Abstract

**Objective:** The aim of this systematic review was to assess the long term remineralizing potential of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) only in paste form compared with fluoride varnish, and or placebo in both naturally occurring and post-orthodontic white spot lesions in vivo. **Data Sources:** The literature search covered the electronic databases: PubMed and Google scholar from 2005-2016. Only articles published in English were included. Randomized control trials in which CPP-ACP delivered by paste form were included. All studies which met inclusion criteria underwent two independent reviews. **Study Selection:** Two ninety five articles were identified from the search after excluding duplications. Abstracts of forty one articles were reviewed independently. Twenty nine articles were excluded after reading abstract. Full text articles were retrieved for fifteen relevant studies. After reviewing articles independently, three articles were excluded after full text reading. Finally twelve studies were selected based on the eligibility criteria. The remineralizing effect of CPP-ACP were compared with placebo and fluoridated toothpaste and fluoride varnish in randomized control trial. **Conclusion:** A high level evidence of remineralizing potential of CPP-ACP on naturally occurring white spot lesion and WSL post orthodontic treatment was found in comparison with placebo/fluoridated toothpaste and fluoride varnish without any statistically significant difference. Well-designed RCTs are, therefore, required to improve the level of evidence in this area.

**Keywords:** Casein phosphopeptide-amorphous calcium phosphate, early enamel caries, postorthodontic white spot lesions, remineralization, systematic review, white spot lesion

Introduction

Dental caries is a multifactorial disease; it is the result of complex interaction between host, agents, environment, and time. Dental caries is an infectious disease caused by acidogenic bacteria, leading to dissolution of enamel, dentin (coronal caries), cementum, and dentin (root caries).[1] It is a common dental problem in the world and affects 60%–90% of children and the majority of adults. [2] Worldwide contribution of dental caries to the burden of oral diseases is about 10 times higher than that of periodontal diseases and other common oral conditions. Owing to its globally high prevalence, dental caries is termed as a “pandemic” disease characterized by a high percentage of untreated carious cavities causing pain, discomfort, and functional limitations.[3] Dental caries results in the dissolution of apatite crystals and the loss of calcium, phosphate, and other ions, which eventually leads to demineralization of the tooth substrate.[4]

Enamel decalcification or the formation of white spot lesions (WSLs) is the first sign of dental caries, usually appearing as chalky white areas on the tooth surface. The subsurface porosity caused by demineralization gives the lesion a milky appearance that can be found on the smooth surfaces of teeth.[5] The prevalence of (WSLs) related to orthodontic treatment ranges from 2% to 96%, and 24% of WSLs may change into cavitated lesions if left untreated.[6] Enamel crystal dissolution begins with subsurface demineralization, creating pores between the enamel rods. The alteration of the enamel refractive index in the affected area of a carious WSL is a consequence of both surface roughness and loss of surface shine plus alteration of internal reflection, all resulting in visual enamel opacity because porous enamel scatters more light than sound enamel.[7]

If suitable treatment is presented to these lesions, enamel caries is capable to arrest, reharden and revert to healthy enamel...
condition through a remineralization process involving the diffusion of minerals into the defective tooth structure. For this purpose, remineralizing agents such as fluorides, xylitol, bio-active glass, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), tricalcium phosphate, and self-assembling peptides have been used. CPP-ACP application is one of the many techniques that have been proposed for simultaneously enhancing remineralization and reducing the occurrence of WSLs and dental caries.

The clinical use of calcium and phosphate ions for remineralization has not been successful in the past due to the low solubility of calcium phosphates, particularly in the presence of fluoride ions. Insoluble calcium phosphates are not easily applied and do not localize effectively at the tooth surface. In addition, acid is required to produce ions capable of diffusing into enamel subsurface lesions. In contrast, soluble calcium and phosphate ions can be used only at very low concentrations due to the intrinsic insoluble nature of the calcium phosphates. Hence, soluble calcium and phosphate ions do not substantially incorporate into dental plaque or localize at the tooth surface to produce effective concentration gradients to drive diffusion into the subsurface enamel.

To overcome these difficulties, a new calcium phosphate remineralization technology has been developed based on CPP-ACP, where CPP stabilizes high concentrations of calcium and phosphate ions, together with fluoride ions, at the tooth surface by binding to pellicle and plaque. The calcium phosphate-based remineralization technology has been shown as a promising adjunctive treatment to fluoride therapy in the management of early caries lesions. Casein phosphopeptide forms nanoclusters with amorphous calcium phosphate, thus providing a pool of calcium and phosphate which can maintain the supersaturation of saliva. Since CPP–ACP can stabilize calcium and phosphate in the solution, it can also help in the buffering of plaque pH and so calcium and phosphate level in plaque is increased. Therefore, calcium and phosphate concentration within the subsurface lesions is kept high which results in remineralization.

Systematic reviews in the past have assessed the naturally occurring WSL and postorthodontic WSLs separately. In addition, orthodontic appliances are known to impede oral hygiene, which may also affect the clinical efficacy of CPP-ACP on WSLs. The aim of this systematic review was to assess the long-term remineralizing potential of CPP-ACP only in paste form compared with fluoride varnish and or placebo in both naturally occurring and postorthodontic WSLs.

**Materials and Methods**

**Structured question**

- Does CPP-ACP possess remineralizing potential in WSLs *in vivo?*

**PICO analysis**

- Population: WSL
- Intervention: CPP-ACP (paste form)
- Comparison: Other oral regimens (fluoridated toothpaste, fluoride varnish, and placebo)
- Outcome: Whether there is significant increase in remineralization.

The eligibility criteria were set as: the review included studies from 2005 to 2016 concerning population of all groups. Only randomized control trials involving human population were considered. The studies assessing WSL due to postorthodontic treatment were also taken into consideration. Case reports, abstracts, editorials, review articles, and non-English articles were excluded from the study. Animal studies and *in vitro* study were not included in this study. Other formulations of CPP-ACP, such as sugar-free gums, lozenges, fluoridated gels, mouth rinse formulations, antibacterial gels are excluded from the study.

**Search strategy**

The literature search covered the electronic databases: PubMed and Google Scholar. To search databases, strings of search (MeSH) terms, consisting of relevant text words and Boolean links, were constructed. The string of English search terms: “Incipient caries lesion OR early enamel caries OR CPP-ACP OR Tooth mousse OR recaldent AND Fluoride varnish OR remineralization”. Our search strategy attempted to identify all trials that could be considered for possible inclusion in this review. The reference lists of all eligible studies were also hand searched for additional relevant studies.

**Data collection and analysis**

Two calibrated reviewers screened the titles and abstracts (when available) of all identified studies independently. Once the publication was considered by either author to meet the inclusion criteria, the full-text article was obtained and reviewed. Any disagreement during study selection and data extraction was solved by discussion and consensus after consulting a third reviewer. Two ninety-five articles were identified from the search after excluding duplications. A total of 251 articles were excluded after reading titles. Abstracts of forty-one articles were reviewed independently. A total of 29 articles were excluded after reading abstract. Full-text articles were retrieved for fifteen relevant studies. After reviewing articles independently, three articles were excluded after full-text reading. Finally, twelve studies were selected based on the eligibility criteria.

**Data extraction**

Data extraction was completed independently by the two reviewers using a specifically designed data extraction form. Quality assessment criteria to evaluate the studies were decided by two review authors in accordance with CONSORT guidelines. The following data were collected:
...participants and groups

Quality assessment

Each study was assessed using the evaluation method described in the Cochrane Handbook for Systematic Reviews (Higgins and Green, Cochrane reviewers handbook 2009). The quality assessment of the included trials was undertaken independently by two reviewers. The domains evaluated were randomization method, allocation concealment, assessor blinded, dropouts, and risk of bias. Each domain was classified as having a low, high, or unclear risk of bias. Thus, the overall level of risk for each study was subsequently classified as low (if it did not record a “Yes” in three or more of the four main categories), “Moderate Risk” of bias (if two out of four categories did not record a “Yes”), “Low Risk” (if all the four categories recorded were adequate), “Unclear (unclear risk of bias for one or more domain).”

Results

Twelve studies which met the inclusion criteria were taken for the present systematic review [Table 1].

Study characteristics

The age group assessment included in the studies revealed, nine out of twelve studies considered subjects aged between 12 and 20 years. Three studies included an age group of 12–36 months,[13] 2½–3½ years,[14] 6–14 years.[15] Of the twelve studies, five were double-blinded, three-single blinded, and one-triple blinded. Rest of the trials have not mentioned explicitly about the blinding in the methodology.[16–18] The mode of delivery in all the trials included was in tooth paste form. Out the twelve studies, only six studies reported the concentration of CPP-ACP. The concentration used varied from 0.2% w/w, 0.2% w/w, 2% w/w, 10% w/w, 10% w/w, 1 g in studies done by Llena et al., Beerens et al., Rao et al., Bailey et al., Sithisetta-pong et al., and Bröchner et al., respectively.[14,16,22,24] The remaining six of the studies made no mention regarding the concentration of CPP-ACP.[13,17,21]

Primary outcome

The primary outcome for assessment was considered as the remineralization potential of CPP-ACP on naturally occurring caries and WSLs postorthodontic treatment. In the present systematic review among the twelve studies, four evaluated the effect on naturally occurring caries and eight studies evaluated effect on WSLs postorthodontic treatment. The measurement methods used among the twelve studies included a combination of the following; International Caries Detection and Assessment System (ICDAS) II (5 studies), DIAGNODent (3studies), decayed-missing-filled surfaces (DMFS) (2 studies), Qualitative laser fluorescence (3 studies), digital photograph (3 studies), and enamel decalcification index (2 studies) [Table 1].

Among the studies evaluating the effect of CPP-ACP on naturally occurring caries lesion, three studies showed a significant reduction in caries increment using CPP-ACP compared with placebo. There were significant differences between groups in the mean DMFT index and decrease in the mean WSL area was also reported. DIAGNODent values were also found to be significantly reduced. However, one study reported that there was no significant difference in the enamel caries lesion transition using CPP-ACP compared to fluoridated toothpaste.

The remaining eight trials assessed the effect of CPP-ACP on WSLs associated with postorthodontic treatment. The studies reported that there was no significant difference among the intervention and comparison group. However, there was significant improvement in lesion depth over a period, but no significant difference between the groups among four studies. DIAGNODent values were found to be decreased in one study and enamel decalcification index was decreased in two studies. One study lack adequate information regarding the primary outcome.

Secondary outcome

One or more nonserious adverse events such as minor gastrointestinal symptoms were recorded in the trial conducted by Bailey et al.[16] Only two studies reported information about side effects of using CPP-ACP.[22,23] The rest of the studies included in this systematic review did not present information on incidence of any adverse events.

Risk of bias

The risk of bias of the studies included in this review is summarized in Tables 2 and 3. Out of twelve studies which met eligibility criteria, seven studies have low risk of bias, three studies were judged to have moderate, and two studies were high risk of bias. The main risk of bias associated with these studies included inadequate sample size, unexplained allocation concealment, and lack of mention about attrition rates.

Discussion

The primary objective of this systematic review was to determine the remineralization effect of CPP-ACP through studying the published clinical trials. The present review has highlighted a lack of relevant research with low risk of bias on the effect of CPP-ACP on carious lesions, suggesting that CPP-ACP has remineralizing effect on early caries lesions in vivo compared with placebo and fluoridated toothpaste and fluoride varnish.
| Type of demineralization | Serial number | Author and year | Study design | Participants and groups | Intervention | Comparative/ control | Outcome criteria | Results |
|-------------------------|---------------|-----------------|--------------|-------------------------|-------------|----------------------|-----------------|---------|
| Early enamel caries lesion | 1 | Sitthisettapong, 2012 | 1-year, double-blind, controlled clinical trial | 2½-3½ years of age group 2 Groups 150/148 | 10% w/v CPP-ACP paste, Tooth Mousse | Control group: Placebo paste/ fluoridated toothpaste | ICDAS II criteria Baseline to 6 months and 1 year | There was no significant difference in the enamel caries lesion transition scores between two groups at 6 months and 1 year (OR=1.002, 95% CI [0.86-1.17]) |
| 2 | Memarpour, 2014 | 1-year, parallel, double-blind, randomized controlled trial | 12-36 months of age 4 Groups 35/35/35/35 | Group 4: CPP-ACP (GC, Tokyo, Japan) toothpaste twice a day | Group 1 (control): placebo, colored water solution Group 2 (oral hygiene) Group 3 (oral hygiene and sodium fluoride varnish 5%) | DMFT index in all groups Baseline, 4, 8, 12 months | | There were significant differences between groups in the mean dmft index only at the end of the study (P<0.001) with the mean percent WSL area decreased with time in Group 3 (51%) and 4 (63%). The dmft index after 12 months was lowest in Group 4 |
| 3 | Rao et al. (2009) | A randomized triple blind study | 12 and 15 years 3 groups 45/47/47 | 2% CPP-ACP toothpaste twice a day | 0.76% w/w SMFP toothpaste and placebo toothpaste | Clinical assessment with DMFS index and OHI index Baseline, 12, 24 months | | The increment was significantly smaller in the CPP and SMFP groups than in the placebo group, but the CPP and SMFP groups were not significantly different No new lesion: 34 (72.3%), 25 (53.2%), 14 (31.1%) in respective groups |
| 4 | Llena (2015) | A double-blind prospective, randomized clinical study | 6 and 14 years Four groups 20/20/20/20 | Group A: CPP-ACP toothpaste 0.2%w/w | Group B: MI paste plus toothpaste Group C: Fluoride varnish 5% NaF Group D: Nonfluoridated paste | ICDAS II Laser fluorescence using DIAGNOdent Baseline, 4, 8, 12 weeks | | Diagnodent values were significantly reduced in Group B (3.76±2.21) at 4 weeks, and in Groups A (4.03±3.63) and C (4.21±3.20) at 8 weeks There no effect of any group at the pit and fissure site |
Table 1: Contd...

| Serial number | Author and year | Study design /Participants and groups | Intervention | Comparative/ control | Outcome | Results |
|---------------|-----------------|--------------------------------------|--------------|----------------------|---------|---------|
| 5             | Bailey, 2009    | Randomized clinical trial 12-18 years 2 groups 23/22 | Remineralizing cream (Tooth Mousse) containing 10% w/v CPP-ACP | Placebo cream (without CPP-ACP) | QLF | Digital photographs ICDAS II Baseline to 4, 8, and 12 weeks The difference in the transition score distributions between the two treatment groups was not statistically significant (OR=1.67, P=0.16) at 12 weeks |
| 6             | Beerens et al., 2010 | A double-blind prospective randomized clinical trial 12 and 19 year of age 2 groups 28/27 | CPP-ACP + sodium fluoride 0.2%w/w | Fluoride-free control paste + calcium + fluoride toothpaste | QLF | After debonding and 6 and 12 weeks thereafter There was significant improvement in lesion depth over a period but no significant difference between the groups 12 week: Test=7.52±1.78 Control=7.96±2.76 There was no change in lesion area over time and between the groups |
| 7             | Robertson, 2011 | Double-blind, randomized clinical trial 12 years 2 groups 26/24 | MI paste plus Fluoride varnish | | Photographic records EDI ICDAS Baseline at 0, 4, 8, 12 weeks The mean EDI scores decreased in the MI paste plus group and increased for each surface in the placebo group at 12 weeks: 126 and 258 respectively EDI results indicated that the mean EDI decreased significantly (P<0.01) after using Tooth Mousse over the 6-month |
| 8             | Wang, 2012      | A single-blinded clinical study 12-14 years 2 groups 20/20 | GC Tooth Mousse Recaldent Toothpaste (Colgate, China) containing 1100 parts per million (ppm) of fluoride | | An intraoral images and an EDI Baseline at 0 and 6 months An EDI results indicated that the mean EDI decreased significantly (P<0.01) after using Tooth Mousse over the 6-month A significant improvement of the clinical WSL-scores was found overtime in both groups, but there was a statistically significant difference (P<0.01) in the CPP-ACP regime, 63%compared with 25% (control), respectively |
| 9             | Andersson, 2007 | Randomized control trial 12 and 16 years 2 groups 13/13 | CPP-ACP tooth paste Conventional 0.05% sodium fluoride toothpaste | | Visual examination Laser fluorescence with diagnodent Baseline, 1, 3, 6, 12 months |
WSLs resulting from orthodontic treatment were also included in our literature search because they represent the preliminary stage of subsurface enamel demineralization and are generally considered the early stage of the carious process. In contrast to normal population, however, the microecology of orthodontic patient seems to change following the placement of fixed appliances and due to inability to maintain proper oral hygiene, this may influence the effect of CPP-ACP in this population group. The WSLs, which determine the earliest phase of the caries process and which are reversible can be treated by conventional approaches, involving the disadvantage of being invasive. Therefore, remineralization agents can be used to promote ion-exchange mechanism instead of invasive techniques.

CPP-ACP has been reported to have the potential in promoting remineralization and which maintains calcium and phosphate at a supersaturated level compared to calcium in saliva and helps to preserve them in proximity to the enamel lesion, thereby decreasing demineralization and enhancing remineralization of enamel lesion.

The age group assessment included in the studies revealed, nine out of twelve studies considered subjects aged between 12 and 20 years. CPP-ACP used in the included studies were marketed under the trade names of “GC Tooth mousse”, “MI Paste”, “MI Paste plus,” and “Topical C-5”. The highest concentration of CPP-ACP that is currently available in commercial dental products is 10%w/w (ex: 5%w/w “Topical C-5” and 10%w/w in “GC Tooth mousse”, “MI Paste” and “MI Paste plus”). The strength or concentration is an important requirement in clinical trials since CPP-ACP has promising effect on dose-related increase in enamel remineralization.

The twelve studies included in this systematic review utilized the following methods to assess the primary outcome measures; clinical assessment using the ICDAS criteria or decayed surface/DMFS index, clinical or photographical assessment using enamel decalcification index, bitewing radiography for proximal caries increment, and reading of fluorescence-based devices (QLF/DIAGNOdent). Since no single method provides adequate reliability for caries

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### Table 1: Contd...

| Type of demineralization | Serial number | Author and year       | Study design                              | Participants and groups | Intervention | Comparative/Outcome control | Result |
|--------------------------|---------------|-----------------------|-------------------------------------------|-------------------------|--------------|-----------------------------|--------|
| 10                       | Vashisht, 2013 | A randomized          | 18 years                                  | 2 groups 29/31          | CPP-ACP-tooth mousse (1 g) Fluoridated toothpaste 1450 ppm | Diagnodent ICDAS II Baseline at 0 and 3 months | There was a decrease in DIAGNOdent measurements in the test and control group, but this was not statistically significant in test group ($P=0.217$) 3 months test=$14.31±8.34$ Control=$14.14±10.3$ |
| 11                       | Huang, 2013   | A single-blind,       | 12 and 20 years                           | 3 groups 45/42/48       | MI paste plus Fluoride varnish 5% Home-care group (control) | Digital photographs | No significant differences were found in the test groups compared to the control group at the end of the 8 week |
| 12                       | Brochner, 2011| Randomized, single-blind, controlled design with two parallel groups | 13-18 years 2 groups 22/28 | CPP-ACP tooth mousse cream 1 g | Standard fluoride toothpaste (Colgate, 1100 ppm F) | QLF (measurements) Digital photographs Baseline at 0 and 4 weeks | The average lesion area was decreased by 58% in the CPP-ACP group and by 26% in the control group, which was significantly different to baseline in the intervention group ($P<0.05$) |

CPP-ACP = Casein phosphopeptide-amorphous calcium phosphate, OR=Odds ratio, CI=Confidence interval, DMFT=Decayed, missing, and filled teeth, dmft=Decayed, missing, and filled teeth, WSL=White spot lesion, DMFS=Decayed, missing, filled surface, OHI=Oral Hygiene Index, ICDAS=International Caries Detection and Assessment System, QLF=Quantitative light-induced fluorescence, EDI=Enamel Decalcification Index, GC=GC Global pvt Ltd. Australia, SMFP=Sodium monofluorophosphate
Table 2: Risk of bias of the included study

| Major criteria | Randomization | Allocation concealment | Assessor blinded | Dropouts described | Risk of bias |
|---------------|---------------|------------------------|-----------------|--------------------|--------------|
| Effect of CPP-ACP paste on dental caries in primary teeth: A randomized trial (Sitthisettapong et al., 2012) | Yes | Yes | Yes | Yes | Low |
| Efficacy of fluoride varnish and casein phosphopeptide-amorphous calcium phosphate for remineralization of primary teeth: A randomized clinical trial (Memarpour et al., 2014) | Yes | No | Yes | Yes | Low |
| Study of the efficacy of toothpaste containing casein phosphopeptide in the prevention of dental caries: A randomized controlled trial in 12-15-year-old high caries risk children in Bengaluru, India (Rao et al., 2009) | Yes | Yes | Yes | Yes | Low |
| CPP-ACP and CPP-ACFP versus fluoride varnish in remineralisation of early caries lesions. A prospective study (Llena et al., 2015) | Yes | No | Yes | No | Moderate |
| Regression of postorthodontic lesions by a remineralizing cream (Bailey et al., 2009) | Yes | Yes | Yes | None | Low |
| Effects of casein phosphopeptide-amorphous calcium fluoride phosphate paste on WSLs and dental plaque after orthodontic treatment: A 3-month follow-up (Beerens et al., 2010) | Yes | No | Yes | Yes | Low |
| Effectiveness of MI Paste Plus and Previ Dent fluoride varnish for treatment of WSLs: A randomized controlled trial (Huang et al., 2013) | Yes | Yes | Yes | Yes | Low |
| Treatment of postorthodontic WSLs with casein phosphopeptide-stabilized amorphous calcium phosphate (Brochner et al., 2011) | Yes | No | Yes | None | Moderate |
| MI Paste Plus to prevent demineralization in orthodontic patients: A prospective randomized controlled trial (Robertson et al., 2010) | Yes | No | Yes | No | Moderate |
| Clinical evaluation of remineralization potential of casein phosphopeptide-amorphous calcium phosphate nanocomplexes for enamel decalcification in orthodontics (Wang et al., 2012) | No | No | Yes | No | High |
| Effect of a dental cream containing amorphous calcium phosphate complexes on WSL regression assessed by laser fluorescence (Andersson et al., 2007) | Yes | No | Yes | Yes | Low |
| Role of casein phosphopeptide-amorphous calcium phosphate in remineralization of WSLs and inhibition of streptococcus mutans? (Vashisht et al., 2013) | Yes | No | No | No | High |

| Minor criteria | Sample justified | Baseline comparison | I/E criteria | Method of error |
|----------------|-----------------|---------------------|-------------|----------------|
| Effect of CPP-ACP Paste on dental caries in primary teeth: A randomized trial (Sitthisettapong et al., 2012) | Yes | Yes | Yes | No |
| Efficacy of fluoride varnish and casein phosphopeptide-amorphous calcium phosphate for remineralization of primary teeth: A randomized clinical trial (Memarpour et al., 2014) | No | Yes | No | No |
| Study of the efficacy of toothpaste containing casein phosphopeptide in the prevention of dental caries: a randomized controlled trial in 12-15-year-old high caries risk children in Bengaluru, India (Rao et al., 2009) | Yes | Yes | Yes | No |
| CPP-ACP and CPP-ACFP versus fluoride varnish in remineralization of early caries lesions. A prospective study (Llena et al., 2015) | Yes | Yes | Yes | No |
| Regression of postorthodontic lesions by a remineralizing cream (Bailey et al., 2009) | Yes | Yes | Yes | No |
| Effects of casein phosphopeptide-amorphous calcium fluoride phosphate paste on WSLs and dental plaque after orthodontic treatment: A 3-month follow-up (Beerens et al., 2010) | Yes | Yes | Yes | No |
| Effectiveness of MI Paste Plus and Previ Dent fluoride varnish for treatment of WSLs: A randomized controlled trial (Huang et al., 2013) | No | Yes | Yes | No |

Contd...
Table 2: Contd...

| Minor criteria | Study                                                                 |
|----------------|----------------------------------------------------------------------|
|                | Treatment of postorthodontic WSLs with casein phosphopeptide-stabilized amorphous calcium phosphate (Brochner et al., 2011) | Yes | Yes | Yes | No |
|                | MI Paste Plus to prevent demineralization in orthodontic patients: A prospective randomized controlled trial (Robertson et al., 2010) | No | Yes | Yes | No |
|                | Clinical evaluation of remineralization potential of casein phosphopeptide-amorphous calcium phosphate nanocomplexes for enamel decalcification in orthodontics (Wang et al., 2012) | No | Yes | Yes | No |
|                | Effect of a dental cream containing amorphous calcium phosphate complexes on WSL regression assessed by laser fluorescence (Andersson et al., 2007) | No | Yes | Yes | No |
|                | Role of casein phosphopeptide-amorphous calcium phosphate in remineralization of WSLs and inhibition of streptococcus mutans? (Vashisht et al., 2013) | No | Unclear | Yes | No |

CPP=Casein phosphopeptide, ACP=Amorphous calcium phosphate, ACFP=Amorphous calcium fluoride phosphate, WSL=White spot lesion

Table 3: Quality of evidence of the assessed studies

| High risk of bias (low evidence) | Moderate risk of bias (moderate evidence) | Low risk of bias (high evidence) |
|---------------------------------|------------------------------------------|---------------------------------|
| If it did not record a “Yes” in three or more of the four main categories | If two out of four categories did not record a “Yes” | If all the categories recorded a “Yes” |

Two studies: 1. Clinical evaluation of remineralization potential of casein phosphopeptide-amorphous calcium phosphate nano complexes for enamel decalcification in orthodontics (Wang et al., 2012) 2. Role of casein phosphopeptide-amorphous calcium phosphate in remineralization of WSLs and inhibition of streptococcus mutans? (Vashisht et al., 2013) Three studies: 1. MI Paste Plus to prevent demineralization in orthodontic patients: A prospective randomized controlled trial (Robertson et al., 2010) 2. Treatment of postorthodontic white spot lesions with casein Phosphopeptide-stabilized amorphous calcium phosphate (Brochner et al., 2011) 3. CPP-ACP and CPP-ACFP versus fluoride varnish in remineralization of early caries lesions. A prospective study (Llena et al., 2015) Seven studies: 1. Effect of a dental cream-containing amorphous calcium phosphate complexes on white spot lesion regression assessed by laser fluorescence (Andersson et al., 2007) 2. Regression of Postorthodontic Lesions by a Remineralizing Cream (Bailey et al., 2009) 3. Study of the efficacy of toothpaste containing Casein Phosphopeptide in the Prevention of Dental Caries: a randomized-controlled trial in 12-15-year-old high caries risk children in Bengaluru, India (Rao et al., 2009) 4. Effects of casein phosphopeptide-amorphous calcium fluoride phosphate Paste on WSLs and dental plaque after orthodontic treatment: A 3-month follow-up. (Beereens et al., 2010) 5. Effect of CPP-ACP Paste on dental caries in primary teeth: a randomized trial (Sithisettapong et al., 2012) 6. Effectiveness of MI Paste Plus and Previ Dent fluoride varnish for treatment of white spot lesions: A randomized-controlled trial (Huang et al., 2013) 7. Efficacy of fluoride varnish and casein phosphopeptide-amorphous calcium phosphate for remineralization of primary teeth: A randomized clinical trial (Memarpour et al., 2014)

CPP=Casein phosphopeptide, ACP=Amorphous calcium phosphate, ACFP=Amorphous calcium fluoride phosphate, WSL=White spot lesion

detection, it may be beneficial to compile at least two of these detections methods in the future trials.29

Four of the twelve studies evaluated the effect of CPP-ACP on naturally occurring early caries lesions, out of which three studies concluded that there was a significant reduction in caries increment after using CPP-ACP compared with placebo. Other eight studies assessed the effect of CPP-ACP on WSLs that were associated with orthodontic treatment, among which four concluded that there was no clinical advantage after using CPP-ACP supplements compared to fluoride varnish.
In contrast, four of the studies found that CPP-ACP promotes remineralization of enamel subsurface lesion in postorthodontic WSL population.

The follow-up time of studies also varied from 1 month to 2 years. Evidence from studies on CPP-ACP suggests that a follow-up period of more than 3 months is usually needed to observe the changes of demineralization/remineralization. Moreover, a relatively long follow up is required to determine the efficacy of CPP-ACP. Reporting of adverse effects due to the use of CPP-ACP was lacking in most of the studies. Safety assessment should always be considered as an important and necessary part of a well-designed randomized controlled trial.[29]

Quality assessment of the studies showed that among twelve trials, seven studies showed low risk of bias. However there was a difference in the concentration of CPP-ACP, intervention measurement methods, outcome assessments, and follow-up period, randomization and blinded methods which could affect the trial results.

Conclusion

Within the limitation of this systematic review, a high level of evidence of remineralizing potential of CPP-ACP on naturally occurring WSL and WSL postorthodontic treatment was found in comparison with placebo/fluoridated toothpaste and fluoride varnish without any statistically significant difference. Reporting of such trials should follow the CONSORT statement and in particular, carry out blinding for reducing the risk of bias which influences the outcome. Well-designed randomized controlled trials are, therefore, required to improve the level of evidence in this area of research.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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