

Evaluation of the Remineralization Treatments of White Spot Lesions in Primary Teeth: A Systematic Review

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Abstract Background: This study investigated the effect of the remineralization treatments on regression or disparition of white spot lesions (WSLs) in primary teeth. Materials and methods: Databases (Embase, MEDLINE, CENTRAL and CINAHL) were searched. The searches were limited to English and French languages publications and to within the abstract field. The searches were limited to the period from 01-12-2000 to 01-12-2018. Additional studies were identified by scanning the bibliographies of relevant reviews and full-text articles. Randomized controlled human clinical trials in which fluoride and non-fluoride agents were delivered by any method to treat white sopt lesions in primary teeth were considered. Results: Of the 2350 studies screened, 1706 full articles were scrutinized and 6 selected for inclusion in the final sample. Three chemical agents, namely fluoride, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and chlorhexidine were investigated in these included studies. There is evidence that fluoride varnish applications may be an effective measure in reversing active pit- and-fissure enamel lesions in the primary dentition, the combined application of chlorhexidine and fluoride varnish is more effective on plaque and remineralization of incipient caries after 3 months than the same agents applied separately and finally the twice daily topical applications of CPP-ACP containing paste as an adjunct to a standard oral hygiene with fluoridated toothpaste, significantly improve the remineralisation of white spot lesions in primary teeth. However, quantitative synthesis could not be carried out because of the clinical and methodological heterogeneity of the included studies. Conclusion: A limited number of studies were included in this systematic review. Few of these has a low risk of bias, with most having high risk due to weaknesses in many quality items or due to other biases, such as problems associated with the evaluation method or inadequate study design. High quality human randomized controlled trials are needed in order to make a conclusive recommendation.

Keywords: white spot lesions, primary teeth, remineralization treatments, systematic review

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1. Introduction

Dental caries in primary teeth is one of the most common diseases of early childhood. The process of caries formation is a cycle of remineralization and demineralization which can be arrested or reversed by preventive factors in the oral environment or oral hygiene practices [1]. Caries lesions usually develop more rapidly in primary teeth than in permanent teeth due to the differences in enamel structure and dietary habits between childrens and adults. The enamel in primary teeth is thinner and the surface micro-hardness is relatively lower, compared with permanent teeth. Also, primary teeth have a less well-

structured crystal arrangement and comparatively less mineralization [1]. These differences in enamel structure may lead to the caries susceptibility and faster caries progression in primary teeth. White spot lesions (WSLs) are defined as enamel surface and subsurface demineralization, without cavitation [2]. These manifestations represent the first clinical observation of the progression of dental caries, with the possibility of being reversed. These lesions are characterized by a white, chalky, opaque appearance and are commonly located in pits, fissures, proximal and smooth surfaces of teeth [3]. The white appearance of early enamel caries is due to an optical phenomenon which is caused by mineral loss in the surface or subsurface enamel [4]. Enamel crystal dissolution begins with subsurface demineralization, creating pores between

the enamel rods. The resultant alteration of the refractive index in the affected area is then a consequence of both surface roughness and loss of surface shine and alterations in internal reflection, all resulting in greater visual enamel opacity [5]. Numerous therapies are cited in the literature, for instance, oral hygiene instructions, fluorides agents and non fluorides agents, like phosphopeptide compounds and chlorhexidine. Thus, numerous clinical trials have been conducted to test the ability of fluoride and non-fluoride agents to remineralize white spot lesions in primary teeth [7,8].

The aim of this systematic review was to investigate the effect of the remineralization treatments on regression or disappearance of white spot lesions (WSLs) in primary teeth.

2. Material and Methods

This systematic review followed the preferred reporting Items for systematic reviews and Meta-analyses (PRISMA) statement guidelines [10]. Research protocol was registered in the International prospective register of systematic reviews (PROSPERO) before data collection, under ID : CRD42018111391, available from: www.crd.york.ac.uk/PROSPERO/display_record.php.

The PICO question used in this study was “in young patients aged between 0 to 5 years old with white spot lesions in primary teeth, what are the remineralization treatments more effective at regression or disappearance of lesions” (Table 1).

Table 1. Representing table of PICO question

Population	Young patients with white spot lesions in primary teeth (ICDAS 1 and 2).
Intervention	Remineralization treatments with different agents and techniques.
Comparison	Comparing the different therapies and agents with each other.
Outcome	Regression or disappearance of white spot lesions.

2.1. Search Strategy and Databases

A methodic search to identify all the relevant studies was conducted on the following four data-bases: MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials) and CINAHL. The searches was limited to English and French languages publications and to within the abstract field. The searches will be limited to the period from 01-12-2000 to 01-12-2018. Additional studies will be identified by scanning the bibliographies of relevant reviews and full-text articles.

In the PubMed database, the following search equation was used: ((white spot)) AND ((primary teeth)) AND (remineralization treatments) OR (remineralization agents).

2.2. Selection Criteria

2.2.1. Type of Studies

The inclusion criteria were all human randomized controlled clinical published between 01-12-2000 and 01-12-2018, in English and French, with abstract. Studies in which participants had white spot lesions in the primary dentition at the start of the study were considered for

inclusion in this review, irrespective of the baseline caries experience.

2.2.2. Types of Participants

Young patients aged between 0 to 5 years old, having white spot lesions on primary teeth and all early caries lesions (including ICDAS 1 and 2) in their primary teeth and having a good general health status. Studies in which participants had systemic disease were excluded.

2.2.3. Type of Intervention Reviewed

Studies using fluoride and non-fluoride agents to treat white spot lesions in primary teeth that will be compared with placebos was included. No restrictions were implemented regarding the dose, frequency, duration or method of fluoride or non-fluoride agents administration. Any study in which the participants underwent any non remineralizing therapy for white spot lesions treatments such as bleaching, enamel microabrasion or restoration and studies of remineralization treatments of white spot lesions in permanent teeth.

2.3. Data Extraction

Two academic reviewers (H.M. and B.F.) screened the titles and abstracts of the identified studies from the four database independently and in duplicate. Consensus was obtained by discussion and consultation with the third calibrated reviewer (R.H.) to resolve any disagreements during study selection and data extraction. Studies not respecting the pre-cited inclusion criteria were excluded. The two reviewers (H.M. and B.F.) independently extracted data from the studies using a data extraction form. The following data were collected in the form of a table : author and year of publication, number and age of participants and controls, follow-up period, intervention modality, assessment methods and conclusion with presented primary and secondary outcomes.

3. Results

3.1. Study Selection

A total of 2350 articles were screened for relevance. After applying inclusion and exclusion criteria, 1706 studies were scrutinized, 1700 studies were excluded and a total of 6 full papers were retained in the systematic review. The recapitulatif of our strategy of research of articles is represented on the systematic review flow diagram (Figure 1).

3.2. Study Characteristics

In the 6 articles included in our systematic review, a total of 401 participants were evaluated, all of them were classified as healthy by the authors. All studies reported the age of participants (age range, 0 to 5 years) and the duration of studies varied from 1 to 12 months. Three chemical agents, namely fluoride, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and chlorhexidine were investigated in the included studies. The delivery modalities of the agents were varnishes and pastes.

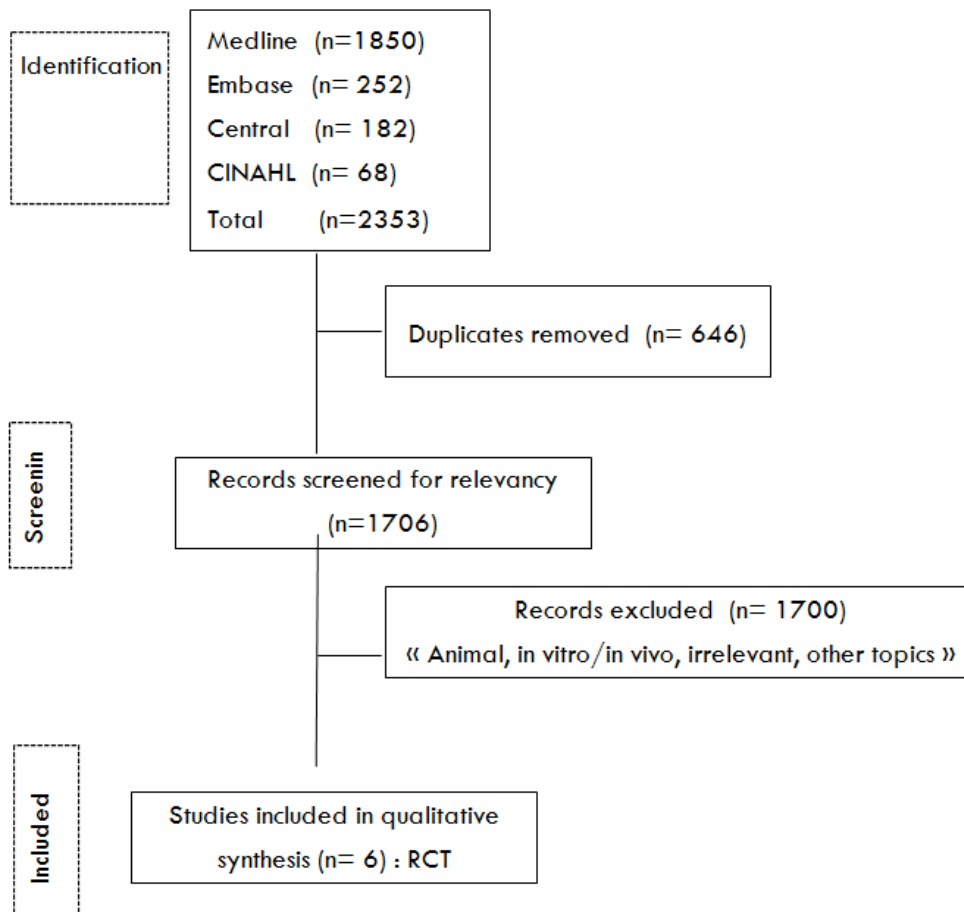


Figure 1. Systematic review flow diagram. (RCT = Randomized controlled trials)

One study reported the topical application of fluoride varnish for reversing active pit- and-fissure enamel lesions in the primary dentition. Two studies investigated the efficacy of the combination between chlorhexidine and fluoride varnish on the remineralization of incipient enamel lesions in primary dentition. Three studies compared the effect of daily application of CPP-ACP on white spot lesions in preschool children and the effect of daily application of CPP-ACP with fluoride toothpaste.

3.3. Outcomes of Studies

Of the 2350 studies screened, 1706 full articles were scrutinized and 6 selected for inclusion in the final sample. Three chemical agents, namely fluoride, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and chlorhexidine were investigated in these included studies.

The primary outcome measures used in the 6 studies included clinical assessment using the International Caries Detection and Assessment System (ICDAS) criteria or dmfs/dmft index, clinical assessment for the white spot lesions using WSL scores and the size of WSL, laser fluorescence DIAGNOdent and Enamel biopsy. One study found that fluoride varnish applications may be an effective measure in reversing active pit- and-fissure enamel lesions in the primary dentition compared with placebo after 4 months and 9 months. Two studies showed that the combined application of chlorhexidine and fluoride varnish is more effective on plaque and

remineralization of incipient caries after 3 months than the same agents applied separately. Finally, three studies showed that twice daily topical applications of CPP-ACP containing paste as an adjunct to a standard oral hygiene with fluoridated toothpaste, significantly improve the remineralisation of white spot lesions in primary teeth. However, quantitative synthesis could not be carried out because of the clinical and methodological heterogeneity of the included studies. The summary of different results obtained from included studies are shown in the [Table 2](#).

3.4. Risk of Bias

Using the guidelines in the Cochrane Handbook, 3 reviewers independently assessed the quality of the identified studies. The reviewers categorized the following 7 quality items as “low” (low risk of bias), “unclear” (uncertain risk of bias) and “high” (high risk of bias): sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. The level of risk for each study was then classified as low (all quality items with low risk), medium (1 or 2 quality items with high risk or unclear risk) and high (more than 3 items with high risk or unclear risk). Every included study that was analyzed presented some biases. After a critical reading of every one of them, we proceeded through the realization of the table presenting the biases risks ([Table 3](#)).

Table 2. Summary of included studies

Type of intervention	First Author (year)	Participants Intervention/control (age)	Follow-up Protocol	Intervention modality
Fluorides	Autio-Gold et al, (2001)	I (n=68) / C (n=115) (3-5y)	Baseline, 9m	Fluoride varnish (Duraphat, Colgate-Palmolive Co)
Fluoride and Chlorhexidine	Amorim, R.G. (2008)	20/20/20/20 (boys and girls) (3-5y)	Baseline, 1m, 3m	(1) Chlorhexidine varnish (cervitec) : weekly application during 4 weeks. (2) Fluoride varnish (Fluormiz) : weekly application during 4 weeks. (3) Chlorhexidine and fluoride varnish : weekly application during 4 weeks.
	Sarika N, (2016)	15/15/15/15 subjects (3-6y)	Baseline, 3m	(1) Fluoride varnish once a week for 1m. (2) Chlorhexidine varnish once a week for 1m. (3) Chlorhexidine and fluoride varnish once a week for 1m.
CPP-ACP	Sitthisettapong, T. (2012)	117/112 subjects (2.5/3.5y)	Baseline, 6m, 1y	10% CPP-ACP mousse + fluoride toothpaste
	Memarpor, M. (2015)	35/35/35/35 subjects (1-3y)	Baseline, 4, 8, 12m	(1) Oral hygiene and CPP-ACP mousse, twice a day. (2) Oral hygiene and 5% NaF varnish. (3) Oral hygiene + diet counselling.
	B Kargul (2017)	6 subjects (4 boys, 2 girls) ; (3-4.5 y)	Baseline, 1m	Oral hygiene (fluoride toothpaste 500ppm F- as NaF) and CPP-ACP (GC tooth mousse with a finger for 1min), twice a day.
Type of intervention	Comparative/Control	Assessment Method	conclusion	
Fluorides	Control group (no professional fluoride applications) (n=115)	Clinical assessment was performed at 9m follow-up.	Control / Fluoride varnish (Mean \pm SD), ($d_{E}mfs/d_{E}mft/d_{E}s$)* - Baseline (no difference) - 9m : ($p < 0.0001$) ** * $d_{E}mfs$: Decayed with initial enamel lesions, missing and filled surfaces; $d_{E}mft$: decayed with initial enamel lesions, missing and filled teeth; $d_{E}s$: decayed surfaces with initial enamel lesions. ** $d_{E}mfs$: $4.63 \pm 6.52 / 5.71 \pm 5.02$ ($p < 0.01$) / $d_{E}mft$: $2.51 \pm 2.74 / 4.02 \pm 2.85$ ($p < 0.001$) / $d_{E}s$: $1.20 \pm 1.96 / 3.05 \pm 2.99$ ($p < 0.0001$). Conclusion : fluoride varnish applications may be an effective measure in reversing active pit-and-fissure enamel lesions in the primary dentition.	
Fluoride and Chlorhexidine	Control group (no treatment, except restorative treatment when necessary)	Clinical assessment was performed at 1m and 3m follow-up with VPI and WS scores. VPI : visible plaque index. WSs : white spot scores .	Test1/test 2/test 3/control (Mean \pm SD) WS score (T1-T3): $-0.89 \pm 1.45 / 1.05 \pm 1.54 / -1.4 \pm 2.21 / 0.37 \pm 1.01$ ($p < 0.004$) Conclusion : The combined application of chlorhexidine and fluoride varnishes is more effective on plaque and remineralization of incipient caries after 3 months than the same agents applied separately.	
	Control group (no treatment)	DIAGNOdent and enamel biopsy at 3month follow-up.	Groups I, II, and III showed a significant decline in DIAGNOdent values at the end of 3 months when compared to baseline DIAGNOdent values ($p < 0.008$, < 0.001 , and < 0.001 respectively). Reduction of WS lesions from baseline to the end of 3m : 40% / 30% / 55% / 0%. Conclusion : The combined therapy with fluoride and chlorhexidine varnish may be considered an alternative therapy for early reversal of incipient lesions.	

CPP-ACP	Placebo toothpaste + fluoride toothpaste	Clinical assessment with ICDAS criteria	Test 1/ test 2/ control (Mean \pm SD) Baseline to 12 month (No progression/ progression) : OR : 1.002, 95% ; CI (0.86, 1.17) ; p=0,96). Conclusion : Daily application of 10% w/v CPP-ACP paste + regular toothbrushing with a fluoride toothpaste for 1 year had no significant added effect in preventing caries in the primary dentition of these pre-school children.
	Control (no treatment)	Change in mean WSL size and change in dmft index	G1/ G2 / G3 / Control Baseline to 12 m: -0.63 \pm 0.62/- 0.51 \pm 10.56/0.1 \pm 1.12/1.15 \pm 1.26. (p < 0.001/ p < 0.001/ p = 0,594 / p < 0.001). Conclusion : Oral hygiene along with four fluoride varnish applications or constant CPP-ACP during the 12 month period reduced the size of WSL in the anterior primary teeth.
	No control groupe	(ICDAS II; grades 0-3). + DIAGNOdent, 1m	Baseline to 4 weeks : LF results for WSLs before CPP-ACP : 8.41 \pm 12.43 and after CPP-ACP : 1.95 \pm 4.69 (p<0,001). Number of lesions that experienced regression : 77%. Conclusion : twice daily topical applications of CPP-ACP containing paste as an adjunct to a standard oral hygiene programme which includes fluoridated toothpaste, significantly improve the remineralisation of white spot lesions.

Table 3. 1. Low risk of bias / 2. Unclear risk of bias / 3. High Risk of bias

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective outcome reporting (reporting bias)	Other bias
Autio-Gold et al, (2001)	3	3	3	3	2	2	2
Amorim, R.G. (2008)	2	2	3	2	2	2	1
Sarika N, (2016)	1	1	1	1	2	1	2
Sithissetapong, T. (2012)	3	1	1	1	1	1	3
Memarpor, M. (2015)	1	2	3	1	1	1	2
B.Kargul (2017)	3	3	3	2	3	3	2

4. Discussion

The current review systematically investigated the effect of the remineralization treatments (fluoride and non fluoride agents) compared with control groups on regression or disparition of white spot lesions (WSLs) in primary teeth. Three fluoride agents and one non fluoride agent were used in the included studies: Fluorides, fluorides and chlorhexidine and CPP-ACP. The most relevant assessment methods of these lesions described in the literature are visual inspection, tactile examination with probing, photographic examination and enamel biopsy [17]. Other technologies allow WSL detection such as: quantitative light-induced fluorescence (QLF), laser fluorescence (Diagnodent), light-emitting diode refraction and reflection, digital fiber-optic transillumination (FOTI), electrical resistance caries monitoring device and optical coherence tomography [18]. In our review, four approaches for assessing were used: clinical examination, determination of the size of WSL, enamel biopsy and DIAGNOdent. These assessment methods are essential in the diagnosis of WSL, but should also be applied in the monitoring of the remineralization treatments of these lesions [20].

The exigence of a control group study design was a criterion for inclusion in our review (clinical controlled trial randomized), such as another agent to control, placebo or no intervention. However, ideally there should always be more than one control group: a positive (another agent or placebo) and a negative (no intervention) [25]. This standardization study design could reduce the study bias and increase the probability of quantitative comparison studies, increasing the strength of evidence [26]. Even with all the limitations of this review due to the different methods of diagnosis, the different follow-up, the non-standardization of the control group and the limited number of patients enrolled in some studies, it is confirmed to almost all included studies in this review that remineralization treatments with the different agents studied are effective for reducing the white spot lesions in primary teeth (size or visual appearance).

Fluoride is generally known to promote enamel remineralization in primary and permanent teeth [27]. Autio-Gold (2001) concluded that fluoride varnish applications may be an effective measure in reversing active pit- and-fissure enamel lesions in the primary dentition [11]. But the use of fluoride alone has been

reported to be insufficient to prevent progressive mineral loss [29]. Chlorhexidine, a cationic bis-biguanide with a broad spectrum of antibacterial activity, has been well recognized as a chemotherapeutic agent active against *Streptococcus mutans*, which plays a major role in tooth decay [36]. Several clinical trials and in vitro studies have demonstrated that combination treatment with chlorhexidine and fluoride is effective in caries reduction [37]. However, the synergistic effect of chlorhexidine and fluoride is still unclear. Indeed, Amorim, R.G. (2008) and Sarika N (2016) confirmed that The combined application of chlorhexidine and fluoride varnishes is more effective on plaque and remineralization of incipient caries after 3 months than the same agents applied separately [15]. Numerous studies have demonstrated the anti-caries effect of CPP-ACP by promoting remineralization and inhibiting demineralization. They also reported that CPP-ACP was effective in repairing the microstructure of enamel through significantly increased hydroxyapatite crystal size and calcium/phosphorus mol ratios. The result is in agreement with the studies of Sithisetapong, T. (2012), Memarpour, M. (2015) and B.Kargul (2017). They concluded that the application of CPP-ACP containing paste as an adjunct to a standard oral hygiene programme which includes fluoridated toothpaste, significantly improve the remineralisation of white spot lesions [13,14,16]. However, all the studies included in this review used traditional and electronic methods for detecting and monitoring white spot lesions in primary teeth. It would be beneficial in future studies to use more sophisticated electronic diagnosis methods to investigate the initiation, progression and reversal of white spot lesions in primary teeth.

5. Conclusion

A limited number of studies were included in this systematic review. Few of these has a low risk of bias, with most having high risk due to weaknesses in many quality items or due to other biases, such as problems associated with the evaluation method or inadequate study design. High quality human randomized controlled trials are needed in order to make a conclusive recommendation.

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