality study to supporting our hypothesis.

5. Conclusions

During these 7 clinical studies, the conclusion of effectiveness of common topical fluoride application on preventing WSLs in orthodontic treatment is positive.
Meanwhile, during the studies made significantly positive conclusions about effectiveness on preventing WSLs in orthodontic treatment by CPP-ACP contained applications.
However, there is no significant difference between two applications with common topical fluoride and CPP-ACP containing on prevent WSLs during or after orthodontic treatment. Thus, the conclusion of hypothesis will be rejected about that the agent content CPP-ACP have better effectiveness than common topical fluoride application on preventing WSLs during or after orthodontic treatment.

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