Efficacy of CPP-ACP GC Tooth Mousse in remineralization of teeth of Syrian orphan Children-results of a double-blind, randomized controlled clinical trial

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Research Article

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Abstract

Objectives

A double-blind randomized controlled clinical trial was undertaken to evaluate the efficacy of Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) in the remineralization of teeth of Syrian children aged 6-8 years enrolled in orphanage of the city of Damascus.

Materials and Methods

The study sample included 50 children randomly divided into two treatment groups to receive either CPP-ACP GC Tooth Mousse™ (Group A) or placebo (Group B) with 25 participants per group. After the application of the product in the mouth for 3 minutes, saliva samples were collected four time (T0, T1, T2, and T3) to measure the pH of saliva and the rate of salivary flow.

Results

There was no significant difference between group A and B in the mean value of salivary flow rate and salivary pH. However, there was significant difference between different time points in the mean value of salivary pH and salivary flow rate.

Conclusion

The GC Tooth Mouse (CPP-ACP) is not superior to placebo mousse at tooth remineralization according to salivary pH measure and the rate of salivary flow. Further studies are still essential to assertion findings.

Trial registration: ISRCTN17509082, Registration date 22/11/2022

Clinical Relevance

The application of CPP-ACP products may not be effective for the remineralization of teeth of children as it was similar to placebo in increasing the rate of salivary flow and saliva pH. Other alternatives should be considered.

Introduction

Dental caries is one of the most common multifactorial diseases that occurs in children, due to imbalance between protective and pathological factors [1, 2] causing loss of calcium and phosphate ions as well as demineralization. However, this process can be reversed by the so-called remineralization process[3]. Saliva, fluoride supplements and diet are preventive regimes against tooth demineralization[4]. In addition, several materials have been introduced to inhibit demineralization and enhance the effect of remineralization. such as xylitol, bio-active glass, tricalcium phosphate and CPP-ACP [5, 6].
The CPP–ACP is a bioactive material derived from the milk protein casein [7]. It has been reported to inhibit enamel demineralization by maintaining the supersaturation of calcium and phosphate in saliva, buffering of plaque pH and increasing the calcium and phosphate ions level in plaque[8].

The application of topical CPP-ACP was found to be beneficial for remineralization process of teeth as it was able to raise salivary pH and salivary flow rate [9, 10].

In developing countries such as Syria, parents do not give priority to the dental health of their children until they complain of pain [11]. In this phase, dental caries may progress into irreversible stage in which remineralization protocols cannot be implemented [12].

There is a need to adopt protective protocols and apply materials that can enhance remineralization among Syrian children. A recent systematic review has indicated to the limited evidence about the cariostatic activity of CPP-ACP and addressed the need for further clinical trials [13]. Furthermore, the effect of CPP-ACP on physiochemical salivary properties is still controversial. Although its effect is recognized, more evidence of its impact on saliva PH and salivary flow rate is needed. Therefore, this clinical trial was undertaken to investigate the effectiveness of CPP-ACP in remineralization of teeth through measuring the changes in saliva pH and salivary flow rate of Syrian children.

**Materials And Methods**

**Trial design**

This study was a double-blind randomized controlled clinical trial conducted on 50 children aged 6 to 8 years. They were recruited from the Ambulance Charity Orphanage, Damascus, Syria. This trial was in accordance with the ethical standards of the institutional and national research committee of the study institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. It was approved by the Research Ethics Committee of Faculty of Dentistry of Damascus University and was registered at the ISRCTN registry (https://doi.org/10.1186/ISRCTN17509082)

This randomized controlled clinical trial was designed, conducted and reported according to the CONSORT statement over a period of 7 months https://www.equator-network.org/reporting-guidelines/consort/

The trial was a double blinded one in which the patients and the researcher had no idea about the agent that has been used.

A random allocation list was designed using the website https://www.randomizer.org/ as computer-based methods for randomization are more reliable and easier to use than other manual methods.

**Sampling**
Sample size was calculated according to previous similar study using the G*Power software (v. 3.1) (Franz Faul, Universitat Kiel, Germany). The significant level was set at $P$ value of less than 0.05, and statistical power of study was set at 85%. It was considered that 50 patients were sufficient to demonstrate an effect size of 0.7. Therefore, 50 children aged between 6–8 years were selected in this study. All children who had good oral hygiene, not taking antibiotics or any kind of medications for more than two weeks that can affect the flow rate of saliva were included. In addition, The inclusion criteria addressed that all participants should not have any confirmed or suspected allergy to milk protein and/or the presence of the sensitivity of benzoate (preservative). All children who had diseases that may affect the flow rate of saliva such as diabetes were also excluded from study.

**Study Groups**

After full explanation about the aim of the study, written informed consent from the manager of the orphanage and their carers were obtained. All children recruited in this trial were volunteers who accepted to take part in this study. All children who met the inclusion criteria were equally and randomly assigned into either Group A which included 25 children who had CPP-ACP (GC Tooth Mousse™) application (Intervention), or Group B that contained 25 children who received placebo mousse as controls. Figure 1 shows the CONSORT flow diagram of the participants.

**Chemical Preparation Of The Placebo Cream**

The placebo cream was prepared by the researcher in the Department of Pharmaceutical Industries at the Faculty of Pharmacy, Damascus University. The prepared placebo cream mimics the intervention mousse (GC tooth Mousse™) with the physical characteristics (color, flavor and texture) in order to help in the blinding process.

**Topical Application Of The Studied Mousse**

Supervisors of the orphanage were asked to brush the children's teeth with water only on the day before the experiment. A thick layer of the material was applied within the upper and lower trays for 3 minutes. Then, after removing the tray, child was asked to distribute the remaining material on the teeth by the tongue without swallowing it. This method of application was used for the both groups in this trial and the period was standardized to two minutes for all children. Children were asked to dispose of the substance, but without rinsing the mouth. They were also asked not to eat or drink until the end of the saliva sampling period.

**Clinical Intervention And Saliva Collection**
Salivary samples were collected in the morning between 08:00 and 10:00 am. At the first stage, children were given paraffin wax to be chewed and they were asked to swallow the pooled saliva. Then, they were asked to spit their saliva into saliva collecting glass tube for five minutes. The amount of collected saliva was then calculated and divided into 5 in order to report the amount of saliva collected per minute (ml/m). This process was performed four times: before the application of the studied agents (T0), directly after the application (T1), after half an hour (T2) and after one hour (T3). Salivary flow rate was measured in four time points. In addition, pH of saliva was measured in each time point using pH test strips (Saliva-Check Buffer, GC Int). The pH test strips were soaked within saliva for one minutes. Accurate color change indicating pH values was observed and compared with the accompanying chromatography table.

Data Analysis

Data were analyzed using IBM SPSS version 23 (IBM Corp., Armonk, USA). Descriptive data, including minimum, maximum, mean, and standard deviation, were calculated for the studied groups. Shapiro Wilk-test of normality showed that data were normally distributed. Two-way repeated measures ANOVA test was used to test the differences existed between the two groups and different time points regarding the saliva pH and salivary flow rate with Bonferroni Test post hoc application for multiple comparisons. Greenhouse-Geisser correction test was applied when the assumption of the sphericity of Mauchly's test is violated. The two-tailed probability value of $P \leq 0.05$ was considered statistically significant.

Results

The research sample included 50 children (30 boys and 20 girls), who were distributed according to the random distribution tables and categorized into two groups in which 25 children were included in each group. Descriptive data of the enrolled participants are summarized in Table 1.

Table 1
Descriptive data of the enrolled participants

<table>
<thead>
<tr>
<th>Descriptive data</th>
<th>Group A (CPP-ACP)</th>
<th>Group B (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12 (48%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (52%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Mean of age (years)</td>
<td>7.6 years</td>
<td>7.0 years</td>
</tr>
</tbody>
</table>

The mean values for the salivary flow rate for both groups at T0, T1, T2, and T3 were 0.41 ± 0.30, 0.65 ± 0.36, 0.53 ± 0.28, and 0.56 ± 0.34 respectively. The findings of the independent $t$-test indicated that there was no significant difference between group A and B in the mean value of salivary flow rate at baseline ($t = 1.08, P = 0.28, 0.57 \pm 0.28$ versus $0.56 \pm 0.38$ respectively). However, the one-way ANOVA test indicated to the presence of significant difference between different time points in the mean value of salivary flow rate within groups ($F = 4.5, df = 196, P = 0.004$). According to Bonferroni post hoc test, which assessed the
effects of treatment and time, salivary flow rate increased significantly in T1 and then decreased significantly.

In addition, the mean values for the salivary pH, for both groups, at T0, T1, T2, and T3 were 6.99 ± 0.44, 7.46 ± 0.36, 7.36 ± 0.32, and 7.26 ± 0.32 respectively. There was no significant difference between group A and B in the mean value of salivary pH ($t = 0.61, P = 0.54, 7.28 ± 0.44$ versus $7.25 ± 0.36$ respectively). However, the one-way ANOVA indicated to the presence of significant difference between different time points in the mean value of salivary pH within groups ($F = 15.23, \text{df} = 196, P = 0.000$). According to Bonferroni post hoc test, which assessed the effects of treatment and time, the salivary pH increased dramatically in T1 and then decreased significantly. Descriptive data of both salivary pH and salivary flow rate for all children in each time point are presented in Table 2.

Table 2
Descriptive data of both salivary pH and salivary flow rate

<table>
<thead>
<tr>
<th>Measures</th>
<th>n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva pH</td>
<td>200</td>
<td>7.2675</td>
<td>0.4037</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Salivay flow rate</td>
<td>200</td>
<td>0.5309</td>
<td>0.3363</td>
<td>0.10</td>
<td>2.24</td>
</tr>
</tbody>
</table>

<sup>a</sup>n the total number of measurements done for the all children in each time point

Table 3 presents the findings of the two-way repeated measures ANOVA test. It showed that the difference between the two treatments was not significant in the mean value of saliva pH ($F = 0.92, \text{df} = 1, P = 0.346$). However, there was a statistically significant difference ($F = 29.861, \text{df} = 3, P = 0.00$) between the different time points in the mean value of saliva pH (Table 2). In addition, the two-way repeated measures ANOVA test indicated that there was no statistically significant difference between group A and B ($F = 0.066, \text{df} = 1, P = 0.211$) in the rate of salivary flow (Table 3) although the difference was statistically significant ($F = 11.74, \text{df} = 3, P = 0.000$) between the time points (Table 4).

Table 3
findings of the two way repeated measures ANOVA test to analyze the difference in the mean value of saliva pH and salivary flow rate in-group A and B over time

<table>
<thead>
<tr>
<th>Variables</th>
<th>Within Subjects Effect</th>
<th>Sum of squares type III</th>
<th>df</th>
<th>F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva pH</td>
<td>Treatment group</td>
<td>0.281</td>
<td>1</td>
<td>0.923</td>
<td>0.346</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>6.324</td>
<td>3</td>
<td>29.861</td>
<td>0.000*</td>
</tr>
<tr>
<td>Salivary flow rate</td>
<td>Treatment group</td>
<td>0.019</td>
<td>1</td>
<td>0.066</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>1.239</td>
<td>3</td>
<td>11.74</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

<sup>*statistically significant difference</sup>
findings of the two way repeated measures ANOVA test to analyze the difference between the time points in each group regarding the two variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva PH</td>
<td>A</td>
<td>6.88 ± .415</td>
<td>7.50 ± .32</td>
<td>7.34 ± .37</td>
<td>7.26 ± .326</td>
<td>1.226</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>7.12 ± .46</td>
<td>7.46 ± .406</td>
<td>7.4 ± .25</td>
<td>7.30 ± .353</td>
<td>1.425</td>
<td>0.002*</td>
</tr>
<tr>
<td>Salivary flow rate</td>
<td>A</td>
<td>.34 ± .26</td>
<td>.68 ± .334</td>
<td>.57 ± .274</td>
<td>.54 ± .207</td>
<td>1.001</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>.51 ± .34</td>
<td>.62 ± .388</td>
<td>.49 ± .3</td>
<td>.58 ± .451</td>
<td>0.993</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*statistically significant difference

Multiple comparisons with baseline using Bonferroni correction showed significant differences in the mean value of saliva pH of group A over time from baseline to T1 and then a significant decrease (P < 0.001) from T2 to T3 (Fig. 2). In addition, multiple comparisons with baseline using Bonferroni correction showed significant differences in the salivary flow rate of group A from baseline to T1 and then a significant decrease (P < 0.001) from T2 to T3 (Fig. 3).

The two-way repeated ANOVA using a mixed model between subject and within-subject factors revealed that Mauchly's test of sphericity has been met, (x² = 5.58, P > 0.05). For the time points, there was no significant difference in the rate of salivary flow between two groups over time (x² = 5.78, P > 0.05). However, the results showed that the variances between group A and B were significantly different from one another based on an alpha of 0.05, P < 0.001, indicating the sphericity assumption was violated for time (Table 5). Since the sphericity assumption has not been met, the Greenhouse–Geisser correction has been taken into consideration for multivariate analysis. The Greenhouse–Geisser correction showed that there were no statistically significant effects (P > 0.05) or changes between group A and B over time in the rate of salivary flow (Table 5).

In addition, the two-way repeated ANOVA using a mixed model between subject and within-subject factors revealed that Mauchly's test of sphericity has not been met, (x² = 11.338, P = 0.04). For the time points, there was no significant difference (x² = 7.02, P > 0.05) in saliva pH between groups over time (Table 5). However, the results showed that the variances between group A and B were significantly different from one another based on an alpha of 0.05, P < 0.001, indicating the sphericity assumption was violated for time. Therefore, the Greenhouse–Geisser correction has been taken into consideration for multivariate analysis. The Greenhouse–Geisser correction showed that there were no statistically significant effects or changes (P > 0.05), between group A and B over time in saliva pH (Table 5).
Table 5
Mauchly's Test of Sphericity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within Subjects Effect</th>
<th>Mauchly’s W</th>
<th>Approx. Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva pH</td>
<td>Treatment group</td>
<td>1</td>
<td>0.000</td>
<td>0</td>
<td>0.000*</td>
</tr>
<tr>
<td>Time</td>
<td>0.734</td>
<td>7.020</td>
<td>5</td>
<td>0.220</td>
<td></td>
</tr>
<tr>
<td>Treatment* Time</td>
<td>0.61</td>
<td>11.338</td>
<td>5</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Salivary flow rate</td>
<td>Treatment group</td>
<td>1</td>
<td>0.000</td>
<td>0</td>
<td>0.000*</td>
</tr>
<tr>
<td>Time</td>
<td>0.775</td>
<td>5.783</td>
<td>5</td>
<td>0.328</td>
<td></td>
</tr>
<tr>
<td>Treatment* Time</td>
<td>0.782</td>
<td>5.585</td>
<td>5</td>
<td>0.349</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Dental caries is defined as a biochemical process in which dental tissues lost their minerals due to acidogenic pathogens which metabolize carbohydrates to produce acids [14]. This causes the pH value to be dropped below the critical value. As a result, calcium and phosphate ions are lost [15].

CPP-ACP is a compound developed to enable remineralization by generating a pool of calcium and phosphate which maintain the supersaturation of saliva [16].

A recent systematic review showed that there is an evidence regarding the remineralizing effect of CPP-ACP by studying the roughness of enamel. However, the effect on physiochemical properties of saliva has not been studied in this review[17].

Previous studies provided controversial results for the influence of CPP-ACP on physiochemical properties of saliva. For that reason, it is of interest to establish whether the application of CPP-ACP can raise the saliva pH or increase the salivary flow rate in children and consequently contribute to remineralization. To the best of our knowledge, this trial is the first to study the impact of topical application of CPP-ACP for a short period of time on the saliva pH and salivary flow rate in children.

Several studies have reported that the saliva pH can be changed due to variant factors such as metabolic, hormonal and general health changes [18, 19, 20]. However, decreased levels of saliva pH is an important indicator of developing dental caries [21].

Salivary flow rate can be defined as the amount of saliva secreted per minute. It can be considered as an important preventive aspect against demineralization since it protects and lubricates oral surfaces and facilitates the cleaning of bacterial substrates [22]. Consequently, reduced salivary flow can diminish the preventive capacity of saliva [21, 23]. However, a recent review recognized that there is a need to design further studies to make a reliable assessment between hyposalivation and dental caries in young patients [24].
Previous studies indicated that CPP-ACP can be used to inhibit demineralization and to improve remineralization. For instance, a recent review (2020) showed that CPP-ACP can be an effective agent to treat white spot lesions around orthodontic brackets. However, they found that the remineralizing effect of CPP-ACP is not significantly greater than using Fluoride alone [25]. This can be referred to what have mentioned Ferrazzano et al (2011) that the effect of CPP-ACP on demineralized enamel is affected by many elements in the oral cavity that are difficult to control [26].

Similarly, the study of Shen et al (2021) found that the presence of saliva and biofilm is crucial to authenticate the mechanism of action of CPP-ACP in remineralization [27]. The amount of secreted saliva and saliva pH can both alter the way CPP-ACP remineralizes tooth enamel as CPP separates from ACP in the acidic environment [28, 29].

In the present trial, 50 children aged 6 to 8 years old were selected since this age group has been at high risk of caries due to the cariogenic diet they consume[30]. In addition, a limited age range was selected to avoid the age-related differences in physiochemical properties of saliva.

To standardize the diet intake of the participants, all children recruited in this trial was lived in one orphanage. Stimulated saliva was selected to be studied in this trial in different time points before and after the application of CPP-ACP because stimulated saliva is more related with caries prevention than unstimulated saliva [31, 32]. This is due to the higher mineral content that leads to more buffering capacity and greater salivary clearance [31, 33].

In this study, saliva samples were collected in the morning (08:00–10:00 am) to minimize the effect of circadian variation in the salivary flow rate. saliva-check Buffer kit (Saliva-Check Buffer, GC Int) was used to check the salivary pH, as it was an easy to use, and reliable method [34]. In addition, the salivary pH was measured immediately after the determined contact time of the color-changing strip (10 s) to avoid potential misreading of the results. In this trial, there was no significant difference between the two intervention groups regarding the salivary flow rate. This may be attributed to the ability of the placebo cream to stimulate salivary secretion simply due to introducing a new agent into the oral cavity, considering the presence of any substance in the oral cavity induces both chemical and olfactory stimuli by neural reflexes, which leads to raised output of saliva.

Our results were different from those reported by Hegde and Thakkar(2017) which showed that CPP-ACP can increase the salivary flow rate [35]. This variation in the results can be due to the use of chewing gum in their study, which may increase the flow rate of saliva regardless of its composition. However, our results were in accordance with another study, which indicated that the topical application of CPP-ACP did not alter the salivary flow rate [36].

Moreover, this study showed that there was no significant difference between the two groups in the changes of saliva pH. This can be explained by the results of previous studies which indicated that CPP-ACP can increase salivary pH after a long period[37]. For instance, Ozdas et al (2015) showed that the increase buffering capacity of CPP-ACP was observed since the fourth week of application [38].
Therefore, our results were different from the results of Emamieh et al (2015) which showed that CPP-ACP containing chewing gum can increase the level of saliva pH [39]. This difference may be attributed to the duration of chewing the gum over three weeks assessed during the trial.

Padminee et al (2018) reported that CPP-ACP product can raise the pH of saliva more than xylitol. They attributed that results to the ability of CPP-ACP in bringing down Streptococcus mutans levels which are acidogenic pathogens [40].

The present findings indicated that both salivary flow rate and saliva pH were increased directly after the application of both placebo and CPP-ACP with a statistically significant difference between different time points. These findings were in agreement with Prathima et al study (2021) which showed that maximum peak rise in salivary pH was observed immediately after spitting the CPP-ACP containing gums [41]. Oliveira PRA et al (2022) showed in their study that tooth remineralization of initial teeth demineralization gives better results in the presence of fluoride in conjunction with CPP-ACP. They also reported that placebo-treated specimens incorporated fluoride from the saliva due to the high sensitivity of white spot lesions (demineralized enamel) to pH cycling. For that reason, they found that remineralization process would be better achieved in the presence of fluoride dentifrice [7].

In fact, this study has highlighted the importance of investigating the remineralization products such as CPP-ACP for a short period among children. However, further studies should investigate the effect of CPP-ACP on a longer period of application to ascertain findings. In addition, future work should consider other parameters such as the measurement of calcium concentration, which might provide further understanding about the effect of CPP-ACP in remineralization process.

**Conclusion**

This study has provided information that topical application of CPP-ACP can raise the level of saliva pH and the salivary flow rate immediately after the application for a short period of less than half an hour. Consequently, single topical application of CPP-ACP for a short period has no effect on remineralization of teeth. Further studies are still important with increased sample size to ascertain findings.

**Declarations**

**Acknowledgments**

Authors would like to thank all children who accepted to take part in this study and all staff in the Ambulance Charity Orphanage, Damascus, Syria for their cooperation. This study is part of MSc dissertation to obtain master degree in pediatric Dentistry and is financially supported by Damascus University.

**Authors’ contributions**
LA and MD, designed the study protocol, performed the search and data extraction. LA collected the data and did the field work and statistically analyzed data. MD supervised the study, overviewed data extraction and data analysis. MA registered the trial. LA, MA, and MD worked on the data interpretation and manuscript preparation. LA, MA and MD read and approved the final manuscript.

Ethics approval and consent to participate

Ethical Approval was obtained from the ethics committee of the Faculty of Dentistry in Damascus University. In addition, a formal permission was obtained from the Ministry of Social Affair and Labor to get access to orphanage and perform the required examinations on children. A written informed consent from the manager of the orphanage and their carers were obtained. This trial was in accordance with the ethical standards of the institutional and national research committee of the study institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. It was approved by the Research Ethics Committee of Faculty of Dentistry of Damascus University and was registered at the ISRCTN registry (https://doi.org/10.1186/ISRCTN17509082)

Conflict of Interest

The authors declare that they have no competing interests.

Funding

The project was funded by Damascus University, Syria, which is a public University.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Various Management Strategies: The Role of Advanced Polymeric Materials in the Treatment

Figures
Figure 1

CONSORT flow diagram of participants
Figure 2

The change of saliva PH values of groups A and B in the studied time points

X-axis: T0,T1,T2 and T3

Y-axis: pH values
Figure 3

The change of salivary flow rate values of groups A and B in the studied time points

X-axis: T0, T1, T2 and T3

Y-axis: salivary flow rate values (ml/min)