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FLUORIDE ALTERNATIVES FOR REMINERALIZATION OF EARLY ENAMEL CARIOUS LESIONS, FACT OR FICTION? - A SYSTEMATIC REVIEW

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ABSTRACT

Aim: The purpose of this study was to systematically assess the quality of evidence supporting fluoride's alternatives for treating early enamel caries.

Methods: A broad search strategy using PubMed and other sources was performed. For sensitive search strategy, we used MESH database and the following search queries: (''Remineralization'' [Mesh] OR ''Remineralisation'') AND (''Caries'' [Mesh] OR ''Decay'') AND (''Fluoride''). Predetermined criteria were: parallel, randomized, controlled trial studies with 6 to 18 years old children.

Results: 1919 articles from PubMed advanced search were initially revealed then 79 papers were picked up, in addition to 536 from other sources. One paper only removed as a duplicate (by the author, title and reference). The remaining articles were indicated for closer assessment. Out of 614 papers were screened by title, only 29 met the inclusion criteria of this review. Additional screening by abstract was done independently by the three researchers to result in 7 articles.

Conclusion: From this review, there is moderate clinical evidence to support preventive agents as fluoride substitutes. This review suggests the use of resin infiltration and fluoridated Miswak as remineralizing agents.

KEYWORDS: Early enamel caries – Fluoride – Remineralizing agents.

INTRODUCTION

There is no doubt that the introduction of different remineralizing agents such as fluoride products has contributed to a significant decrease in the severity and prevalence of dental caries, particularly in developed countries. Despite this progress, dental caries remains the most common oral disease and a challenge for the dental team [1].

According to the previous researches, Dental caries can be defined as a multifactorial disease results in the dissolution of dental hard tissues due to loss of minerals by substantial pH fluctuations by

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cariogenic bacteria located in the dental biofilm[2]. Yet, the carious process alternates remineralization and demineralization cycles with reversible or irreversible stages [3].

White spot lesions (WSL) are the first visual clinical observation of dental caries and may be either active (rough and opaque) or inactive (smooth and shiny) due to demineralization of the enamel subsurface, with increased porosity due to the removal of minerals from the deep tissue to the outside surface [2]. If de-mineralization remains untreated, however, dental caries can progress into irreversible stages of enamel breakdown and apparent cavitation [1]. Approaches to prevent or treat WSLs are of great importance, particularly in young ages [4]. Topical fluorides, including fluoride toothpaste, fluoride mouth rinses, and fluoride varnishes, are the most commonly used agents for treating WSLs [5].

Many reports support that the preventive strategies, especially the use of fluorides, can arrest or even reverse the demineralization process of early enamel carious lesions. Moreover, the prevention of these lesions can be achieved in combination with other preventive measures such as dental biofilm control and diet control [6]. However, several researches have also investigated other remineralizing agents which could be valuable to control dental caries [7].

On the other hand, concerns about exposure to fluoride from multiple sources are growing, potentially increasing their risk of developing dental fluorosis [8]. Another concern regarding fluoride therapy for the treatment of WSLs is the potential hyper-mineralization of the surface layer in the presence of high concentrations of fluoride ions which prevents the subsequent penetration of phosphate and calcium ions into the body of the lesion [9]. Nevertheless, a recent systematic review by Cochrane stated that the 6-week application of fluoride varnish was effective in preventing the formation of WSL. However, this approach is onerous, requires professional input and can be expensive [10].

For ideal remineralization system, calcium, phosphate, and fluoride must all be available at sufficient levels in a bioavailable form in the oral environment to enhance the remineralizing ability of saliva and oral reservoirs without increasing the risk of calculus formation [11]. In recent years, the development of novel enamel remineralization systems has significantly progressed with many of them already in clinical use such as bioactive glass, casein phosphopeptide-amorphous calcium phosphate, self-assembling peptide, and resin infiltrate [12].

The anti-caries benefits of calcium phosphate-based remineralization systems have been tested to remineralize WSL. Various randomized controlled clinical trials of post-orthodontic WSL demonstrated considerable results after the use of CPP-ACP preparations [13-15]. However, other studies could not prove any benefits of CPP-ACP-based remineralization products [16, 17].

Recently, various studies have shown the effectiveness of resin infiltrate in preventing further demineralization. This technique is based on a low-viscosity resin with a high penetration coefficient to prevent further progression of the lesion by sealing the enamel intercrystalline spaces [18]. An interesting addition to remineralizing agents is natural products such as:

G. Chinensis, grape seed extract and fluoride impregnated miswak that have demonstrated the ability to beneficially shift the de-/remineralization caries equilibrium [12, 19]. However, chemical characterization and standardization of the natural products will be required before further application in clinical trials [12].

There is a large amount of clinical evidence supporting the potential preventive effect of different fluoride formulations. However, the clinical evidence of the effectiveness of other remineralizing agents is far less convincing and lacking for head to head comparison. So, the aim of this systematic

review is to answer the following question: "Do we have an effective preventive clinical intervention other than fluoride for early enamel caries?"

METHODS

For the preparation of this review, we followed the guidelines of the PRISMA statement.

Literature search strategy

A literature search through the computer, in all of PubMed, Springer, and Thomson Reuters, Thomson Reuters (conferences), Wiley, Nature, Science direct, and Scopus was performed to capture all the published studies. For the sensitive strategy of search, we employed the database of MESH and search queries as follows: (''Remineralization'' [Mesh] OR ''Remineralisation'') AND (''Caries'' [Mesh] OR ''Decay'') AND (''Fluoride''). Screening the titles and abstracts of the retrieved articles were done by three authors. The screening for eligibility was completed in two steps. The first step involved screening abstracts for eligibility, and the second step involved retrieving and screening the full - text articles of eligible abstracts. A study was included in this review if, after discussion, at least two of the authors agreed that it was appropriate.

Inclusion and exclusion criteria

The criteria for inclusion used to filter the studies identified were:

- Participants: children of any gender with an age ranging from 6 to 18 years and have initial enamel carious lesions.
- Interventions: any remineralizing agent other than standard fluoride (with any form).
- Comparisons: standard fluoride or any other remineralizing agent if not found.
- Outcomes: Recognized clinical measures of early caries lesions or enamel demineralization.
- Study Design: Randomized parallel Clinical trials.

Whereas the exclusion criteria were:

- Reviews, case reports, abstracts, letters to editors, editorials, commentaries, in vitro and in situ studies utilizing bovine or human enamel were excluded.
- Non-English language studies were excluded.
- Studies utilizing an artificial caries model or enamel demineralization model were excluded.
- Studies contain placebo were excluded.

Data extraction

The data were extracted independently by three authors, using online data extraction form "Endnote". The data that extracted involved the following: (1) study design; (2) study population; (3) risk of bias domains; and (4) study outcomes. Disagreements were resolved by discussion between the three researchers.

Quality assessment OR Risk of bias

The quality of the recovered RCTs was assessed on the basis of the Cochrane Handbook for Systematic Intervention Reviews 5.1.0 (updated March 2011) using the quality assessment table contained in the same book (part 2, chapter 8.5) [20]. The Cochrane Bias Risk Assessment Tool included the following areas: sequence generation (selection bias), concealment of allocation sequence (selection bias), participants and personnel blinding (performance bias), blinding in outcome assessment (detection bias), and shortage in outcome data (attrition bias), selective reporting of outcomes (reporting bias) and other potential sources of bias. Authors 'final judgment was classified as low, high, or 'Unclear bias risk.'

RESULTS

A broad search through database was done by three researchers in 2-1-2019 that revealed initially a total of 1919 articles from PubMed advanced search which, after applying filters (randomized clinical

trials – Humans- English – 6-18 years old) the results were 79 papers. A total of 536 from different sources (Springer 97, TR 100, TR conferences 97, Wiley 18, Nature 24, ScienceDirect 100 and Scopus 100).

A total of 615 articles were explored to the Endnote program. One paper only removed as a duplicate (by the author, title and reference) and the remaining articles were indicated for closer evaluation. These 614 papers were screened by title, most of these articles did not meet the inclusion criteria of this review. This filter reduced the articles to 29 that were screened by abstract independently by the three researchers and reduced to 7 articles.

The 22 papers were excluded due to either in-vitro, in-situ, including placebo or agents other than standard fluoride in control groups or the age of participants is out of age range included in this study. Finally, all the remaining seven studies were included in this review after full-text screening as in table 1.

All the seven included studies are in vivo randomized clinical studies. Three studies [3, 11, 15] were conducted to evaluate the effect of CPP-ACP on WSLs in comparison with standard fluoridated toothpaste [3, 15] or with fluoride varnish [11] in children and adolescents. Aykut et al. and Brochner et al. [3, 15] presented no clear significant differences between CPP-ACP and fluoride toothpaste in follow up endpoints. According to Brochner et al.[15], both groups showed a significant reduction in measurements of WSLs after 4 weeks of follow up. Llena et al. [11] reported that CPP-ACP paste and CPP-ACP containing 900 ppm fluoride both gave fewer scores of WSLs in comparison with professionally used 5 % sodium fluoride varnish after 8 and 12 months of follow up but without significant difference. The only significance between the groups, at a given time point, was that between Groups of CPP-ACP at four weeks.

Aykut et al [3] showed that CPP-ACP presented a reduction in the scores of WSLs from baseline to 3 months of follow up but without significant difference while a group of fluoride paste only showed a significant increase in scores of WSLs after 3 months of follow up. Ferreira J.M.S. et al. [6] compared the effect of two fluoride varnishes (5%NaF and 6% NaF + 6% CaF2) in controlling carious development with WSLs. In their results, despite the mean value of the difference in reduction was higher in the group including CaF2 there was no significant difference presented between both fluoride varnish formulations. Almeida M.Q. et al.[2] evaluated the therapeutic effect of FL- Fluorniz (5% NaF); DUO– Duofluorid XII (6% CaF2+6% NaF); and DF- Durafluor (5.5% NaF) in remineralization of WSLs and no significant difference was presented between the three fluoride varnish types regarding measurements through using a WHO periodontal probe.

Baeshen et al. [19] add a 0.5% sodium fluoride to natural Miswak and compared it with natural Miswak without fluoride (used in one quadrant in comparison with the other quadrant that treated only by fluoridated toothpaste) for remineralization of WSLs. They showed in their results that fluoridated miswaks presented a significant reduction in scores of WSLs scored by Diagnodent and ICDAS II scoring system in comparison with fluoridated toothpaste in the contralateral quadrant while the non-fluoridated miswaks presented no difference.

Cifici et al. [4] treated WSLs by resin infiltrate in comparison with fluoride varnish for 3 months of follow up and a significant decrease was evident in both groups. By comparing measurements after one, two and three months of follow up the difference were significant in resin infiltrate group and not significant in fluoride varnish group.

Quality of included studies

The included studies were of quality in the range from low to moderate as recommended by the assessment tool of the risk of bias of Cochrane. The quality assessment of domains was summarized in figure 1.

The evidence strength, of the group of studies included in this systematic review, is moreover weakened due to short observation periods (Five studies [2,6,11,15,19] with duration shorter than 3 months, varying outcome measures (clinical indices [2,4,6,11,19] laser and light-induced fluorescence [3,4,15,19]) and the small total number of participants (360 participants for all included studies).

TABLE (1) Summary of included studies

Study ID	Type of study design	Objectives	Study population	Comparison groups (follow up)	Other sources of fluoride	Primary outcome (measurement)	Results for primary outcome
Ferreira JMS et al, 2009	RCT	Preventive effect (5%NaF and 6% NaF + 6% CaF2).	15 subjects (7- to 12-years) with 45 active WSLs	At baseline and after 4 Weeks	Fluoridated toothpaste and prophylactic paste	Maximum WSL dimensional changes were measured and lesion activity	No statistically significant differences between all groups
M.Q. Almeida et al	RCT	Preventive effect (5% NaF, 6% CaF2+6% NaF and 5.5% NaF)	78 (7-13 years) of 67 WSLs	At baseline and after 5 weeks	Dentifrice of 1500 ppm fluoride	Maximum WSL dimensional changes were measured and lesion activity	No statistically significant differences between all groups
Baeshen et al	RCT	Therapeutic effect of fluoridated and non-fluoridated Miswak on WSLs	19 orthodontic patients (mean age, 17.2 years) with 150 WSLs	At baseline and 2, 4, and 6 weeks	Fluoridated toothpaste (1450 ppm)	WSLs scored using DIAGNOdent pen and ICDAS II index	Statistically significant differences between the 2 quadrants in the test group but not in the control group
Brochner et al	RCT	Therapeutic effect of 10% CPP-ACP on WSLs	Children (13-18 years) with 327 WSLs	At baseline and after 4 weeks	Water fluoridation (<0.2 ppm F)	Readings of QLF and clinical inspection of WSLs	No statistically significant differences between the groups
Cifci ZZ 2018	RCT	Therapeutic effect of resin infiltrate or fluoride varnish on (WSLs)	132 teeth from 68 patients (8-16 years) with WSLs	Before, just after the application, and after 1 month and 3 months	Toothpaste with 1,500 ppm fluoride	Lesions were scored with DIAGNOdent and ICDAS II	Statistically significant differences was obvious in all groups
Llena et al 2015	RCT	Therapeutic effect of CCP-ACP and CPP-AC FP and 5% fluoride varnish on WSLs	60 children (6-14 years) with 786 WSLs	At baseline and at 4, 8, and 12 weeks	Fluoride toothpaste (1100 ppm of fluoride)	Lesions severity scored using ICDAS II and Diagnodent also lesions activity evaluated using the Ekstrand criteria	A significant difference was clear between groups at different intervals
Aykut et al 2014	RCT	Therapeutic effect of CPP-ACP and fluoridated toothpaste on WSLs	60 children of age (13±0.68) with 60 WSLs	At baseline and after 3 months	The toothpaste of 1450 ppm F	Lesions were Recorded using DIAGNOdent device	No statistical significant in reduction of WSLs in the test group and a statistically significant increase in scores of WSLs in control group

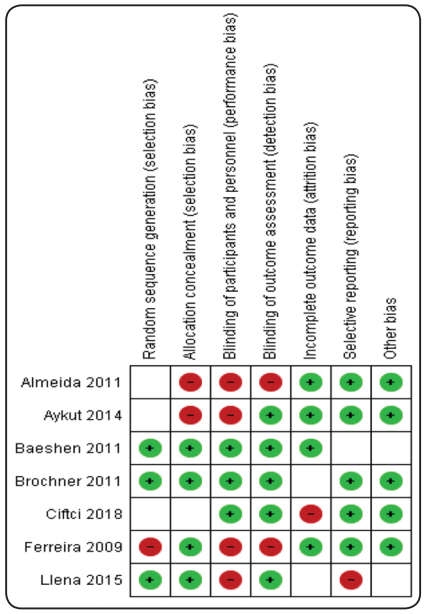

Fig. (1) Presentation of the risk of bias assessments for the studies included in the review

DISCUSSION

A relatively large number (2455) of publications resulted from the initial literature search on remineralizing agents; however, a deep assessment of the results recorded 29 articles that were inspected in details. Finally, this systematic review selected seven articles.

It may be considered slightly strange that the majority of the evidence on remineralization studies arises from orthodontic patients who are considered a selective group of people undergoing specialized dental care and not mimic the general population. Despite the small specificity of the target group for the included studies, the results shouldn't be ignored 7 as a meta-analysis of 14 studies had demonstrated that the WSLs incidence and prevalence rates were 45.8 and 68.4%.during the orthodontic treatment [21].

White spot lesions (WSLs) can naturally remineralize by taking minerals from the saliva without the need for any treatment, but this approach had a little effect on deeper lesions structure [22, 23]. Enaia et al.[24] showed that 57.1% of WSLs improved, 26.2% remained the same, and 16.7% became worse after a 1-year follow-up without any treatment.

WSL remineralization by a fluoride varnish can assist in the improvement of oral hygiene with fluoridated dentifrices. The favorable combination of fluoride and oral hygiene in reducing WSL wouldn't, therefore, be ignored, as the success of fluoride therapy relies on children's incentive to improve oral hygiene [25].

Three of the included studies [3, 11, 15] in this systematic review reported that CPP-ACP offers a benefit in terms of reduction of white spot lesions in children and young adolescents similar or even more beneficial (CPP-ACFP) than standard fluoride. Therefore, it would be from wise to recommend CPP-ACP and CPP-ACFP for prevention of these lesions.

Treatment with CPP-ACFP seemed to reduce the severity of caries lesion faster than treatment with CCP-ACP. This improved rate of remineralization may be attributed to the presence of calcium, phosphate and fluoride ions in unstabilized form, which will simply form fluoroapatite. In the lack of CPP, this reaction is weakened by prompt development of calcium phosphate phases [26], but when stabilized by CPP, these ions spread down into the deeper enamel layers [27]. In addition, some studies found that CPP-ACFP solutions could have an advanced remineralization capacity than CPP - ACP at acidity levels beneath pH 5.5, suggesting its function in highly acidic environments [28].

The results confirm that CPP - ACFP is superior to both CPP - ACP and fluoride varnishes in the instant to very short periods after the beginning of treatment [11].

Nevertheless, because of parental safety concerns, the fluoride-free CPP – ACP appears to be a worthy substitute to lesion reversion in patient groups that are unwilling to use fluoride products. It was reported that CPP - ACP has the potential

to enhance remineralization [29-33] as it maintains calcium and phosphate at a supersaturated state on the enamel surface compared to that in saliva, thus decreasing demineralization and enhancing enamel remineralization [34].

The children used the CPP - ACP paste directly after a routine fluoridated toothpaste reported that fluoride tends to interfere with the ACP component of the casein complex and precipitate as calcium fluoride resulting in ineffectiveness of both inorganic components [35]. But this could only happen if there is massive fluoride, as there is also a fluoride containing CPP-ACP as shown by Reynolds [36] who observed that toothpaste containing 2% CPP-ACP plus 1100 ppm F was higher to all other mouth rinse and dentifrice constructions containing CPP-ACP and fluoride. Controversially, in a study by Beerens et al. 2010 [16], which evaluated the effects of CPP - ACPF paste on the remineralization of enamel WSLs, it was reported that there were no variances between the CPP - ACFP and the free fluoride paste in the remineralization of enamel.

Two of the included studies [2, 6] comparing different forms of fluoride-containing CaF2 with the standard fluoride NaF. They also found that there is no significant difference between these forms as regarding the reduction of initial caries. WSL remineralization can be primarily clarified by the rise in oral CaF2 reservoirs after fluoride varnish applications and later the solubilization of these reservoirs at low pH release fluoride ions [25].

There is evidence that NaF varnishes effectively increase fluoride absorption and reduce enamel mineral loss under various circumstances [37, 38]. Even though the CaF2 formula may extend the occurrence of fluoride in the oral cavity due to an increase in calcium binding sites [39].

Of course, one valuable aspect of the CaF2 varnish is the enhancement of cost-benefit ratio in caries control programs since this product is about 10 times less costly than the NaF and other comparable fluoridated varnishes [6].

The only two studies reported with a significant reduction of WSL than standard fluoride were Baschen et al. [19] who showed the significant effect of fluoridated Miswak and Cefitci et al. [4] who reported the significant effect of resin infiltrate.

This effect is related mainly to the rapid fluoride release from Miswak, as the remineralizing effect of non-fluoridated Miswak was much smaller [40, 41]. The bristle-containing fluoride easily reaches the teeth's buccal surfaces. An additional advantage of using fluoridated Miswak is no requisite for the post-brushing water rinsing; water rinsing has been found to have a deleterious effect on the retention of oral fluoride [42].

Munoz et al. [43] reported that resin infiltrate penetrates into active decay lesions when compared with inactive lesions, which is caused by the more porous and thinner surface layer of active lesions. Resin infiltrates block further diffusion of the bacteria by creating barriers and stops lesion development allowing spontaneous remineralization from the saliva [4].

Meta-analysis couldn't be done due to varied protocols of study designs and different outcome measures in this group of studies. Clearly, more randomized longer-term trials are required.

CONCLUSION

The findings of this systematic review raise the attention to different remineralizing agents over the standard fluoride for the prevention of early enamel caries. With regards to the use of CPP-ACP and CPP-ACFP for regression of WSLs, there is a direction toward the advantages for their use but the quality of the evidence is limited. On the other hand, there is a significant effect of resin infiltration and fluoridated Miswak over the standard fluoride in the prevention of WSLs. Future well-conducted RCTs considering long-term follow-up periods is needed to establish the best clinical practice.

Abbreviations

WSLs: White spot lesions

CPP-ACP: casein phosphopeptide-amorphous calcium phosphate.

CPP-ACFP: Casein phosphopeptide-amorphous calcium fluoride phosphates.

RCT: Randomized clinical trials.

NaF: Sodium fluoride.

CaF2: calcium fluoride.

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