NEW FRONTIERS IN THE EARLY MANAGEMENT OF ENAMEL CARIES LESIONS AND DEFECTS

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

1.1.1. What is the topic?

The topic investigates non-invasive strategies for managing enamel caries lesions and molar-incisor hypomineralization (MIH). Specifically, it evaluates the efficacy of remineralizing agents such as fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) in addressing demineralization and hypersensitivity associated with these conditions.

1.1.2. What is the problem to solve?

Despite the advances in preventive dentistry, the efficacy of early management strategies for early enamel caries lesions and MIH, including remineralizing agents, remains unclear. Enamel caries can progress to cavitation when not treated early, requiring invasive treatments and potentially leading to tooth loss. The hypomineralized enamel in MIH is more porous, less mineralized, and prone to breakdown, complicating treatment and prognosis. Hypersensitivity, which affects nearly half of MIH patients, increases clinical challenges. There is a lack

of robust clinical evidence and standardized guidelines for the non-invasive management of enamel caries lesions. EAPD guidelines for MIH management offer only conditional recommendations. The goal is to provide evidence to improve early intervention and oral health outcomes for patients.

1.1.3. What is the importance of the topic?

Caries is the most common oral health condition, with over 2.3 billion people affected (James et al., 2018), while MIH affects around 13% worldwide (Schwendicke et al., 2018). Their impact on oral health, aesthetics, and quality of life, particularly in children and adolescents, represents a public health concern. Early management strategies can help arrest the progression of lesions, prevent invasive treatments, and alleviate other associated functional and psychosocial burdens.

1.1.4. What would be the impact of our research results?

This research addresses critical knowledge gaps by systematically analyzing the efficacy of CPP-ACP and

other non-invasive strategies for remineralization and hypersensitivity management of early caries lesions and MIH. The findings could inform clinical decision-making, improve patient outcomes, and ultimately lead to the development of standardized, evidence-based clinical protocols and guide future research.

2. Objectives

2.1. Study I. – Investigating the efficacy of CPP-ACP on remineralization of white spot lesions compared to fluoride therapies alone

We aimed to investigate whether the combination of CPP-ACP and topical fluoride has superior effects on remineralizing early carious lesions compared to fluoride alone.

2.2. Study II. – Investigating non-invasive strategies for the management of hypersensitivity and remineralization of Molar-Incisor Hypomineralization teeth

We aimed to understand the efficacy of different non-invasive strategies used for remineralization and hypersensitivity reduction in teeth affected by MIH.

3. Methods

Studies I and II complied with the guidelines described in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 recommendations (Page et al., 2021). Additionally, our study protocols were registered at the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42021286245 and CRD42022321486 to ensure transparency.

3.1. Search Strategy

A systematic literature search was done using three databases: MEDLINE (via PubMed), Cochrane Library (CENTRAL), and Embase for Study I and Study II. A manual search in the reference lists of relevant articles was also performed to find eligible records. No filters or restrictions were applied.

3.2. Eligibility Criteria

3.2.1. Study I

Eligible randomized controlled trials (RCTs) included patients with early stages of carious lesions who underwent treatment with CPP-ACP agents and combined fluoride, compared to a control group of fluoride therapies alone. Our primary outcome was remineralization potential measured by fluorescence-based methods – LF (Laser fluorescence) and QLF (Quantitative light-induced fluorescence). Visual evaluation through visual change in lesion area (value obtained as the ratio between the total lesion and total surface area of teeth) was a secondary outcome. Studies were excluded when trials had no fluoride-only control group and when unbalanced intervention and control group could directly or indirectly influence outcome variables. Furthermore, patients with any associated enamel defects would be excluded to avoid confounding factors.

3.2.2. Study II.

Studies involved subjects under 18 years of age diagnosed with MIH according to any validated diagnostic criteria – EAPD, Ghanim, Weerheijm – that underwent any non-

invasive remineralization and hypersensitivity therapy. Remineralization potential was measured instrumentally through fluorescence-based methods: LF and QLF. Hypersensitivity management was a secondary outcome measured instrumentally and visually through any validated pain outcome measure, such as the visual analog scale (VAS), SCASS, WBFS, and others. We have included any *in vivo*, clinical, and observational studies for a more extensive evidence review. Studies were excluded if patients had associated enamel defects other than MIH.

3.3. Study selection and data extraction

In both studies, two independent authors performed the study selection, using EndNote X20.2 (V.7), and the data extraction, with a standardized data collection form. If any disagreements remained after discussion, a third reviewer was consulted, or authors were contacted for clarification.

3.4. Quality Assessment

Two independent authors conducted the quality assessments, and disagreements were addressed through

discussions, reviewing the study details, or consulting a third reviewer. Based on Cochrane Handbook, for non-randomized studies, the ROBINS-I tool was used, and for randomized controlled trials, the ROB 2 tool. GRADE system was used to rate the quality of evidence for each outcome.

3.5. Data synthesis and analysis

3.5.1. Study I

Mean differences (MDs) or standardized MDs (SMDs) for continuous data were calculated to summarize the effect of treatment from each study. MDs would be used if outcomes were homogeneous, while SMDs would be utilized for non-homogeneous. 95% confidence intervals (CIs) were estimated using the restricted maximum-likelihood estimator. Random-effects models were used to combine the studies due to the existing clinical and methodological heterogeneity. After data collection, statistical heterogeneity was examined using the I^2 and $\chi 2$ statistics. Forest plots were used to display the measured effect sizes with their 95% CIs for all studies included.

3.5.2. Study II

A random-effects model was used, MDs were expressed as an effect size measure with 95% CIs. The sample size, mean, and corresponding standard deviation (SD) were extracted to calculate MDs and SMDs. For hypersensitivity, outcome measures from different scales were standardized to a 0–10 scale to ensure comparability, and MD was used. The inverse variance weighting method was used to pool mean values and MD. Heterogeneity variance (τ^2) was estimated using the restricted maximum likelihood method, with Q-profile methods providing confidence intervals. The t-distribution-based method was used for the CI of MD calculations of individual studies. The Hartung–Knapp adjustment was applied to improve the robustness of CIs for MDs. A fixed-effects "plural" model (mixed-effects) was utilized for subgroup analysis, and a standard τ^2 value was assumed. Differences between subgroups were tested using the Cochrane Q (omnibus) test, and the null hypothesis was rejected at a 5% significance level.

4. Results

4.1. Study I.

Fifteen RCTs were included in the meta-analysis: eight studies measured the remineralization potential of CPP-ACP with LF and five with QLF at one, three, and six months. Visual change was measured in three studies. No significant difference was found between CPP-ACP and fluoride versus fluoride alone in LF at 1, 3, and 6 months of use: SMD −0.30(−0.64;0.04); SMD –0.47 (−1.02; 0.07); SMD–0.49 (−1.13; 0.15), respectively. For QLF, no significant differences between the two groups at 1 and 6 months were found: MD 0.21 (−0.30;0.71); MD 0.60 (−1.70; 2.90). However, at 3 months, higher QLF values were found in the fluoride-only group compared to the CPP-ACP and fluoride combination regarding the WSLs: MD 0.58 (0.25;0.91). In contrast, data showed a small but statistically significant decrease in the lesion area in favor of the CPP-ACP plus fluoride versus fluoride alone at 6 months MD –0.38 (−0.72; −0.04). None of these observed changes indicated a substantial clinical relevance.

4.2. Study II

Fifteen studies involving 740 patients and 1,997 teeth were included in the quantitative synthesis. Six studies evaluated remineralization potential using LF (0-99), and nine studies analyzed hypersensitivity on VAS (0-10) pain scale. CPP-ACP showed no statistically significant advantage over fluoride in remineralization with LF (MD −3.80, 95% CI: −8.57; 0.98), but it significantly reduced hypersensitivity compared to fluoride varnish (MD −2.36, 95% CI: −3.83; −0.89). Although this reduction in hypersensitivity may be clinically relevant, the high heterogeneity (I^2 = 83%) and wide confidence intervals limit the reliability of these findings. Five studies reported four agents on mild MIH lesions in 435 teeth. Fluoride varnish showed the greatest reduction in LF values (mean −2.74, 95% CI: −5.91–0.43; I^2 = 60% [CI: 0%, 89%]) followed by CPP-ACP agents with a pooled mean reduction of −1.40 (95% CI: −1.84; −0.97; I^2 = 0 [CI: 0%, 71%]) in 190 teeth. CaGP showed a reduction of −1.04 in the LF scale in 160 teeth (mean −1.04, 95% CI: −2.34; 0.26; I^2 = 0). When fluoride toothpaste alone was used, a pooled mean reduction of −0.53 was found for 48 teeth (mean −0.53, 95% CI: −1.44–0.37; I^2 = 0). Overall, pooled

effects were not clinically relevant, and findings should be interpreted cautiously due to the wide confidence intervals.

Five studies reported four different agents on severe MIH lesions in 434 teeth. CaGP showed a reduction of −7.85 in the LF scale for 123 teeth (mean −7.85, 95% CI: −13.95–−1.76; I^2:57% [CI: 0%, 90%]), whereas fluoride varnish showed the greatest mean reduction in LF (mean −9.88, 95% CI: −24.18; 4.43; I^2:93% [CI: 60%, 95%]) for 45 teeth, however the low number of studies and wide CIs indicate less certainty in effect sizes. CPP-ACP products showed a reduction of −4.83 (mean −4.83, 95% CI: −7.11; −2.55; I^2 :0% [CI: 0%, 79%]) in 131 teeth. The narrower CI indicates a more precise effect estimate. When fluoride toothpaste alone was used, an actual increase of 9.89 on the LF scale was found for 54 teeth (mean 9.89, 95% CI: −17.52; 37.31; I^2:93% [CI: 77%, 98%]). However, the wide confidence intervals should be considered for careful interpretation of results.

5. Conclusions

5.1. Study I.

The combination of CPP-ACP and fluoride is not significantly superior to fluoride alone in improving WSLs, when assessed through laser fluorescence and visual area change. Additionally, topical fluoride could arrest or reverse the progression of early carious lesions, suggesting its effectiveness on WSLs. However, the certainty of evidence supporting these findings is very low. These results highlight the need for further high-quality studies and the development of more effective treatments than CPP-ACP in complementing fluoride to improve WSLs substantially.

5.2. Study II.

Although CPP-ACP did not demonstrate a significantly superior effect than fluoride in remineralizing MIH lesions through fluorescence-based methods, it is more effective than fluoride in reducing hypersensitivity. Other agents such as SDF, CaGP, and low-level laser demonstrated mild-to-moderate effects on remineralization and hypersensitivity, though the evidence remains inconclusive. These results are limited by heterogeneity, wide variability in treatment protocols,

and short-term analysis. High-quality RCTs with longer follow-ups on the effectiveness of combination treatments and lesion severity are needed to strengthen the evidence and establish more precise clinical guidelines for managing MIH.

6. Bibliography

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