ORIGINAL RESEARCH

Estimation of the Efficacy of Remineralizing Agents on the Microhardness of Deciduous Teeth Demineralized Using Pediatric Formulations

Nishna T[1], Amith Adyanthaya[2], Ann Meera Johnson[3], Jipsa Venugopal[4], Malini Venugopal[5], Anju RV[6]

Abstract

Aim: This study aimed to evaluate the demineralizing effect of commonly used pediatric syrup formulations on primary teeth and the efficacy of two readily available remineralizing agents in treating this effect.

Materials and methods: Ninety primary teeth were used for sample preparation and divided into three groups: antibiotic syrup (group A), cough syrup (group B), and control (group C) groups. These groups were further categorized into intragroups according to the treatment with remineralizing agents: groups A1, B1, and C1 received GC Tooth Mousse (casein phosphopeptide-amorphous calcium phosphate, CPP-ACP paste) and groups A2, B2, and C2 received Clinpro Tooth Crème. The samples were subjected to a series of demineralization cycles for 14 days, and remineralization cycles until 30 days were performed using two remineralizing agents, that is, GC Tooth Mousse (CPP-ACP paste) and Clinpro Tooth Crème and were evaluated using Vicker's microhardness test.

Results: Antibiotic syrup (group A) and cough syrup (group B) showed a significant decrease in surface microhardness compared with control (group C). All intragroups showed an increase in surface microhardness after treatment with remineralizing agents, which was significantly higher in intragroups A1, B1, and C1 treated with GC Tooth Mousse (CPP-ACP paste).

Conclusions: Oral liquid medications showed definite demineralization potential. CPP-ACP paste was found to be better than Clinpro Tooth Crème for demineralized teeth.

Clinical significance: The use of over-the-counter drugs has increased among the average Indian population, especially for the treatment of fever, cold, and cough. Unwise use of medications by the present population without proper medical guidance will lead to irreparable changes in future generations.

Keywords: Clinpro Tooth Crème, CPP-ACP, Dental erosion, f-TCP, GC Tooth Mousse, Pediatric syrups, Remineralizing agents.

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Introduction

The American Dental Association defines dental erosion as "the chemical loss of mineralized tooth substance caused by exposure to acids not derived from oral bacteria."[1] Erosion is derived from the Latin verb erodere, erosum (to gnaw, to corrode). Etching away from the enamel surface, either by acid or chemical chelation without any bacterial involvement, results in dental erosion or erosio dentium.[2]

Based on the etiology, tooth erosion is classified as extrinsic, intrinsic, or idiopathic. Extrinsic erosion results from the presence of exogenous acids. Dietary acids are undoubtedly the principal causative factor for extrinsic tooth erosion.[3] Medically compromised children suffering from conditions such as asthma, congenital cardiac defects, and neurotic problems such as epilepsy, autism, and mental retardation might be taking long-term oral medications, predisposing them to dental erosion.[4]

If no prompt action is taken against dental erosion, its initial effects start on the enamel surfaces and then advance to the next layer of the tooth structure, that is, dentine. In the initial stages of erosion, the enamel surface softens.[5] The contact time and characteristics of acids present in these medications determine the degree of corrosion. Further continuation of the erosive attack leads to the dissolution of enamel crystals, which leaves a superficial rough surface on the enamel.[6] At the "critical pH" of the enamel, saliva is saturated with different organic and inorganic components. The enamel surface achieves equilibrium with saliva at the critical pH, where no further enamel dissolution occurs. Deciduous teeth are reported to have more dissolution than permanent teeth.[7] The potential for enamel dissolution exists below the critical pH at which saliva is under-saturated. The reverse occurs when pH rises, resulting in the deposition of minerals back onto the tooth structure.[8] This process will enrich the enamel surface with minerals

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that had previously leached out. So, when the pH is increased, the remineralization process occurs, resulting in the formation of fluorapatite by settling different minerals such as calcium, phosphate, and fluoride ions. The newly formed fluorapatite crystals can withstand the dissolution caused by organic acids.[9,10]

The rational difference between the rates of demineralization and remineralization determines the microhardness of the enamel. Apart from the main ingredients present in the medications, specific external coloring and flavoring agents are added to improve their palatability and perception by children.[11] The excipients added to the medicines include artificial sweeteners, preservatives, alcoholic solvents, emulgents, suspensors, sweeteners, antioxidants, viscosity agents, moisturizing agents, and dispersing agents.[12] Certain preservatives such as benzyl alcohol, ethyl alcohol, and solvents such as lactose have been found to cause acidosis. One commonly used viscosity agent, glycerol, causes electrolyte disturbances. Most of the inventions in the pharmacy field have focused on the adult population, and fewer drugs are approved for pediatric use.[13] Artificial sweeteners such as sucrose, fructose, or a combination, used in medications to enhance the flavor, often cause dental caries. They are primarily associated with lowering plaque pH during long-term drug therapy.[14] The acidogenicity caused by the high amount of fermentable carbohydrates in pediatric liquid medications may make them more cariogenic. The use of syrup formulations without the guidance of medical practitioners has increased unbearably in the past few years.[15] Children of poor socioeconomic status may not be necessarily guided by their parents about the importance of maintaining proper oral hygiene, which in turn will enhance the decimation of the present scenario.[16]

As the enamel is the hardest non-living tissue incapable of regeneration, some treatment must be performed to cease further dissolution. Proper guidance using routine remineralizing agents to reverse the side effects of medicinal formulations is necessary to prevent enamel erosion in the pediatric population. Daily exposure of a child's oral cavity to pharmaceutical syrups, suspensions, carbonated soft drinks, and beverages is a new challenge compared with that in older generations. Some innovative methods for regenerating the enamel, which can be introduced into daily routine, must be initiated. Pediatric dentists should focus on a child's medical and dietary history. Dentists should develop the habit of prescribing remineralizing agents to patients in the abovementioned category, where calcium and phosphate ions are readily available.

Remineralizing agents are a revolutionary innovation in minimally invasive dentistry (MID).[17] Remineralizing agents fabricated an excellent saturated habitat around the early lesion. These agents, including fluorides, xylitol, casein calcium phosphopeptides, functionalized tricalcium phosphate (TCP), and bioactive glass, are available in the market under different brand names.[18]

In 1998, the School of Dental Sciences, University of Melbourne, Victoria, Australia, developed an innovative product in the field of MID. The product was marketed under the commercial name "GC Tooth Mousse." The manufacturers state that the product contains casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), also known as Recaldent, derived from a milk protein called casein. The first professionally available product to contain the CPP-ACP complex is GC Tooth Mousse, which is supplied in various flavors. Recaldent is rich in bioavailable calcium and phosphate ions that help remineralize eroded teeth. A molecule of CPP can hold 25 Ca+ ions, 15 P+ ions, and 5 F–ions, which are chemically available for remineralization. Saliva is a metastable solution that contains calcium, phosphate, and fluoride ions. Casein phosphopeptide firmly attaches to ACP with the help of these ions, and the supersaturated state of saliva is maintained, which prevents further dissolution of the enamel.[19–21]

The 3M ESPE company, situated in Minnesota, United States of America, has a wide range of dental products. Clinpro Tooth Crème 0.21% w/w Na F is a product containing TCP. Clinpro Tooth Crème is a rich source of fluoride, approximately 950 ppm F–. This phenomenon helps reverse the white spot lesions and arrest further dissolution of the enamel.[22] A "smart Ca-P" system, called TCP, which is present in Clinpro, can potentially deliver Ca+ and P+ ions to teeth, which works synergistically with F–ions. A functionalized TCP is created by blending TCP with organic minerals and fluorides, and it acts as a fluoride dispenser. The principal mineral in teeth is hydroxyapatite crystals, and TCP is a precursor of these hydroxyapatite crystals. TCP is created skilfully to coexist with fluoride under different pH conditions inside the oral cavity. As the tooth crème comes in contact with the tooth surface, TCP releases functionalized Ca ions, which interact with the tooth's surface and enhance the enamel's mineral content. Most calcium phosphate additives require an acidic pH for their complete action. However, functionalized TCP needs only a neutral pH environment for its deposition, which is more beneficial to the tooth.[23]

The novelty of this research is the demineralization of the deciduous enamel using pediatric syrup formulations and its treatment using remineralizing agents. Studies have reported on the difference in tooth dissolution between deciduous and permanent teeth enamel and identified higher dissolution in deciduous teeth than in permanent teeth.[7] Studies on the erosion in deciduous teeth are essential, as children are continuously exposed to such medications at a higher rate than in previous generations. Many studies have reported the erosive properties of pediatric syrups and carbonated drinks. A comparison of the remineralizing effects of agents such as CPP-ACP and TCP on enamel has also been reported. However, all these studies were published as separate studies, and no study has combined demineralization using pediatric syrups and remineralization processes using the readily available crème in markets. Here, we assessed the erosive effect of two commonly used pediatric syrups on primary tooth enamel microhardness and the role of two different remineralizing agents on the microhardness of primary tooth enamel.

Methods

Study Design

In vitro comparative study (Flowchart 1).

Duration of Institutional Ethics Committee Approval:

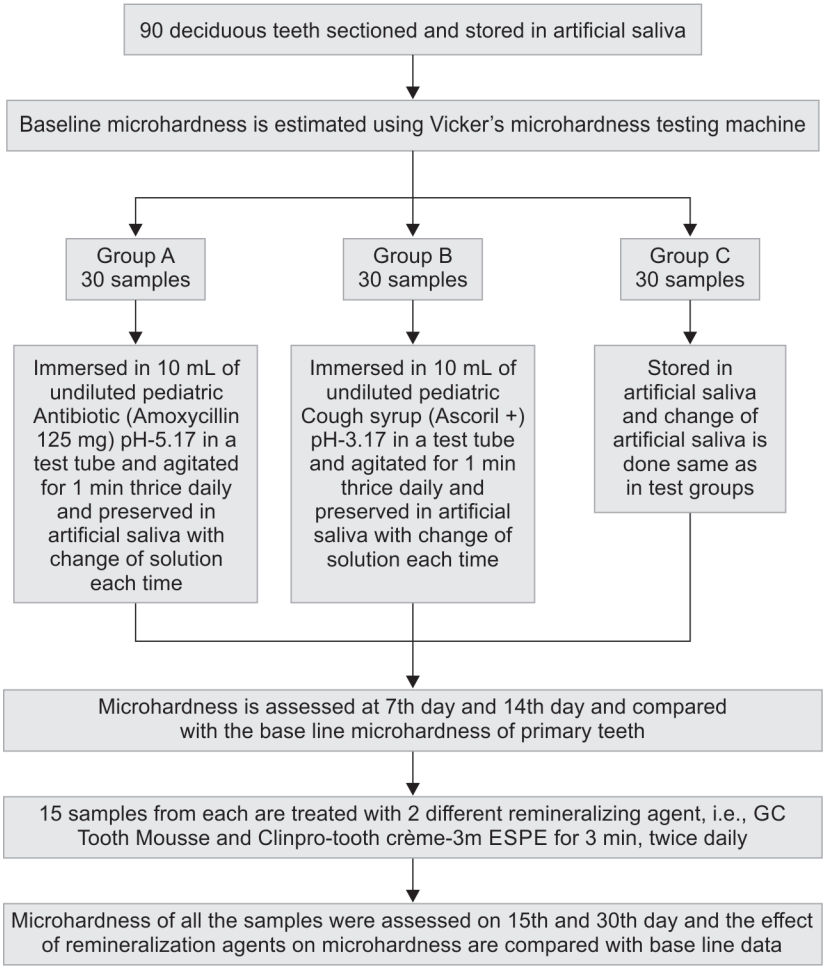
The research received approval on 8 November 2015, with approval IEC/IRB No.: KMCTDC/IEC/2015/13, for 2 years.

Sample size calculation:

$$n = \frac{(Z\alpha + Z\beta)^2\, SD^2 \times 2}{d^2}$$

where $Z\alpha = 1.96$ (constant)
$Z\beta = 0.84$ (constant)
SD = standard deviation
d = expected average

Flowchart 1: Study design



For the present study, the standard deviation was 7 and $d = 5$, which was used to calculate the sample size as follows:

$$n = \frac{(1.96)^2 \times (0.84)^2 \times \text{SD} \times 2}{5^2} = 30$$

Each group consisted of 30 patients; therefore, the total sample size was calculated to be 90. Thus, with the reference study standard deviation and *d* value, we had a sample size of 90 teeth.

This experimental *in vitro* study was conducted in the Department of Pedodontics and Preventive Dentistry, KMCT Dental College, Calicut. The Institutional Ethics Committee of KMCT Dental College, Calicut, approved the study.

Inclusion Criteria

Pediatric patients reported in the Department of Pedodontics and Preventive Dentistry to KMCT Dental College, Calicut, for extraction of the deciduous tooth due to pre-shedding mobility with the sound crown structure were selected for this experimental *in vitro* study.

Exclusion Criteria

Teeth with the following conditions were excluded:

- Dental caries
- Restorations
- Grossly destructed crown
- Non-vital tooth
- Any trauma
- Enamel cracks
- Any developmental defects
- Congenital anomalies

Sample Preparation

Pediatric outpatients who visited the KMCT Dental Institution were selected for tooth sample collection. The primary tooth, which was non-carious, was chosen for extraction. For the initial preparation of the sample, the teeth were washed using pumice slurry water, and then a slow-speed straight handpiece, NSK Japan, was used at 15000 rpm to remove the root. The buccal surface to be evaluated was smoothened using 600- and 1200-grit abrasive paper. Later, two layers of cosmetic nail polish were painted on all surfaces, except the buccal area. All specimens were collected and preserved in artificial saliva at room temperature.

Microhardness Assessment

The baseline microhardness of the teeth specimens was assessed using Vicker's microhardness testing machine (HMV Microhardness tester, Shimadzu) at Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram. The specimen was placed at the center of

a cuboidal acrylic block using a piece of red wax. An automatic diamond intender with a force of 50 gf for 15 s was applied to the enamel surface at three points 100-µm apart. The average of the readings was obtained as the Vicker's microhardness value.

Materials and Methods

Artificial Saliva Preparation

At the Department of Chemistry, St. Thomas College, Thrissur, Kerala.

Composition of Artificial Saliva

The artificial saliva used was similar to that described by McKnight Hanes and Whitford.[24]

Methyl hydroxybenzoate (2.0 gm; carboxymethylcellulose 10.0 gm, KCl 0.625 gm, $MgCl_2.6H_2O$ 0.059 gm, $CaCl_2.2H_2O$ 0.166 gm, K_2HPO_4 0.804 gm, and KH_2PO_4 0.326 gm dissolved in 1000 mL of deionized water). The pH was 7.2. The pH of normal saliva is in the range of 7.2–7.4.

Steps in Artificial Saliva Preparation

All ingredients were measured using a high precision balance (Kerry) machine, and carboxymethylcellulose (10.0 gm) was added to deionized water using an ultrasound probe sonicator. These were used to dissolve carboxymethyl cellulose lumps. Subsequently, methyl hydroxybenzoate 2.0 gm was added to deionized water using a magnetic stirrer with a hot plate until all the particulates were blended well. All components were mixed and made up to 1000 mL. The pH was measured using a digital pH meter, and it was measured as 7.25.20.

Pediatric Medications used for Demineralization

Commonly used pediatric medications were selected for the study:

- Group A: Pediatric antibiotic suspension: amoxicillin 125 mg suspension (pH 5.17).
- Group B: Pediatric cough syrup: Ascoril + (terbutaline sulfate, bromhexine hydrochloride, guaiphenesin and menthol expectorant) (pH 3.17).

The following process achieves demineralization:

Ten milliliters of undiluted syrup were taken in a clean test tube, and 30 teeth each from both groups A and B were immersed and agitated for 1 min three times daily for 7 days with the change in artificial saliva three times daily. In contrast, in group C, artificial saliva was changed three times daily without any syrup exposure. Each tooth was washed with running tap water in a test tube after immersion in the syrups for 1 min and preserved in artificial saliva. The specimens were preserved in artificial saliva and moved to a testing laboratory, where they were removed to assess the microhardness. The procedure followed for the baseline microhardness assessment was repeated. After the microhardness assessment, all teeth were demounted, and the cycle was repeated for 7 days. All samples were immersed for 1 min three times daily into 10 mL of syrups for 7 consecutive days with the change in artificial saliva each time. Later, all specimens were transported and mounted again for microhardness assessment at the end of the 14th day.

Remineralizing agents used for remineralization:

- CPP-ACP (GC Tooth Mousse).
- f-TCP (Clinpro Crème-3M ESPE): 0.21% w/w sodium fluoride anticavity paste with TCP.

The following process achieved remineralization:

In the first remineralization cycle of 15 days, using cotton applicator tips, the remineralizing agents were applied to the buccal surfaces of specific group specimens for 3 min, twice daily for 15 consecutive days. All samples were washed with running tap water in a test tube, and for the next 15 days, they were stored in artificial saliva, which was changed daily. These specimens were later taken to the laboratory to determine their microhardness. This process was repeated in the next remineralization cycle, following the earlier protocols. At the end of 30 days, all specimens were subjected to microhardness assessment.

Expected Outcome

All samples were placed in commonly used pediatric formulations and expected to demineralize the enamel. The remineralizing agents were anticipated to show increased enamel microhardness compared with the baseline microhardness and demineralized enamel.

Statistics

All data were entered into a data entry form. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20. Results obtained were subjected to analysis of variance and paired *t*-test.

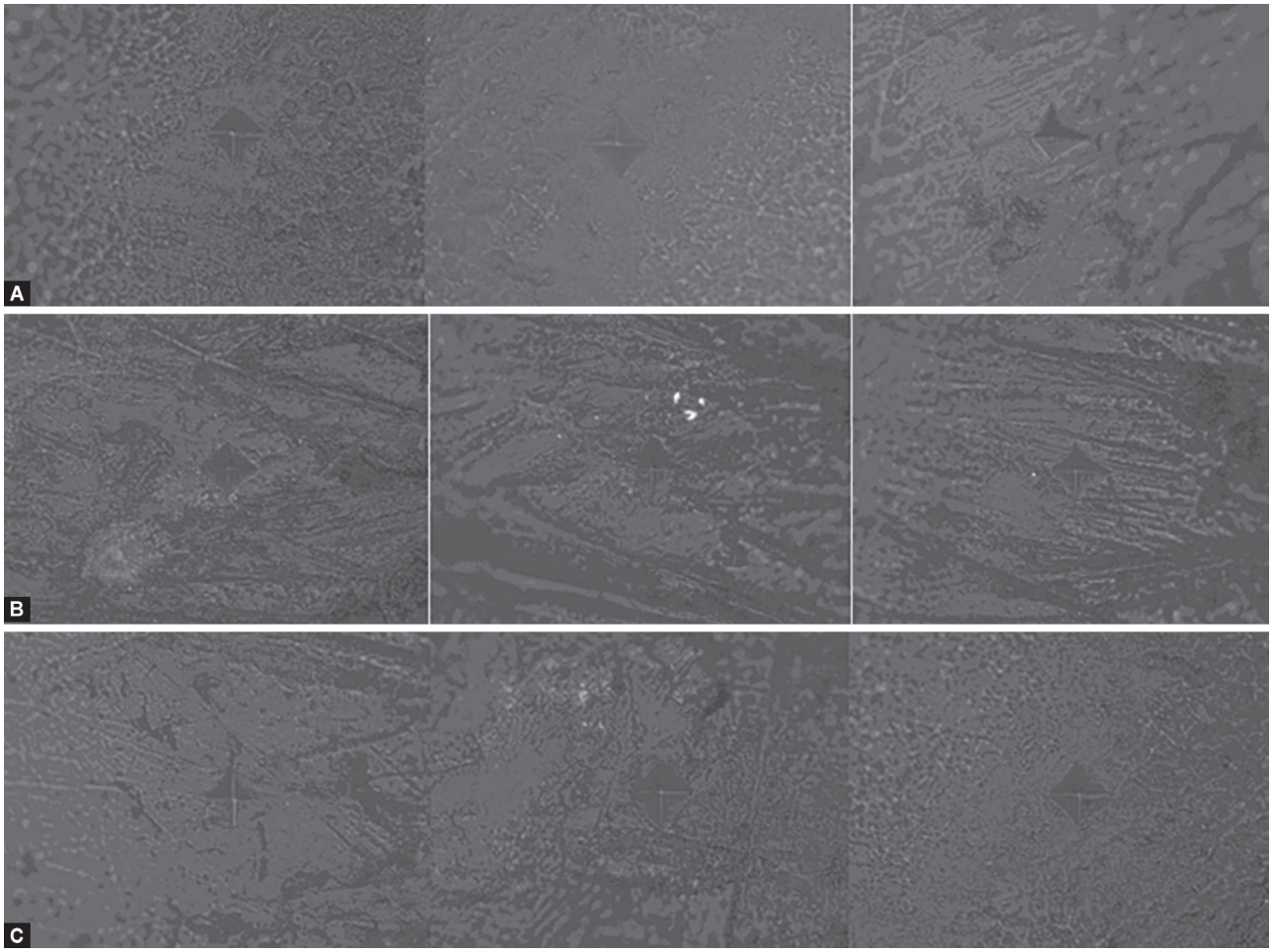
Results

A total of 90 specimens were divided into three groups of 30 each; the tooth was subjected to Vicker's microhardness test. The significance of the 90 samples was tested using a paired *t*-test and found to be statistically insignificant. The baseline microhardness was measured, which was 308.97 in group A, 307.72 in group B, and 309.01 in group C (Figs 1 and 2, Table 1).

On the following demineralization cycles, on 7th day, group A had undergone demineralization using antibiotic syrup and showed a microhardness of 279.56; group B, after demineralization using cough syrup, showed a microhardness of 263.96; and group C, which was exposed to artificial saliva, had a microhardness of 310.82 (Table 2). Compared with baseline microhardness, on the 7th day, group A had a mean difference of 29.41 ± 11.38; group B, 43.75 ± 13.27; and group C, –1.81 ± 17.09, which was highly significant for groups A and B when subjected to paired *t*-tests but statistically insignificant for group C (Table 2).

On the 14th day, demineralization in group A resulted in a microhardness value of 247.13, 212.18 in group B, and 311.05 in group C (Table 2). Compared with baseline microhardness, on the 14th day, group A had a mean difference of 61.83 ± 10.02; group B, 95.53 ± 12.95; and group C, –2.03 ± 14.10, which was highly significant for groups A and B when subjected to paired *t*-tests but statistically insignificant for group C (Table 2).

During the remineralization cycles, all three groups containing 30 samples each were divided into intragroups containing 15 samples each. Group A was divided into groups A1 and A2, group B into groups B1 and B2, and group C into groups C1 and C2. The intragroup groups A1, B1, and C1 were treated with the remineralizing agent GC Tooth Mousse containing CPP-ACP, whereas groups A2, B2, and C2 were treated with Clinpro Tooth Crème. In the following remineralization cycles on the 15th day after remineralization with GC Tooth Mousse, group A1 showed a microhardness value of 288.24; group B1, 291.92; and group C1, 326.75. Regarding the intragroups treated with Clinpro Tooth



Figs 1A to C: Microhardness indentation images on groups A–C

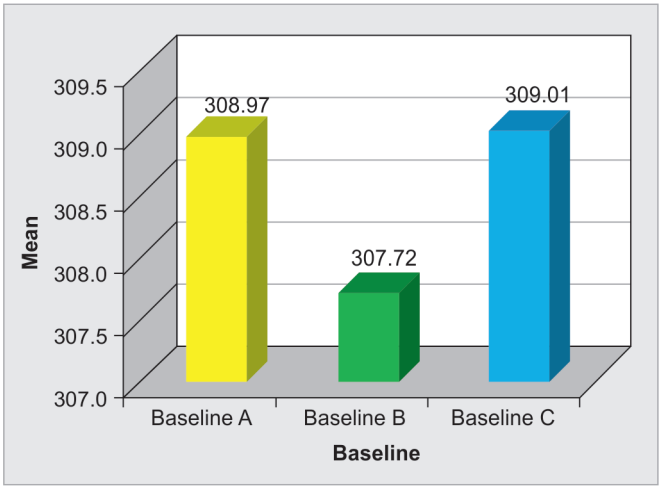


Fig. 2: Baseline microhardness of three groups

Crème, after 15 days, group A2 showed a microhardness of 263.70; group B2, 263.32; and group C2, 315.54 (Table 3 and Fig. 3).

After 30 days of remineralization, the GC Tooth Mousse groups, that is, group A1, showed a microhardness of 289.12; group B1, 313.69; and group C1, 337.05. In the groups treated with Clinpro Tooth Crème, after 30 days of remineralization, the microhardness value was 290.95 in group A2, 284.12 in group B2, and 324.50 in group C2 (Table 3 and Fig. 4).

Table 1: Comparison of Baseline microhardness of Groups A, B, and C with the 7th day and 14th day microhardness

Groups	*N*	*Baseline microhardness*	*Microhardness at 7th day*	*Microhardness at the 14th day*
			Mean (HV)	*Mean (HV)*
A	30	308.97	279.56	247.13
B	30	307.72	263.96	212.18
C	30	309.01	310.82	311.05

HV, Vicker's number (microhardness unit)

The mean microhardness value was 289.12 ± 3.53 in group A1, 290.95 ± 9.6 in group A2, 313.69 ± 9.47 in group B1, 284.12 ± 4.02 in group B2, 337.05 ± 4.74 in group C1, and 324.50 ± 3.42 in group C2 (Table 3).

The mean of all six subgroups A1, B1, C1 and A2, B2, C2 on 14th day demineralization was compared to 30th day remineralization and their mean difference were calculated (Table 4).

Discussion

The occurrence of dental caries and enamel dissolution is higher in primary teeth due to variations in the mineralization of the enamel

Table 2: Comparison of mean difference on the 7th day and 14th day in all the three base groups

		On the 7th day of demineralization			*On the 14th day of demineralization*		
Groups	*Baseline mean (HV)*	*7th day mean (HV)*	*Baseline,7 days mean difference Mean (HV) ± (SD)*	*p-value*	*14th day mean (HV)*	*Baseline, 14 days mean difference Mean (HV) ± (SD)*	*p-value*
A	308.97	279.56	29.41 ± 11.38	<0.001	247.13	61.83 ± 10.02	<0.001
B	307.72	263.96	43.75 ± 13.27	<0.001	212.18	95.53 ± 12.95	<0.001
C	309.01	310.82	−1.81 ± 17.09	0.56	311.05	−2.03 ± 14.10	0.43

Table 3: Comparison of remineralization on 15th day and 30th day in all six intragroups A1, B1, C1 and A2, B2, C2

		Remineralization on the 15th day			*Remineralization on the 30th day*		
Groups		*Mean*	*SD*	*p-value*	*Mean*	*SD*	*p-value*
GC Tooth mousse	A1	288.24^{abcd}	4.30	<0.001	289.12^{abcd}	3.53	<0.001
	B1	291.92^{ehij}	6.16	<0.001	313.69^{beikl}	9.47	<0.001
	C1	326.75^{cfikm}	1.90	<0.001	337.05^{cgkmo}	4.74	<0.001
Clinpro Tooth crème	A2	263.70^{aefg}	4.33	<0.001	290.95^{aefgh}	9.6	<0.001
	B2	263.32^{bhkl}	5.66	<0.001	284.12^{fimn}	4.02	<0.001
	C2	315.54^{dgjlm}	3.76	<0.001	324.50^{dglno}	3.42	<0.001

The same alphabets indicate significant differences from each other according to Bonferroni's *post-hoc* test

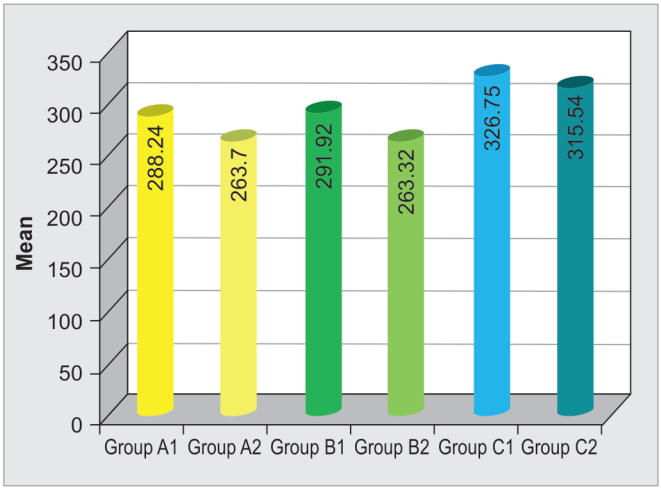


Fig. 3: Comparison of remineralization among all groups at 15 days

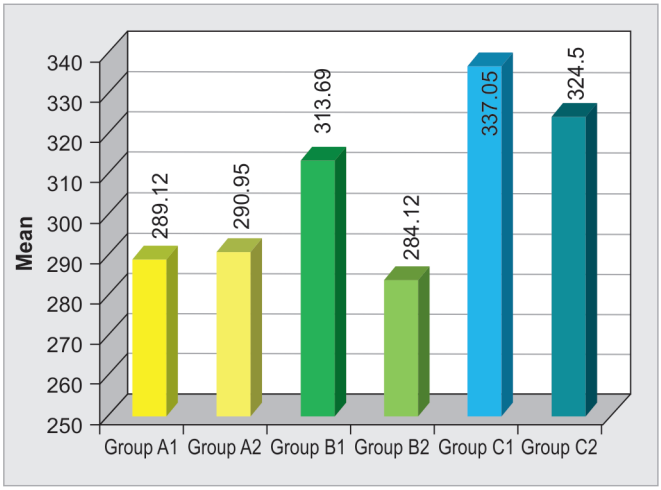


Fig. 4: Comparison of remineralization among all groups at 30 days

structure compared with that in permanent teeth. Primary enamel is immature and less calcified than permanent teeth, making dental erosion easier in children.[7,25–27] Dental erosion is defined as "a progressive loss of dental hard tissues by chemical dissolution in the absence of bacterial involvement."[2] Several factors are involved in the tooth erosion process—intrinsic, extrinsic, and idiopathic, leading to irreversible changes on the tooth surfaces. Causative agents include acidic medications, carbonated energy drinks, and diet routines. Syrup formulations and suspensions are commonly prescribed to pediatric patients because they aid in compliance, and the medicines are made sweet to make them more palatable for children. Children are more vulnerable to dental erosion leading to dental caries, as they are the most exposed to liquid medications. This is the reason for selecting deciduous tooth samples over permanent teeth. Most *in vitro* studies have focused on premolars extracted for orthodontic purposes. The premolar tooth samples were not selected because our intention was to evaluate the erosive effect of pediatric formulations exclusively on the primary tooth enamel.

The purpose of this study was to determine the damaging effects of pediatric liquid medications on children. We selected medications that are readily available in the market and commonly prescribed by medical practitioners. Parents are almost unaware of the hidden challenges of self-prescribing liquid formulations to their children. Pharmaceutical companies mainly produce and market liquid oral medicines for pediatric use. The purpose of adding more acidic preparations to the drug is to maintain drug properties such as dispersion and chemical stability, which will play essential roles in the physiological compatibility and flavor of the drug. Children under medical conditions who have to take this medication compulsorily for an extended period are at greater risk.[25] The dosage and frequency are also a concern as bedtime

Table 4: Comparison of mean difference on the 14th day demineralization and 30th day remineralization in all six intragroups A1, B1, C1 and A2, B2, C2

Groups	*N*	*14th day mean (HV) after demineralization*	*30th day mean (HV) after remineralization*	*Remineralization mean difference at 30th day Mean (HV) ± (SD)*	*p-value*
A1	15	247.13 ± 7.58	289.12 ± 3.53	43.85 ± 8.36	<0.001
A2	15	247.13 ± 7.58	290.95 ± 9.6	45.68 ± 12.15	<0.001
B1	15	212.18 ± 13.15	313.69 ± 9.47	101.50 ± 12.17	<0.001
B2	15	212.18 ± 13.15	284.12 ± 4.02	71.93 ± 14.47	<0.001
C1	15	311.05 ± 9.03	337.05 ± 4.74	25.81 ± 10.67	<0.001
C2	15	311.05 ± 9.03	324.50 ± 3.42	13.25 ± 9.55	<0.001

dosage and reluctance in children to perform oral clearance, along with decreased salivary flow at night, make the situation worse.[25,28,29] The salivary glands are wholly developed only at the age of 15 years.[25,29] Children belonging to preschool and primary school age groups show less interest in eliminating any retained food particles compared with adolescents.[29] The prolonged and frequent use of highly viscous liquid medications have unfavorable effects on tooth surfaces, which may be accompanied by reduced salivary cleansing, eventually resulting in medically induced dental erosion. The erosive potential of liquid medicines usually increases due to certain excipients, such as acid, ethyl alcohol, benzyl alcohol, glycerol, and lactose.[13] The rise in the use of self-prescribed medication among the population has worsened the scenario.

The medicines used in this study have an acidic nature, low pH, and a low percentage of compounds such as calcium, phosphates, and fluorides.[30] It is necessary to study the erosive capacity of syrup used daily, as some studies have mentioned that deciduous teeth have more demineralization liable to dental erosion and caries.[7] So, self-prescribed medications have more deteriorating effects on the pediatric population than the adult population. So, we should be aware of the remedial methods available to prevent enamel dissolution caused by these acidic medications. The remineralizing agents used in minimal intervention dentistry offer an innovative remedy for this dilemma.

The novelty of the present study is that we assessed both the potential erosive effect of commonly used pediatric syrups on primary tooth enamel microhardness and the role of remineralizing agents on it. The same tooth samples were subjected to demineralization and remineralization cycles. Many studies have reported the demineralization potential of different medications and soft drinks. Several studies have compared the remineralizing potential of fluorides and remineralizing agents.[31] Here, we suggest a new way to prevent demineralization caused by pharmaceutical formulations by prescribing remineralizing agents as adjuvants and pediatric liquid medications.

Tooth sample preparation and sectioning were performed as described by Scatena et al.[32] and Mali et al.[33] The Vicker's microhardness testing machine was chosen over the Knoop hardness testing machine because the Knoop method is best suited for use with rigid and brittle specimens, whereas Vicker's method is better for small, rounded specimens. For Vicker's method, the specimens should be polished for microhardness testing; the specimen should be kept stable. While testing, we placed the specimen inside an acrylic block and fixed it with red wax; after the measurement, we dislodged it each time from the acrylic socket and placed it back in artificial saliva.[33] We used the Vicker's microhardness testing machine for deciduous tooth samples as done in the study by Mali et al.[33]

The artificial saliva used in this study was a composition described by Mcknight Hanes and Whitford in 1992,[24] without the addition of sorbitol; the same was used by Scatena et al.,[32] Mali et al.,[33] and Amaechi et al.[34] The saliva produces a salivary protein-based pellicle that covers the enamel surface. It decreases demineralization by creating a protective layer over the tooth. Certain minerals and elements in artificial saliva have remineralizing effects on enamel microhardness because normal human saliva also contains many remineralizing agents. Therefore, in this study, we used artificial saliva to replicate human saliva while maintaining a pH of 7.25. We changed it daily as human saliva in the oral cavity is never stagnant.[33,35,36]

We chose 7 and 14 days for assessment in this study because antibiotic and cough syrup formulations are administered within 7–14 days. Chronic medically compromised patients are subjected to a long-term antibiotic course that does not extend beyond 14 days.[31,33] The long-term effects of medications can only be assessed by selecting a 14-day duration.[33]

Ten microliters of undiluted syrup was taken in a clean test tube, and the tooth samples were agitated for 1 minute three times daily. This protocol was selected because Mali et al.[33] and Amaechi et al.[34] suggested that when the child takes the medication without dilution, it can cause dental erosion at specific concentrations.

In some studies, assessments were performed after 5 days of remineralization;[37] however, we selected a span of 30 days of remineralization to determine the evident changes in microhardness. Lata et al.[37] suggested that remineralizing agents such as ACP-CCP do not have much effect in treating early caries lesions, as the days selected were 5 days. The effect of remineralizing agents may be slow; therefore, we selected 30 days. Balakrishnan et al.[31] performed remineralization in 30 days and assessment on the 15th and 30th days; similarly, we selected a long span of 30 days.

Remineralizing agents were applied for 3 minutes twice daily according to the manufacturer's instructions. Previous studies have shown that the increased time of contact of remineralizing agents with the tooth surface will benefit more by showing a noticeable change in dental erosion.[31,38]

In a study by Xavier et al.,[11] the tooth was exposed to medication once and the dental erosion assessment was conducted soon after, which may give unreliable results. In some studies, multiple tooth exposures to medications were performed, including the study by Valinoti et al.,[39] in which exposures were performed for over 12 days; that by Costa et al.,[40] 14 days; and that by Scatena et al.,[32] 28 days. Consecutive exposures to liquid medications will give more authentic results than a single exposure. Most surface changes are unrecognized in a single exposure but can be highly predicted on multiple exposures. Therefore, in the present study, we adopted multiple exposures.

In the present study, the baseline surface microhardness of 90 samples ranged from 307.72 ± 9.66 HV to 309.01 ± 10.67 HV (Fig. 2 and Table 1). These values were in the range of 254.0–383.0 HV in the study by Haghgoo et al.[41] The primary and succedaneous teeth have structural as well as morphological variations. Primary teeth are less mineralized and less mature than permanent teeth. Although the permanent teeth share the same morphological features as the primary teeth, the latter have lower prismatic density and shorter prismatic diameter.[42] The resistance of the enamel to masticatory forces is determined by the amount of minerals present. The extreme hardness makes the enamel more brittle, resulting in an increased risk of fractures, whereas dentine is more resilient than enamel, which helps to maintain the integrity of the tooth.[43]

The mean difference in microhardness after 7 days from the baseline was 29.41 ± 11.38 in group A and 43.75 ± 13.27 in group B, which was highly significant (Table 2). The findings of Scatena et al.,[32] Valinoti et al.,[39] and Costa et al.[40] revealed that the difference between groups A and B may be due to the disparity in ingredients, which will affect the characteristics such as citable acidity, buffering capacity, and pH of the medication.

The mean difference in microhardness from baseline on the 7th day was –1.81 ± 17.09 in group C (Table 2). There was a slight increase in surface microhardness, but it was not statistically significant. This slight increase was due to the composition of artificial saliva, which includes magnesium chloride, calcium chloride, potassium chloride, dipotassium hydrogen orthophosphate, and methyl para-hydroxy benzoate; these components help to remineralize the enamel. These findings are consistent with those reported by Eisenburger et al.[36] According to his research, human enamel was eroded using 0.3% citric acid and divided into seven groups. Six groups were treated using artificial saliva, and 7th group was control kept in isotonic saline. Later ultrasonication was done at different intervals to soften the enamel. The specimens stored in artificial saliva for time intervals of 1, 2, and 4 hours showed signs of partial rehardening of the eroded enamel, and samples stored in artificial saliva for 6, 9, and 24 hours showed less surface erosion after the ultrasonication procedure. Eisenburger et al.[36] suggested that enamel stored for 6 hours or more can work with stand the demineralization process of ultrasonication. He reported that complete remineralization of eroded enamel *in vitro* happens after 6 hours of remineralization in artificial saliva.

When microhardness was estimated on the 7th day after exposure in groups A and B, a marked decrease in the surface microhardness was observed. On the estimation of surface microhardness on the 14th day for the various groups, a further decline in microhardness was observed (Table 2).

The mean difference in microhardness from baseline on the 14th day was 61.83 ± 10.02 in group A, 95.53 ± 12.95 in group B, and –2.03 ± 14.10 in group C, which was statistically significant (Table 2). This observation is consistent with that reported by Mali et al.[33] The substantial decrease in microhardness in group B was because the endogenous pH of liquid medications in the cough syrup used in this study had a pH of 3.17. In the previous studies conducted by Scatena et al.,[32] enamel erosion increased as the pH of the substances decreased.

The diffusion of calcium and phosphate ions from artificial saliva aided in remineralization, which was observed in the control group on the 14th day. Similar observations were made by Featherstone[44] and Feather et al.[45] Agents based on milk products have been studied for several years. Currently, several remineralization paste formulas are available, such as GC Tooth Mousse and Clinpro Tooth Crème (3M ESPE). In principle, there are two possible methods to prevent erosion: the agents are either added to an erosive solution or applied directly to the tooth surface to form a protective layer that inhibits demineralization. Casein phosphopeptide-amorphous calcium phosphate paste promotes a supersaturated state close to dental hard tissue by reducing demineralization and enhancing remineralization of enamel subsurface carious lesions[46] (Table 3).

In the present study, the remineralizing potential of GC Tooth Mousse and Clinpro Tooth Crème was evaluated on the demineralized tooth. The demineralized and control groups of 30 samples were divided into two groups of 15 each. The remineralization potential was estimated on the 15th and 30th days for all groups. In group A, after the specimens were subjected to two remineralizing agents for 15 days, both the subgroups treated with GC Tooth Mousse and Clinpro Tooth Crème showed signs of remineralization. Both remineralizing agents showed an increased rate of remineralization (Table 3). Bader[46] has proposed that CPP-ACP localizes ACP on the tooth surface. This property of CPP-ACP creates a supersaturated niche of calcium and phosphate around the enamel surface, encouraging remineralization and impeding the demineralization process.[46] A definite increase in the mean value was observed when compared with the baseline in all the groups. According to Panich and Poolthong,[47] CPP-ACP improves enamel strength by boosting remineralization.

After 30 days, a sharp increase in enamel surface microhardness was observed among all the groups that received GC Tooth Mousse, that is, A1, B1, and C1, and Clinpro Tooth Crème, i.e., A2, B2, and C2. GC Tooth Mousse increased the surface microhardness significantly compared with Clinpro Tooth Crème (Table 3). The value was highly significant when comparing the two remineralizing agents in the three groups on the 15th day (Table 3 and Fig. 3). A substantial increase in the mean value was observed at 30 days, which was again significant (Table 3 and Fig. 4).

In group A, on the 14th day, demineralization resulted in a microhardness value of 247.13, whereas group B showed a much less value of 212.18. This indicates that the pH was more acidic in group B. Thus, demineralization caused by antibiotics was lesser than that by cough syrup, consistent with the findings of Mali et al.[33]. After 30 days of remineralization cycles, microhardness was better with GC Tooth Mousse (CPP-ACP) among the cough syrup groups; group B1 had a microhardness value of 313.69, whereas Clinpro Tooth Crème was efficient among the antibiotic groups; group A2 had a microhardness value of 290.95. These results indicate that GC Tooth Mousse (CPP-ACP) works better than Clinpro Tooth Crème in more demineralized teeth.

Reynolds et al.[48] reported that the erosion of tooth substrate depends on the number and duration of acid attacks and the pH of the acidic agent. In our study, as the number and duration of exposures to both syrups were the same, the role of pH must be considered. The pH of the cough syrup was lower than that of the antibiotic syrup, which caused a more detrimental effect on the surface hardness of the teeth.

Meurman and Gate[49] stated that the erosion pattern in enamel is caused by initially dissolving interprismatic areas and affecting the prism cores at the microscopic level; this results in an irregular enamel pattern, making it less prismatic, and when the enamel is breached, erosion affects the intertubular and peritubular dentine. Frequent exposure to acidic syrups enhances the lowering of the critical pH, leading to irreversible loss of enamel hard tissue.

In our study, the tooth samples that were more demineralized with cough syrup with GC Tooth Mousse showed a higher rate of remineralization, which may be due to the action of CPP-ACP to increase the available calcium ions at the tooth surface, which is similar to the findings of Grewal et al.[50]

Both antibiotics and cough syrups have erosive potential, but cough syrups showed more erosive potential than antibiotic syrup in this study. Many studies have suggested avoiding the use of cough syrups over a prolonged period. In 2006, Carolina Covolo da Costa[51] reported in *BDJ news* that medications and cough syrups create cavities. In his opinion, the incidence of caries after fluoride treatment is low. If the child patient is not educated about the importance of oral hygiene, the medications given just before bedtime will become a significant concern as there is decreased salivary flow at night.

Mayo and Ritchie[52] published an article that reported "sugar-free" cough drops sweetened with sorbitol and isomalt (an equimolar mix of glucosyl-mannitol and glucosyl sorbitol) creates an environment suitable for the culture of streptococcus strain. The *Streptococcus sobrinus 6715* strain uses isomalt and sorbitol extensively and lowers the pH. The acidic pH demineralizes the enamel in patients who regularly misuse cough syrups.

Scatena et al.[32] and Anand et al.[53] assessed the erosive potential of three medicinal syrups and found that antitussive syrup has a high erosive potential. They recommended adding calcium, phosphate, and fluoride to the medications, taking medication at mealtime, and maintaining proper oral hygiene measures such as mouth washing after intake.

Dave et al.[54] estimated the pH level of saliva before and after cough syrup intake and found that the pH before cough syrup consumption was 7.09, which dipped to 6.87 after consumption. They concluded that salivary pH dip and acidic medication consumption at bedtime without proper oral hygiene could be risk factors for the development of caries in childhood.

Leme et al.[55] have suggested that cough syrup containing high sucrose levels contributes to the imbalance in resident plaque microflora. According to the "Ecological Plaque Hypothesis", which was explained by Marsh 1994, changing critical environmental factors will lead to a change in resident microflora, resulting in more cariogenic microbes, altering the dental equilibrium. This change in dental microflora promotes demineralization. The presence of sucrose alters biofilm formation at low Ca, P, and F concentrations. These ions play a prime role in the demineralization and remineralization cycles.[55]

In this study, cough syrup showed more demineralizing potential than an antibiotic, consistent with the findings of Mali et al.[33] Studies have also reported the adverse effects of antibiotics. IF Roberts and GJ Roberts [56] in 1979 proposed that a longer duration of medication intake influences caries, plaque, and gingival index in children. The therapeutics in antibiotic syrup initially act as cariostatic agents, but later they act as cariogenic agents because of their high sucrose content.

Most studies have shown that antibiotics and dental caries have a positive correlation, whereas some other studies have reported contradictory findings, such as a decline in dental caries when antibiotic medications were used because of the therapeutic effects of antibiotics. Loesche et al.[57] conducted a study in North European and North American countries and showed that the level of decay in the primary dentition was inversely associated with the reported usage of antibiotics. Frequent use of antibiotics can reduce the incidence of dental caries by delaying tooth colonization by mutant streptococci.

Pediatric medications can cause dental erosion leading to dental caries. Usually, we do not consider them cariogenic and concentrate on diet counseling. We motivate and educate parents and children about sticky foods and their harmful effects. We teach the importance of oral hygiene, cleaning, and brushing teeth after consuming sticky cariogenic foods and during bedtime. We strictly inform them of the harmful effects of not cleaning their teeth before bedtime. However, we did not consider pediatric liquid medications in this category. The cariogenic potential of liquid medications depends on the frequency, pattern, duration, and sugar content.[58] As dental experts, we should consider pediatric liquid medications in the cariogenic group of foods and judicially educate both parents and children about the erosive potential of these medications and advise them to take medications before brushing their teeth at bedtime.

Cough syrups showed a more acidic pH than any other liquid medications.[51,54] The World Health Organization banned certain cough syrups in 2022. A term called "syrup death" was used by some international public media and news agencies. Therefore, the contents of cough syrups remain controversial. Cough syrups can cause several other health hazards in addition to dental erosion. Children must take cough syrups with caution. The unwise use of medications by the present population without proper medical guidance will lead to irremediable changes in future generations.

We suggest that cough syrup be prescribed by medical practitioners only after proper oral hygiene instructions. Neves et al.[59] concluded that pediatricians do not understand the correct relationship between the acidity of pediatric medications and dental erosion. However, they are aware that sweetened medications cause dental caries. In a study by Nirmala et al.,[60] only 29.1% of pediatricians believed that pediatric liquid formulations were acidic, and 68.9% did not provide oral hygiene instructions, such as brushing their teeth after medication intake. They also concluded that patients undergoing long-term drug therapy for >8 months have increased vulnerability to dental caries. Pediatricians should inform parents about the side effects of the long-term use of medications prescribed to children. Medically compromised patients who need long-term medications should be referred to dental experts.

There is a need to mention the side effects of these acidic formulations on pediatric oral health to create more awareness in the society.[61] The use of over-the-counter drugs has increased among the average Indian population, especially for treating fever, cold, and cough, which are usually a part of post-COVID complications. The tendency of the general population to self-prescribe has to be reduced by pharmaceutical shops and online purchasing sites, which is impossible. To ensure safe drug administration, it is advised to follow the five R's—right drugs, right route, right time, right dose, and right patient. Dental experts should thoroughly examine whether the patient is undergoing an extended period of liquid medication use. If so, such patients should be prescribed remineralizing pastes or creams and provided clear motivation and patient education regarding oral hygiene. The use of topical fluoride agents has already been suggested for patients who regularly use medication.[40]

This study was conducted as an *in vitro* study; however, the factors affecting dental erosion and caries differ within the oral cavity and fail to replicate the inherent complexity of the oral cavity in *in vitro* situations. Conditions such as xerostomia, the

high viscosity of saliva seen in medically compromised patients, and personal hygiene habits, diet, and dietary habits will vary according to the geographical area and population. All of these factors affect the overall oral health status of patients. Therefore, more research is required intraorally by estimating the pH levels of saliva in a larger sample size.

The introduction of the "sugar-free" concept has influenced almost all commodities available in the Indian market, including pharmaceuticals. "Sugar-free medications" are available in the market with sugar substitutes. They decrease the side effects of sucrose added to increase flavor acceptability.[62] The expensive cost of these medications is always a concern in the Indian community as it makes it difficult for the working class to afford them. The patients' parents, pharmacists, and medical practitioners should be aware of the benefits of sugar-free medications. Sugar-free medications may not be palatable for children. Therefore, further research is warranted to discover sugar substitutes added to these pediatric drugs. Companies should manufacture sugar-substitute drugs that are readily available in commercial markets. Another way to prevent this adverse effect is to add remineralizing agents such as fluorides, calcium, and phosphate ions to syrup formulations to reduce the erosive effects of syrups.[32,40]

Conclusions

This study estimated the erosive potential of two commonly used liquid medications in daily pediatric medical practice and the remineralizing potential of two agents readily available in markets, that is, GC Tooth Mousse and Clinpro Tooth Crème. These agents were administered for 15 consecutive days and continued for the next 15 consecutive days. The microhardness was estimated on the 15th and 30th days after exposure to pediatric syrups for 14 days. Based on the results of this *in vitro* study, a statistically significant decrease in surface microhardness after demineralization with various liquid medicaments was detected in all groups. A more significant demineralization was observed in the cough syrup group, which was related to the decreased pH of the liquid. All sample groups showed remineralization and increased surface microhardness after treatment with the two remineralizing agents. Significantly higher remineralization was observed with the CPP-ACP paste (GC Tooth Mousse) than with Clinpro Tooth Crème. We suggest that pediatricians inform parents about the possible risks related to oral health during the long-term prescription of formulations and provide proper oral hygiene instructions to the children. They should be asked to take medications before their daily brushing routine at bedtime. Medical practitioners can prescribe sugar-free medications and refer those patients to dental experts. General dental practitioners should prescribe remineralizing crème for such pediatric patients.

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Manufacturer names

1. Amoxycillin oral suspension IP- MOX suspension 125 mg/5 mL Sun Pharmaceutical Industries Ltd., India.
2. Ascoril Syrup 100 mL, Glenmark Pharma, India.
3. GC Tooth Mousse, GC UK Ltd, United Kingdom.
4. Clinpro™ Tooth Crème, 3M ESPE, United States.

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References

1. Schlueter N, Amaechi BT, Bartlett D, et al. Terminology of erosive tooth wear: Consensus report of a workshop organized by the Orca and the Cariology Research Group of the IADR. Caries Res 2019;54(1):2–6. DOI: 10.1159/000503308.
2. Imfeld T. Dental erosion: Definition, classification and links. Eur J Oral Sci 1996;104(2):151–155. DOI: 10.1111/j.1600-0722.1996.tb00063.x.
3. Jarvinen VK, Rytomaa II, Heinonen OP. Risk factors in dental erosion. J Dent Res 1991;70(6):942–947. DOI: 10.1177/00220345910700060601.
4. Dalpian DM, Casagrande L, Franzon R, et al. Cariogenic potential of pediatric liquid medicaments: An in vitro study. J Clin Pediatr Dent 2012;36(4):363–367. DOI: https://doi.org/10.17796/jcpd.36.4.n404t58110t18082.
5. Rytömaa I, Järvinen V, Heinonen OP. Occupational syrup-tasting and Dental Health. Acta Odontol Scand 1994;52(1):20–24. DOI: 10.3109/00016359409096371.
6. Lussi A, Schlueter N, Rakhmatullina E, et al. Dental erosion – An overview with emphasis on chemical and histopathological aspects. Caries Res 2011;45(Suppl. 1):2–12. DOI: 10.1159/000325915.
7. Carvalho TS, Lussi A, Schlueter N, et al. Differences in susceptibility of deciduous and permanent teeth to erosion exist, albeit depending on protocol design and method of assessment. Sci Rep 2022;12(1). DOI: 10.1038/s41598-022-08116-0.
8. Shellis RP, Ganss C, Ren Y, et al. Methodology and models in erosion research: Discussion and conclusions. Caries Res 2011;45(Suppl. 1):69–77. DOI: 10.1159/000325971.
9. Vieira A, Hancock R, Limeback H, et al. How does fluoride concentration in the tooth affect apatite crystal size? J Dent Res 2003;82(11):909–913. DOI: 10.1177/154405910308201112.
10. Vieira A, Hancock R, Dumitriu M, et al. How does fluoride affect dentin microhardness and mineralization? J Dent Res 2005;84(10):951–957. DOI: 10.1177/154405910508401015.
11. Xavier AF, Moura EFF, Azevedo WF, et al. Erosive and cariogenicity potential of pediatric drugs: Study of physicochemical parameters. BMC Oral Health 2013;13(1):71. DOI: 10.1186/1472-6831-13-71.
12. Mennella JA, Spector AC, Reed DR, et al. The bad taste of medicines: Overview of basic research on bitter taste. Clin Ther 2013;35(8):1225–1246. DOI: 10.1016/j.clinthera.2013.06.007.
13. Rouaz K, Chiclana-Rodríguez B, Nardi-Ricart A, et al. Excipients in the paediatric population: A review. Pharmaceutics 2021;13(3):387. DOI: 10.3390/pharmaceutics13030387.
14. Arora R, Mukherjee U, Arora V. Erosive potential of sugar free and sugar containing pediatric medicines given regularly and long term to children. Indian J Pediatr 2011;79(6):759–763. DOI: 10.1007/s12098-011-0543-5.
15. Malik M, Tahir MJ, Jabbar R, et al. Self-medication during COVID-19 pandemic: Challenges and opportunities. Drugs Ther Perspect 2020;36(12):565–567. DOI: 10.1007/s40267-020-00785-z.
16. Singana T, Suma NK. An in vitro assessment of cariogenic and erosive potential of pediatric liquid medicaments on primary teeth: A comparative study. Int J Clin Pediatr Dent 2020;13(6):595–599. DOI: 10.5005/jp-journals-10005-1824.

17. Malhotra G. An update on remineralization agents. J Interdisciplinary Dent 2014;4(1):59. DOI: 10.4103/2229-5194.135017.
18. Garg P, Singh U, Sinha D, et al. An update on remineralizing agents. J Interdisciplinary Dent 2013;3(3):151. DOI**:** 10.4103/2229-5194.131200.
19. Pitts NB, Wefel JS. Remineralization/Desensitization: What Is Known? What Is the Future? Adv Dent Res 2009;21(1):83–86. DOI: 10.1177/0895937409335644.
20. Reddy VN, Snehika G, Achanta A, et al. Enamel erosion: A possible preventive approach by casein phosphopeptide amorphous calcium phosphate—an in vitro study. Int J Clin Pediatr Dent 2020;13(5):486–492. DOI: 10.5005/jp-journals-10005-1827.
21. Reddy D, Azher U, Paul ST, et al. Comparison of remineralization potential of casein phosphopeptide: Amorphous calcium phosphate, nano-hydroxyapatite and calcium sucrose phosphate on artificial enamel lesions: An in vitro study. Int J Clin Pediatr Dent 2022;15(1):69–73. DOI: 10.5005/jp-journals-10005-2339.
22. Tung MS. Calcium phosphates: Structure, composition, solubility, and stability. In: Amjad, Z. (Ed). Calcium Phosphates in Biological and Industrial Systems. Boston, MA: Springer; 1998, pp. 1–19. DOI: 10.1007/978-1-4615-5517-9_1.
23. Gaffar A, Afflitto J. Recent advances in dentifrice technologies. In: Amjad Z (Ed). Calcium Phosphates in Biological and Industrial Systems. Boston, MA: Springer; 1998. pp. 325–55. DOI: 10.1007/978-1-4615-5517-9_14.
24. McKnight-Hanes C, Whitford GM. Fluoride release from three glass ionomer materials and the effects of varnishing with or without finishing. Caries Res 1992;26(5):345–350. DOI: 10.1159/000261466.
25. Girish Babu KL, Jagadeesh KN, Kumaraswamy Naik LR, et al. Pediatric liquid medicaments - are they cariogenic? an in vitro study. J Int Soc Prevent Commun Dent 2014;4(2):108. DOI: 10.4103/2231-0762.137637.
26. Girish Babu K, Rai K, Hedge A. Pediatric liquid medicaments – do they erode the teeth surface? an in vitro study: Part I. J Clin Pediatr Dent 2008;32(3):189–194. DOI: 10.17796/jcpd.32.3.j22m7t8163739820.
27. Babu KLG, Rai K, Hegde A. PH of medicated syrups–does it really matter? An in-vitro study: Part-II. J Clin Pediatr Dent 2008;33(2):137–142. DOI: 10.17796/jcpd.33.2.q5280t3744827v0h.
28. Kılınç G, Çetin M, Ellidokuz H. The relationship of salivary flow rate and salivary pH on dental caries in children. J Pediatr Res 2015;2(2):87–91. DOI: 10.4274/jpr.64935.
29. Crossner CG. Salivary flow rate in children and adolescents. Sweden Dent J 1984;8(6):271–276. PMID: 6597630.
30. Parr TA. An investigation into sugar-containing and sugar-free over-the-counter medicines. Br Dent J 1994;176(1):11. DOI: 10.1038/sj.bdj.4808348.
31. Balakrishnan A, Jonathan R, Benin P, et al. Evaluation to determine the caries remineralization potential of three dentifrices: An in vitro study. J Conserv Dent 2013;16(4):375. DOI: 10.4103/0972-0707.114347.
32. Scatena C, Galafassi D, Gomes-Silva JM, et al. In vitro erosive effect of pediatric medicines on deciduous tooth enamel. Braz Dent J 2014;25(1):22–27. DOI: 10.1590/0103-6440201302344.
33. Mali GV, Dodamani AS, Karibasappa GN, et al. Effect of conventional and sugar free pediatric syrup formulations on primary tooth enamel hardness: An in vitro study. J Indian Soc Pedod Prev Dent 2015;33(4):331. DOI: 10.4103/0970-4388.165707.
34. Amaechi BT, Higham SM, Edgar WM. Factors influencing the development of dental erosion in vitro: Enamel type, temperature and exposure time. J Oral Rehabil 1999;26(8):624–630. DOI: 10.1046/j.1365-2842.1999.00433.x.
35. Hara AT, Ando M, González-Cabezas C, et al. Protective effect of the dental pellicle against erosive challenges in situ. J Dent Res 2006;85(7):612–616. DOI: 10.1177/154405910608500706.
36. Eisenburger M, Addy M, Hughes JA, et al. Effect of time on the remineralisation of enamel by synthetic saliva after citric acid erosion. Caries Res 2001;35(3):211–215. DOI: 10.1159/000047458.
37. Lata S, Varghese NO, Varughese JM. Remineralization potential of fluoride and amorphous calcium phosphate-casein phospho peptide on enamel lesions: An in vitro comparative evaluation. J Conserv Dent 2010;13(1):42. DOI: 10.4103/0972-0707.62634.
38. Darshan HE, Shashikiran ND. The effect of mc innes solution on enamel and the effect of tooth mousse on bleached enamel: An in vitro study. J Conserv Dent 2008;11(2):86. DOI: 10.4103/0972-0707.44058.
39. Valinoti AC, da Silva Pierro VS, da Silva EM, et al. In vitro alterations in dental enamel exposed to acidic medicines. Int J Paediatr Dent 2010;21(2):141–150. DOI: 10.1111/j.1365-263X.2010.01104.x.
40. Costa CC, Almeida IC, Costa Filho LC. Erosive effect of an antihistamine-containing syrup on primary enamel and its reduction by fluoride dentifrice. Int J Paediatr Dent 2006;16(3):174–180. DOI: 10.1111/j.1365-263X.2006.00713.x.
41. Haghgoo R, Haghgou HR, Asdollah FM. Comparison of the microhardness of primary and permanent teeth after immersion in two types of carbonated beverages. J Int Soc Prev Commun Dent 2016;6(4):344. DOI: 10.4103/2231-0762.186803.
42. Gentile E, Di Stasio D, Santoro R, et al. In vivo microstructural analysis of enamel in permanent and deciduous teeth. Ultrast Pathol 2014;39(2):131–134. DOI: 10.3109/01913123.2014.960544.
43. Low IM, Duraman N, Davies IJ. Microstructure–property relationships in human adult and baby canine teeth. Key Eng Mater 2006; 309–311:23–26. DOI: 10.4028/www.scientific.net/KEM.309-311.23.
44. Featherstone JDB. Dental caries: A dynamic disease process. Aust Dent J 2008;53(3):286–291. DOI: 10.1111/j.1834-7819.2008.00064.x.
45. Featherstone JDB, Duncan JF, Cutress TW. A mechanism for dental caries based on chemical processes and diffusion phenomena during in-vitro caries simulation on human tooth enamel. Arch Oral Biol 1979;24(2):101–112. DOI: 10.1016/0003-9969(79)90057-8.
46. Bader JD. Casein phosphopeptide–amorphous calcium phosphate shows promise for preventing caries. Evid Based Dent 2010;11(1):11–12. DOI: 10.1038/sj.ebd.6400701.
47. Panich M, Poolthong S. The effect of casein phosphopeptide–amorphous calcium phosphate and a cola soft drink on in vitro enamel hardness. J Am Dent Assoc 2009;140(4):455–460. DOI: 10.14219/jada.archive.2009.0195.
48. Reynolds EC, Cain CJ, Webber EL, et al. Anticariogenicity of calcium phosphate complexes of tryptic casein phosphopeptides in the rat. J Dent Res 1995;74(6):1272–1279. DOI: 10.1177/00220345950740060601.
49. Meurman JH, Gate JM. Pathogenesis and modifying factors of dental erosion. Eur J Oral Sci 1996;104(2):199–206. DOI: 10.1111/j.1600-0722.1996.tb00068.x.
50. Grewal N, Kudupudi V, Grewal S. Surface remineralization potential of casein phosphopeptide-amorphous calcium phosphate on enamel eroded by cola-drinks: An in-situ model study. Contemp Clin Dent 2013;4(3):331. DOI: 10.4103/0976-237X.118385.
51. Medications and cough syrups may cause cavities. Br Dent J 2006;200(2):70. https://doi.org/10.1038/sj.bdj.4813215.
52. Mayo JA, Ritchie JR. Acidogenic potential of "sugar-free" Cough drops. Open Dent J 2009;3(1):26–30. DOI: 10.2174/1874210600903010026.
53. Anand A, Kulkarni P, Bansal A, et al. Erosive effects of pediatric liquid medicinal syrups on primary enamel: An in vitro comparative study. Indian J Dent 2016;7(3):131. DOI: 10.4103/0975-962X.189338.
54. Dave PH, Gurunathan D, Sudhan Vasantharajan M. Comparison of pH levels of the saliva before and after the consumption of cough syrups in children. Biomed Pharmacol J 2018;11(3):1443–1448. DOI: 10.13005/bpj/1509.
55. Leme AFP, Koo H, Bellato CM, et al. The role of sucrose in cariogenic dental biofilm formation—new insight. J Dent Res 2006;85(10):878–887. DOI: 10.1177/154405910608501002.
56. Roberts IF, Roberts GJ. Relation between medicines sweetened with sucrose and dental disease. BMJ 1979;2(6181):14–16. DOI: 10.1136/bmj.2.6181.14.
57. Loesche WJ, Eklund SA, Mehlisch DF, et al. Possible effect of medically administered antibiotics on the mutans streptococci: Implications for reduction in decay. Oral Microbiol Immunol 1989;4(2):77–81. DOI: 10.1111/j.1399-302x.1989.tb00103.x.

58. Soares DN, Valinoti AC, Pierro VS, et al. Cross-sectional microhardness of bovine enamel subjected to three paediatric liquid oral medicines: An in vitro study. Eur Arch Paediatr Dent 2012;13(5): 261–265. DOI: 10.1007/BF03262882.
59. Neves BG, da Silva Pierro VS, Maia LC. Pediatricians' perceptions of the use of sweetened medications related to oral health. J Clin Pediatr Dent 2007;32(2):133–137. DOI: 10.17796/jcpd.32.2.5773462618772x11.
60. Nirmala SVSG, Nuvvula S, Popuri VD, et al. Oral health concerns with sweetened medicaments: Pediatricians' acuity. J Int Soc Prev Commun Dent 2015;5(1):35. DOI: 10.4103/2231-0762.151973.
61. Sulis G, Batomen B, Kotwani A, et al. Sales of antibiotics and hydroxychloroquine in India during the COVID-19 epidemic: An interrupted time series analysis. PLOS Med 2021;18(7):e1003682. DOI: 10.1371/journal.pmed.1003682.
62. Bradley M, Kinirons MJ. A survey of factors influencing the prescribing of sugar-free medicines for children by a group of General Medical Practitioners in Northern Ireland. Int J Paediatr Dent 2009;6(4):261–264. DOI: 10.1111/j.1365-263x.1996.tb00255.x.