

THE CLINICAL EFFECT OF CASEIN PHOSPHOPEPTIDE AMORPHOUS CALCIUM PHOSPHATE VARNISH ON CARIES AFFECTED DENTINE IN PRIMARY TEETH (A RANDOMIZED CONTROLLED CLINICAL TRIAL)

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ABSTRACT

INTRODUCTION: Dental caries remains the most global widespread disease. To deal with dental caries in a minimal invasive technique, attempts were made to remineralize affected dentine to improve its physical properties.

OBJECTIVES: This study aimed to assess the clinical and radiographic success of applying Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP) under glass ionomer restorations in primary teeth treated with Atraumatic Restorative Treatment (ART).

MATERIALS AND METHOD: Forty primary molars from patients attending the pediatric dentistry clinic were selected for clinical and radiographic assessments after fulfilling the inclusion criteria. The study sample was divided randomly into 2 groups: Group I: 20 molars treated with CPP-ACP varnish then restored with glass ionomer restoration. Group II: 20 molars restored only with glass ionomer restoration. Cavity preparation included the removal of the infected dentine and conserving the affected dentinal tissue. Clinical and restoration assessments were carried out at 1 and 6 months while the radiographic assessment was done at baseline and 6 months.

RESULTS: No significant differences were shown between the 2 groups after 1 and 6 months when comparing the clinical success of CPP-ACP and success of the restoration used with ART. Moreover, no significant differences were found regarding radiographic success after 6 months.

CONCLUSIONS: The use of CPP-ACP before applying RMGI restorations in primary teeth proved to be a successful technique in class I ART restorations, allowing a painless anesthesia-free dental visit and decreasing the incidence of pulp exposure.

KEYWORDS: Casein phosphopeptide Amorphous Calcium Phosphate (CPP-ACP), Dentine repair, primary teeth, Caries affected dentine, Atraumatic restorative treatment.

RUNNING TITLE: Clinical effect of CPP-ACP on ART in primary teeth.

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INTRODUCTION

Dental caries is a widespread global disease, which has a large impact on children physically, socially and financially affecting the quality of life of the family (1). Since dental caries is a reversible disease, preventive dentistry became the major concern of dentists as well as patients around the world (2).

Minimal invasive dentistry (MID) is a new concept that deals with the risk factors leading to the dental disease rather than spending much time and effort in restoring the lost dental tissue. However, when a dental cavity exists and a restoration is inevitable, it is advised to conduct minimal removal of decayed hard tissue as possible in order to decrease the patient's stress and anxiety as well as the incidence of pulp exposure (3). To achieve this process, removing the caries infected dentine (CID) and

preservation of hard caries affected dentine (CAD) is recommended (4).

Atraumatic restorative treatment (ART) is considered one of the minimally invasive techniques. This technique was invented mainly in areas offering no electricity where the use of rotary instruments would be difficult. The ART has been considered by both the WHO in 1994 and the FDI in 2002 as a definitive treatment modality in high standard communities. (5) Resin modified glass ionomer (RMGI) restorative materials are best used with this technique due to their fluoride releasing properties, bonding to the dental hard tissues, easy manipulation, and increased wear resistance than the conventional glass ionomer cements (5).

Data revealed that the inorganic and organic alterations, which occur in CAD changes its nature

(6). For this reason, restoring the physical and mechanical properties of CAD by remineralization, has been proposed for the fulfillment of the MID concepts and minimize the unnecessary removal of tooth structure. Moreover, it has been suggested that remineralizing CAD can increase its bond strength to the restoration (7).

Among the known remineralizing agents in the dental market, Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP) has been claimed to remineralize demineralized dentine in-vitro studies (8) with no available in-vivo studies. The casein phosphopeptide (CPP) is a dairy nano-complex protein, which forms the base of the bioactive CPP-ACP. It was introduced by Reynolds in 1997 (9). The CPP is structured by residues of phosphorylated serine and glutamic amino acid (10). It has the ability to unite with amorphous calcium phosphate (ACP), which acts as a precursor for dental hydroxyapatite. The calcium and phosphate ions become readily available and stored as ACP (11). When exposed to acidic challenge, which is offered by the presence of bacterial toxins and by-products, the clusters of CPP-ACP release these ions leading to a supersaturated environment with calcium and phosphate (12).

Recently, Bou Chebel et al, in 2018 (13) proved that CPP-ACP decreased dentine hypersensitivity when evaluated clinically on exposed root dentine surfaces in permanent teeth. Likewise, Kijssamamith et al, in 2019 (14) proved that CPP-ACP decreased dentine hypersensitivity by partially occluding the dentinal tubules when examined by scanning electron microscope.

However, the literature encourages further clinical research to evaluate clinically the effect of CPP-ACP on dentine of primary teeth, to bridge the knowledge gap and assess the longevity of the restoration. Therefore, the aim of the present trial was to investigate the effect of CPP-ACP as an indirect capping material clinically and radiographically. The null hypothesis of the present study is that no significant clinical difference is expected between ART used with and without CPP-ACP.

MATERIAL AND METHODS

The design of the present study was a two parallel arm, triple blinded randomized controlled clinical trial. It was conducted and reported according to the CONSORT guidelines (15). The PICOT question was, do children receiving treatment for decay in primary molars (Population; P) using CPP-ACP varnish under glass ionomer restorations (Intervention; I) compared to glass ionomer restorations alone (Control; C) show better clinical and radiographic success (Outcome; O) when followed up for 6-month period (Time; T)?

All procedures were conducted according to the code of ethics of the Research Ethics Committee (0109-01/2020), Faculty of Dentistry, Alexandria University. The present study was registered as:

(NCT04303767 – clinicaltrials.gov). The patients were recruited and treated at the outpatient clinic of the Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University. An informed consent was obtained from each patient’s guardian after detailed explanation of the nature of the study and the possible benefits and risks.

An estimated sample size of 40 children (40 teeth) were selected from the Pediatric Dentistry clinic at the Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University. The sample size was estimated based on the following assumptions: confidence level= 95% and study power= 80%. Zhong et al in 2015 (16) who reported that chlorhexidine and CPP-ACP have biomimetic dentin remineralization effect that improves the bonding of dentine and resin materials. Therefore, the other assumptions used to estimate the sample size were based on Mobarak et al in 2019 (17) who reported that the overall survival rate of glass ionomer restorations preconditioned with chlorhexidine after 6 months was 100%. Olegário et al in 2017 (18) reported that the success rate of GIC without cavity preconditioning was 65.33%. Sample size was calculated to be 18 restorations per group, this was increased to 20 to make up for cases lost to follow up. The total sample size= number of groups × number of per group= 2×20= 40 restorations.

Eligibility criteria

Patients participating in the study were healthy children ranging in age from 6 to 9 years. Each patient should have at least one symptomless primary molar, or one that is indicated for indirect pulp capping, with only occlusal caries extending to the dentine (International Caries Detection and Assessment System (ICDAS I) code 5 & 6) (Table 1) (19). Primary molars with more than half of the root resorbed or with periapical pathology as evident radiographically were excluded from the study. Mobile or ankylosed molars with no permanent successors were not included.

Table 1: International Caries Detection and Assessment System (ICDAS). (19)

0	Sound
1	First visual change in enamel
2	Distinct visual change in enamel
3	Localized enamel breakdown (without clinical visual signs of dentinal involvement)
4	Underlying dark shadow from dentine
5	Distinct cavity with visible dentine
6	Extensive distinct cavity with visible dentine

Randomization, blinding, and allocation concealment Initial examination was done on 60 patients, out of which 40 patients with 40 eligible teeth were selected. Randomization was done by using a

computer-generated list of random numbers, which assigned each of the molars to one of the 2 arms (test or control). The list of allocation was generated prospectively using random allocation software where units were allocated in blocks of 4. The patients were randomly assigned to 2 groups using allocation ratio of 1:1 and allocation concealment. The allocation was sealed in sequentially numbered opaque envelopes by the dental assistant and the set of envelopes were kept until the time of intervention. At the time of intervention, the clinical investigator retrieved the allocation. The patient and patient's guardian, the evaluator as well as the statistician were blinded to the treatment provided. During the clinical procedures, the investigator was not blinded.

Grouping

The 40 patients were randomly divided into two groups, where group I (test) included 20 teeth that were treated with CPP-ACP (MI varnish. GC Corp, U.S.A) before receiving the RMGI restoration (RIVA Light cure HV. SDI limited. Australia) and group II (control) included 20 teeth that received only the RMGI restoration.

Intervention and outcome assessment

Children who participated in the study were recruited from the period of February 2020 throughout November 2020 and follow up ended in May 2021. They all received standardized oral hygiene instructions, which included brushing twice daily. (20) Every eligible patient who participated in the study received all needed dental treatment by the investigator other than the tooth selected for the study in the first month after enrolment.

Baseline examinations were done by the investigator, the intra-rater reliability was confirmed through a reevaluation of 10% of the cases. Kappa coefficients were 0.85, 0.82, 0.92 for the clinical, radiographical and the ART success/failure evaluation respectively, thus indicating almost perfect agreement.

Complete clinical examination was carried out using mirror and explorer under the light of the dental unit. Radiographic examination using paralleling technique with an Endoray film holder paralleling device (Dentsply Rinn) and a putty occlusal index for each tooth to ensure standardization in different follow-up exposures. The putty indices were taken with a putty rubber-based impression material (Zhermack SPA – Via Bovazecchino, 100 – 45021 Badia Polesine (RO), Italy) and stored in sterilization packs labelled with the patient's number (21).

Excavation of the occlusal caries was performed using a sharp spoon excavator and the CAD was preserved using the visual tactile method, taking in consideration that the cavity margins were sound (4, 22). Undermined occlusal enamel, if present, was removed using enamel chisels under partial isolation. The cavity was then cleaned and dried with dry cotton pellets.

In the test group (group I) CPP-ACP was applied to the floor of the cavity on the remaining caries affected dentine with a micro-brush, following the instructions provided by the manufacturer, and left to dry before application the final restoration (23). The control group (group II) did not receive CPP-ACP. Cavities in all groups received RMGI as the final restoration, which was light cured using a light curing unit (IVOCLAR VIVADENT Bluephase N MC LED Light Curing Unit) for 20 seconds (24). The adjacent pits and fissures are further sealed with the same RMGI restoration provided that they are caries free.

The follow up was carried out after 1 and 6-month periods for the clinical and the ART assessments. Radiographic assessment was also carried out at baseline and after a 6-month period. Follow up every 3 months was also scheduled for oral hygiene instruction, prophylaxis and fluoride application.

(Figure 1)

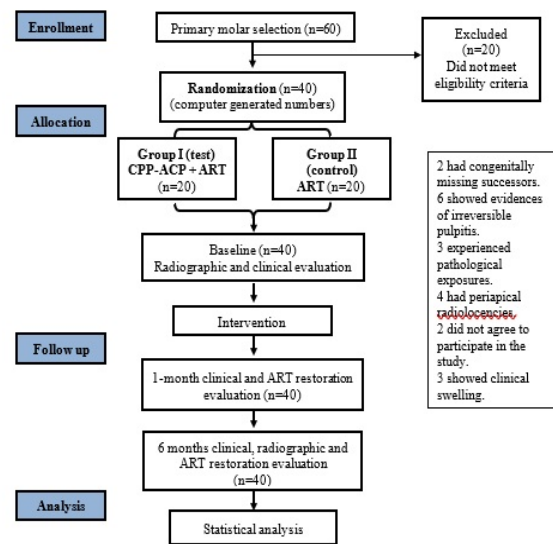


Figure 1: Flow chart of the trial

The clinical assessment examined pain, tenderness to percussion, the presence of sinus tract or fistulae and the presence of swelling or mobility. The radiographic assessment included widening of the periodontal ligament space, the presence of periapical radiolucencies, internal or external root resorption (25). Teeth showing any of the previously mentioned symptoms clinically or radiographically were considered as a failure and were scored 1, otherwise teeth were scored 0. The ART restoration assessment included the evaluation criteria described in table 2 (26). Teeth with scores 0 and 1 were considered successful, whereas those with scores 2-7 were counted as failures. (26)

Teeth experiencing failures were repaired by RMGI restoration or retreated with pulpotomy or extraction, according to the type of failure reported during the follow up periods.

Table 2: ART evaluation criteria used to assess ART restorations. (26)

0	Present, satisfactory
1	Present, slight deficiency at cavity margin of less than 0.5 mm
2	Present, slight deficiency at cavity margin of 0.5 mm or more
3	Present, fracture in restoration
4	Present, fracture in tooth
5	Present, overextension of approximal margin of 0.5 mm or more
6	Not present, most or all of restoration missing
7	Not present, other restorative treatment performed
8	Not present, tooth is not present
9	Unable to diagnose

Statistical analysis

Data was presented using mean and standard deviation (SD) for the age and count and percent for all qualitative variables. Groups were compared regarding success/failure rate using Chi Square test of Fisher’s exact test, while changes within each group were assessed using McNemar test. Significance level was set at p value ≤0.05. Data was analyzed using IBM SPSS for windows version 23.

RESULTS

The participants had an age range of 6 to 9 years with a mean value of 7.05 ± 1.46 for the test group and 6.90 ± 1.51 for the control group. Out of the total sample, 22 were males and 18 were females. Following randomization, no significant difference between the 2 groups was detected regarding age and gender; (P=0.753) and (P=0.204) respectively. (Table 3)

Table 3: Baseline characteristics of the study sample

		Test (n=20)	Control (n=20)	P value
Age: Mean (SD)		7.05 (1.46)	6.90 (1.51)	0.753
Gender: n (%)	Males	9 (45%)	13 (65%)	0.204
	Females	11 (55%)	7 (35%)	
Arch: n (%)	Upper	4 (20%)	7 (35%)	0.288
	Lower	16 (80%)	13 (65%)	
Teeth: n (%)	D	5 (25%)	5 (25%)	1.00
	E	15 (75%)	15 (75%)	

Regarding the clinical success of the ART, there was no significant difference between groups I and II after 1 and 6 months follow up. Data revealed no clinical failures (100% success) in the 2 groups after 1 month, whereas 1 tooth (5%) showed temporary pain on mastication in the control group after 6 months (Figure 2).

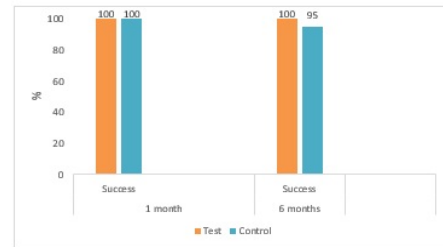


Figure 2: Comparison of the clinical success between the study groups at 1 month and 6 months

Regarding the radiographic success, there were no significant differences between groups I and II at baseline and 6 months follow up. After 6 months, 3 teeth showed widening in the periodontal ligament (PDL) space in group I and only 1 tooth showed periapical radiolucency (20%). Whereas in group II, only 1 tooth revealed internal resorption (5%). (Figure 3)

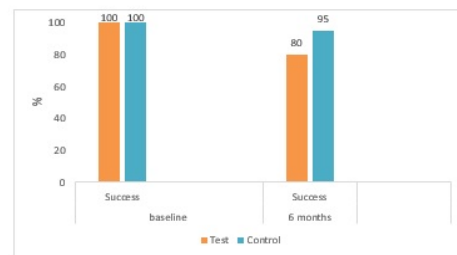


Figure 3: Comparison of the radiographical success between the study groups at baseline and after 6 months

Figure 4 shows comparison between group I and group II regarding the ART restoration success. There were no significant differences between the 2 groups after 1 month and 6 months: (P=0.487) and (P=0.451) respectively. Data revealed failure in the ART procedure in 2 teeth after 1 month in group I (10%). After 6 months, six teeth showed further failures (30%), whereas only 3 teeth showed failure in group II (15%). Three of the reported failures in the ART restorations in group I coincided with radiographic failures, whereas the other 3 failures did not show any signs of clinical or radiographic failures when evaluated in the same follow up period. On the other hand, none of the failures in the ART restorations in group II coincided with any signs of clinical or radiographic failures. An example of the radiographic failure coinciding with

restoration failure in group I is shown in **figure 5**.

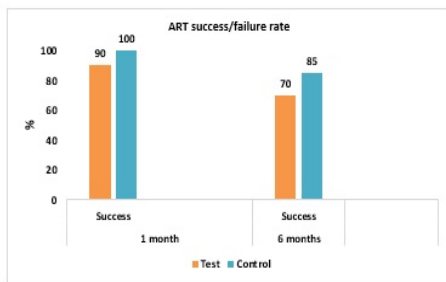


Figure 4: Comparison of ART restoration success between the study groups at 1 month and after 6 months

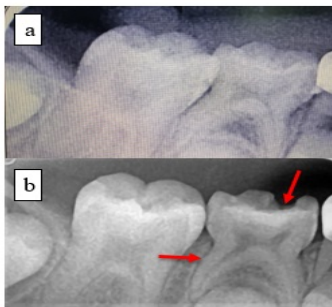


Figure 5: Radiograph showing failure in group I (a) baseline radiograph (b) radiograph after 6 months showing widening of the PDL space as well as fracture in the restoration.]

DISCUSSION

The present study tested the clinical, radiographic and restoration success when CPP-ACP was used as a lining material under glass ionomer restoration. Since the study was designed to be a clinical trial, results were expected to differ from those of laboratory studies. This is because of the different actual hostile oral conditions and stresses that can be experienced by the test material as well as the restoration. The preservation of caries affected dentine in this study was supported by evidence showing that sealing the cavity would allow for remineralization as well as depriving the residual bacteria from their nutrients (25).

The CPP-ACP was placed as an indirect capping material under the restoration to enhance the remineralization ability of the CAD, improve its physical properties and the bond strength of the restoration as assumed by Agob et al in 2018 (27). According to Zhang et al in 2019, CPPACP is one of the biomimetic materials introduced in the field of dentistry for the remineralization of dental hard tissue. Furthermore, they claimed that the biomimetic process mimics that of the natural mineralization by the presence of readily available calcium and phosphate ions (28). However, CPP-ACP can reproduce apatite crystals by depositing calcium and phosphate ions around the partially demineralized crystals. These apatite crystals form the solid ground for chemical bonding of RMGI restorations to the dentine (27).

Resin modified glass ionomer restoration was chosen as it is the material of choice when restoring primary teeth using ART (29). Moreover, CPP-ACP was used in the test group under the RMGI restoration to enhance the remineralizing ability of the restoration. This assumption is supported by the evidence of in-vitro studies (8, 30) as well as the experimental animal study of Zhang in 2019 (28).

In the study of Palma-Dipp et al in 2003 the bonding of RMGI restorations to CAD was tested, and it was reported that RMGI restorations could be appropriately used with ART, despite the relatively decreased bond due to the smear layer formed as a result of cavity preparation. They further recommended the application of tooth conditioning before the final restoration to remove the smear layer (31). In the present study no conditioning to the CAD layer was done because it is not part of the ART procedures (22).

The results of the present study showed no significant differences between the 2 groups regarding clinical, radiographic and ART restoration success. This adds to the evidence that tooth colored bonded restorations show high clinical success when used in primary teeth (29). Clinical success in the test group was 100% after 1 and 6 months. In the control group, one patient reported pain upon mastication after 6 months. The results are in accordance with those of Casagrande et al in 2013 (29) who stated that only 1 tooth showed signs of clinical failure after 6 months of follow up when restored with reinforced glass ionomer restoration in comparison to composite restorations with different bonding agents.

However, after 6 months, 3 teeth in the test group showed signs of PDL space widening without experiencing pain or any other clinical signs of inflammation when examined radiographically. The signs of radiographic PDL space widening are signs of inflammation which might resolve when oral conditions improve. Moreover, one tooth in the same group showed evidence of periapical radiolucency, which was apparent in the furcation area. This could be attributed to a faulty case selection which led to failure in tooth response to CPP-ACP. On the other hand, only 1 tooth in the control group showed signs of internal root resorption after 6 months, which might also be related to tooth selection.

Considering the restoration failure, 2 teeth in the test group showed restoration failure after 1 month. One tooth reported score 3 (fracture in the restoration) and the other reported score 6 (most of the restoration was missing). After 6 months, 6 teeth showed restoration failures. These included 1 tooth reporting score 2 (restoration became at the cavity margin), 3 teeth reporting score 3 (fracture of the restoration) and 2 teeth reporting score 6 (most of the restoration was missing). Only 3 teeth showed failures in the control group after 6 months, where all 3 teeth reported score 3 (fracture of the restoration).

Only 3 of the reported ART restoration failures coincided with the reported radiographic widening in the PDL space. However, no clinical signs of failures were reported.

Similarity between the groups regarding restoration failure might be related to the oral hygiene practices which may differ among patients. This may lead to unfavorable oral conditions, which may hinder the longevity of the restoration. However, it is worthy to state that all patients who participated in the present study received strict oral hygiene instructions and were reinforced every 3 months. The limited number of failures reported in this study may also be contributed to the faulty technique by the operator or due to an uncooperating patient during the procedure. Losing the patient cooperation might be linked to the increase in the operating time which has been noticed by the investigator when CPP-ACP was applied before the restoration.

The addition of CPP-ACP as an indirect capping material under RMGI restoration is considered an innovative technique testing the biomineralization ability of CPP-ACP in-vivo. Further investigations are recommended in this context to link the clinical success with the radiographic and restoration failures experienced in the present study. Also, a histological assessment is recommended for teeth treated using the same ART protocol to document the changes occurring in the CAD after treatment with CPP-ACP. The limitation of the present study was the inability to assess the treated teeth histologically, because none of them were exfoliated during the duration of the study. Also, the incompliance of the patients to strictly follow the oral hygiene instructions given by the investigator. Another limitation to this study may be the fact that no preconditioning of the dentine was done prior to the RMGI placement. However, it is recommended that further studies with preconditioning of the cavity walls and with longer follow up period are done.

Also, further investigations are recommended to test the bond strength of the RMGI filling to the CAD after applying the CPPACP.

CONCLUSION

The use of CPP-ACP before applying RMGI restorations in primary teeth proved to be a successful technique in class I ART restorations, allowing a painless anesthesia-free dental visit and decreasing the incidence of pulp exposure.

Conflict of Interest

The authors declare that they have no conflict of interest.

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