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Original Research

Evaluation of the Erosive Potential of Various Pediatric Liquid Medicaments: An *in-vitro* Study

Abhinaya Reddy Tupalli[1], B Satish[2], Bharath Raj Shetty[3], Someshwar Battu[4], J Phani Kumar[5], B Nagaraju[6]

Contributors:

[1]Senior Lecturer, Department of Pedodontics & Preventive Dentistry, Sri Sai College of Dental Surgery, Vikarabad, Andhra Pradesh, India; [2]Reader, Department of Pedodontics & Preventive Dentistry, Sri Sai College of Dental Surgery, Vikarabad, Andhra Pradesh, India; [3]Senior Lecturer, Department of Prosthodontics, A B Shetty Dental College, Deralakatte, Mangalore, Karnataka, India; [4]Senior Lecturer, Department of Conservative Dentistry & Endodontics, Meghana Institute of Dental Sciences, Nizamabad, Andra Pradesh, India; [5]Reader, Department of Oral & Maxillofacial Surgery, Meghana Institute of Dental Sciences, Nizamabad, Andra Pradesh, India; [6]Reader, Department of Conservative Dentistry & Endodontics, Aditya Dental College, Beed, Maharashtra, India.

Correspondence:

Dr. Abhinaya Reddy Tupalli. Department of Pedodontics & Preventive Dentistry, Sri Sai College of Dental Surgery, Kothrepally, Opp. Shiv Sagar, Vikarabad-501101, Andhra Pradesh, India. Phone: +91-7893275585.

Email: abhi.kidodontist@gmail.com

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Abstract:

Background: The present in-vitro study was a scanning electron microscope (SEM) study conducted in primary teeth in order to evaluate the erosive potential of ten commonly used pediatric liquid medications (PLMs).

Materials & Methods: 10 commonly used PLMs and 33 exfoliated or extracted primary teeth were collected. The 33 teeth were divided into two groups, the control group (n=3) and the study group (n=30). The endogenous pH of all the teeth was measured using a pH electrode meter. The control group teeth were immersed in artificial saliva for three different time intervals- 1 minute, 10 minutes and 8 hours. The study group teeth were also maintained for 1 minute, 10 minutes and 8 hours in various selected PLMs. The primary enamel surface (PES) changes were then observed under the SEM for all the teeth of both groups.

Results: All the PLMs used in the study showed an erosive effect on the PES when viewed under SEM. Majority of the medications caused etched prism pattern followed by crater formation and sporadic rod ends in that order on PES.

Conclusion: There is a need to educate parents and professionals about the association between dental erosion and PLMs which predisposes to dental caries.

Key Words: Acids, dental caries, dental erosion, enamel surface changes, pediatric liquid medications, scanning electron microscope

Introduction

Dental Erosion is defined as irreversible loss of dental hard tissue by a chemical process that does not involvebacteria.[1] It has been increasingly recognized as a problem of all ages. Of particular concern is the wearing of tooth enamel that is caused by dietary erosion, which is usually observed in individuals who consume fruit juices and carbonated soft drinks and in those on long-term acidic medications.[2] Dental erosion has been found to be a common cause of tooth wear and it may be the main contributing factor in severe tooth wear, more than attrition and abrasion.[3]

The prevalence of dental erosion has increased, especially among children and adolescents.[4] High incidence of dental erosive lesions have been reported among pre-school children and adults of all ages, with the percentage of the incidence peaking among teenagers.[5] This has been attributed to the regular use of products with low endogenous pH, high acidity, and absence or low concentrations of ions including those of calcium, fluoride, and phosphate in their composition. These products also include certain medications that may be erosive and which may be of a particular risk when used for treatment of chronic diseases.[4]

Dental erosion becomes a potential issue when medicines with prolonged oral clearance are taken long term for chronic illnesses. The use of liquid pharmaceutical preparations may be a daily routine for such children. While the active ingredients in these medicines are necessary for improvement or maintenance of health, some inactive ingredients may pose dangers like dental caries and dental erosion.[6] Any medication with a low pH that comes in frequent and /or sustained contact with teeth has the potential to cause dental erosion.[7] Studies have confirmed that some pediatric liquid medications (PLMs) are acidogenic and cariogenic in nature.[7-10]

The present in-vitro study was a scanning electron microscope (SEM) study conducted in primary teeth in order to analyze the primary enamel surface (PES)

changes caused by the consumption of 10 commercially available PLMs.

Materials and Methods

The aims of the present study were- (1) to measure the endogenous pH of various commonly used PLMs, (2) to investigate their erosive potential using SEM by observing the PES changes upon exposure and (3) to make appropriate recommendations to prevent the occurrence of erosion in children.

The teeth were stored as per the Occupational Safety and Health Administration (OSHA) regulation until the experiments were performed. The endogenous pH of all the PLMs was measured using a pH electrode meter. The 33 teeth were divided into two groups, the control group and the study group (Figure 1). The control group teeth (n=3) were immersed in artificial saliva for three different time intervals- 1 minute, 10 minutes and 8 hours. The study group teeth(n=30) were also maintained for 1

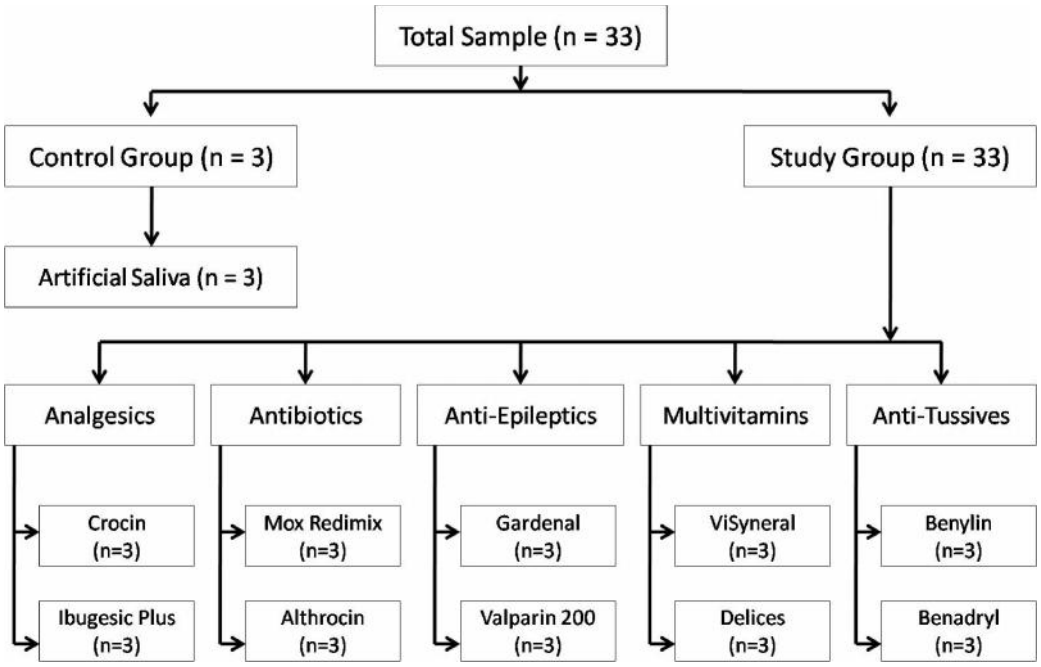

Figure 1: Sample Distribution

Ten commonly used PLMs were included in the study (Table 1). 33 exfoliated or extracted primary teeth, devoid of any caries or restorations, were collected for the study.

minute, 10 minutes and 8 hours in various selected PLMs. The PES changes were then observed under the SEM for all the teeth of both groups and compared using the

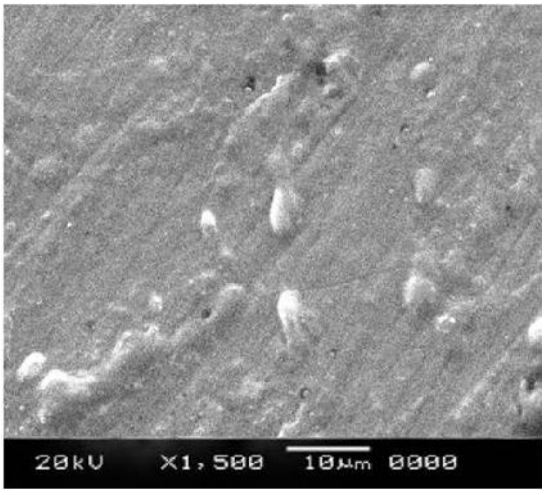

Figure 2: Sporadic rod ends seen in SEM after exposure to Delices® for 1 minute.

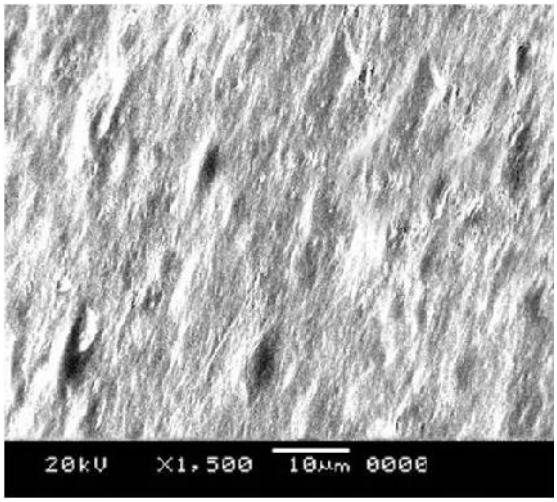

Figure 3: Etched prism pattern seen in SEM after exposure to Althrocin® for 10 minutes.

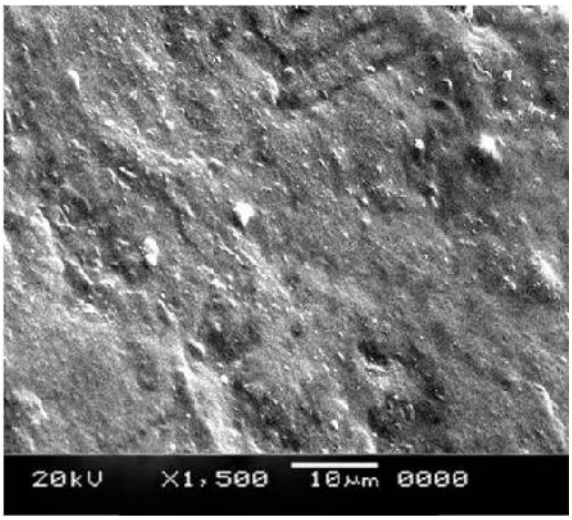

Figure 4: Crater formation seen in SEM after exposure to Gardenal® for 1 minute.

following parameters- [1] sporadic rod ends (Figure 2), [2] etched prism pattern (Figure 3) and [3] crater formation (Figure 4).

causing severe dental erosion which pre-disposesto dental caries.[13] Many parents are aware that sugar causes tooth decay but they are often unaware of the hidden, added sugar in many foods and drinks, including PLMs.[14] In an average day, up to 60% of the population of developed countries takes some form of medicine, of which about half are bought over the counter without prescriptions[15] and 17% of children are given non-prescription cough medicines.[16]

A large number of PLMs contain 30% and 70% sucrose.[7] Sucrose is used as a vehicle for medicines is included in nearly all formulations prepared especially for children in order to make them more palatable. Its advantages are that it is a non-toxic sweetening agent, free from after taste and can be used to preserve the formulation. It remains widely used because it is cheap, easy to process and available in a number of pure, dry, chemically and physically stable forms of different particle size.[17] Sugars, metabolized by bacteria to acid end-products, lower the pH within the

Table1: List of Pediatric Liquid Medications (PLMs) and their Measured pH.

PLMs	Generic Name	Brand Name	Pharmaceutical Company	pH
Analgesics	Paracetamol	Crocin®	GlaxoSmithKline Asia Pvt. Ltd., Nasik, India	6.4
	Ibuprofen	Ibugesic Plus®	Medioral Laboratories Pvt. Ltd., Mumbai, India	6.8
Antibiotics	Amoxicillin	Mox® Redimix	Ranbaxy Laboratories Ltd., Gurgaon, India	6.5
	Erythromycin	Althrocin®	Alembic Ltd., Vadodara, India	6.4
Anti-Epileptics	Phenobarbitone	Gardenal®	Piramal Healthcare Ltd., Mumbai, India	6.9
	Sodium Valproate	Valparin® 200	Sanofi-Synthelabo (India) Ltd., Mumbai, India	7.3
Multivitamins	Multivitamin	ViSyneral®	Crest Healthcare Pvt. Ltd., Solan, India	4.3
	Multivitamin	Delices®	Pharm Products Pvt. Ltd., Chennai, India	4.5
Anti-Tussives	Dextromethorphan Pseudoephedrine	Benylin®	Pfizer (India) Ltd., Mumbai, India	7.2
	Diphenhydramine	Benadryl®		7.1

Results

The pH of the PLMs and artificial saliva as measured by a pH electrode meter are shown in Table 1. The surface changes on the PES caused by various PLMs and artificial saliva are indicated in Table 2.

Discussion

Reports have suggested a decline in the quality of teeth of very young children.[11,12] High intake of acidic drinks, fruits and medications may be possible etiological factors

bacterial plaque that is unavailable to salivary buffering. Low pH causes ionic dissolution from the hydroxyapatite crystals, leading to enamel and dentin demineralization.[18] In some children, who need to use medicines several times a day for long periods of time, sucrose-based medicines contribute significantly to caries experience.[19] Lokken P et al. and Imfeld TN suggested that the cariogenic potential present in medicines was due to the presence of sucrose and its availability to oral plaque bacteria.[8,20]

Table 2: Primary Enamel Surface Changes Caused by Various PLMs.				
PLM	Time Intervals	SEM Surface Mapping		
		Sporadic Rod Ends Visible	Etched Prism Pattern	Crater Formation
Crocin®	1 minute	Nil	Present	Nil
	10 minutes	Nil	Nil	Present
	8 hours	Nil	Nil	Present
Ibugesic Plus®	1 minute	Nil	Present	Nil
	10 minutes	Nil	Nil	Present
	8 hours	Nil	Nil	Present
Mox®Redimix	1 minute	Nil	Present	Nil
	10 minutes	Nil	Nil	Present
	8 hours	Nil	Nil	Present
Althrocin®	1 minute	Nil	Nil	Nil
	10 minutes	Nil	Present	Nil
	8 hours	Nil	Present	Present
Gardenal®	1 minute	Present	Nil	Present
	10 minutes	Present	Nil	Present
	8 hours	Present	Nil	Present
Valparin® 200	1 minute	Nil	Present	Nil
	10 minutes	Present	Present	Nil
	8 hours	Present	Present	Present
ViSyneral®	1 minute	Nil	Present	Nil
	10 minutes	Nil	Present	Nil
	8 hours	Nil	Present	Present
Delices®	1 minute	Present	Present	Nil
	10 minutes	Nil	Present	Nil
	8 hours	Nil	Present	Nil
Benylin®	1 minute	Nil	Nil	Nil
	10 minutes	Nil	Nil	Nil
	8 hours	Nil	Nil	Present
Benadryl®	1 minute	Nil	Nil	Nil
	10 minutes	Nil	Nil	Nil
	8 hours	Nil	Nil	Present
Artificial Saliva	1 minute	Nil	Nil	Nil
	10 minutes	Nil	Nil	Nil
	8 hours	Nil	Nil	Nil

Pharmaceutical preparations with acidic pH and high sugar contents have a potential for increasing dental caries when used several times each day over long periods of time.[17]

In 1977, Imfeld TN studied the deleterious effects of liquid oral medications.[8] Robert IF& Robert GJ and Feigal RJ et al. provided the evidence which showed that continuous administration of sucrose based medicines caused dental caries and related gingivitis.[21,22] Studies done by Greenwood ME et al., Mackie IC & Hobson P and Rekola M confirmed that these preparations were cariogenic and acidogenic in nature.[7,9,10] It was seen that the properties of acids present in foods and medications that contribute to their erosive potential are- (1) the amount of acid available (the titratable acidity), (2) the amount of acid actually present (the concentration of the H^+ ion or the pH) and (3) the relative strength of the acid or ease with which the acid gives up free H^+ ions (the pKa).[2,23] As most liquid syrups are maintained in an acidic pH, the present study was conducted to know the acidogenic potential of commonly used PLMs in day-to-day practice.

In the present study, each of the selected medications had a label clearly displaying the ingredients, but none contained any information regarding the pH of the solution. Therefore, the pH of each of the PLMs used in the present study was measured using a pH electrode meter. pH of the PLMs ranged between 4.3 (ViSyneral®) which was acidic to 7.4(Benadryl®) which had a basic pH. The findings of the present study are similar to those done

by BabuKLG et al. who evaluated the erosive potential of different PLMs and reported pH ranging from 6.77 to 7.11.[6] In a study conducted by Greenwood ME et al., the liquid syrup Dimetapp® (Brompheniramine and Phenylephrine) had an acidic pH of 2.86.[7] The pH of the artificial saliva in the present study was found to be 7.1.

Primary teeth are more liable to erosion as they are known to be less mineralized than permanent teeth and particularly as the enamel surface of deciduous teeth is not as mature as that of permanent teeth.[3]Even though the pH of PLMs was not near the critical pH of the oral cavity, erosion of PES was evident when subjected to study under SEM. This is in agreement with the studies of Babu KLG et al. and Greenwood ME et al. who used SEM to evaluate the erosion potential of liquid syrup on rats' enamel and human extracted primary teeth respectively.[6,7]

Silverstone LM et al. described three basic types to etching patterns i.e. Type-I, Type-II and Type-III.[24] Prism pattern on PES observed in the present study was similar to Type-I etching pattern, where the prism core material was preferentially removed leaving the prism periphery relatively intact in a honeycomb prism appearance**.** The Type-I etching pattern could be easily explained by the fact that the crystals reach the enamel surfaces at different inclinations in the rods as compared to the inter-rod areas. The present SEM micrographs showed that the surface was smooth and slightly etched, revealing faint outlines of scales. Enamel rods were clearly opened. The edges of the sections were deep enough to be visible under SEM.

Typical prism patterns were seen on enamel surfaces treated with Valparin® 200 syrup for 1minute and ViSyneral® syrup for l0 minutes. These findings were in agreement with the findings of Babu KLG et al. who reported similar typical prism patterns on enamel surfaces treated with Amoxicillin for 1 minute, Theophylline for 1 minute and Multivitamin for 10 minutes.[6] Enamel surface treated with Crocin® suspension for 1minute, Ibugesic Plus® suspension for 1minute, Mox® Redimix suspension for 1minute, Althrocin® suspension for 10 minutes and 8 hours, Valparin® 200 syrup for 10 minutes and 8hours, ViSyneral® syrup for 1 minute and 8 hours and Delices® syrup for 1 minute and 8hours all showed the etched prism pattern, but this was not of the classical appearance. This atypical appearance of enamel surface can be supported by the study done by Grando LJ et al. who stated that complexity can be seen in the different patterns of loss of enamel structure in eroded deciduous teeth.[25] In the present study, irregular patterns of pit-like erosion areas were seen in all specimens, varying from site to site. These probably depended on the prismatic versus aprismatic nature and composition of the affected enamel.

In the present study there seemed to be no direct relationship between the pH of the selected PLMs and the erosive changes seen on the PES. This finding is in accordance with that of BabuKLG et al.[6] Chelation is a process by which a molecule encircles and binds to a metal and removes it from the tissue. Chelation is independent of the pH of the medium, so that the removal of metallic ions like calcium from a biological calcium-phosphorus system may occur at a neutral or even alkaline pH.[1] Morch T et al. and Onose H et al. reported that the chelating agents present in PLMs like sodium salt of various aminoacids (alanine, aspartame, glutamate) and lactate, at or near neutral pH, can increase the uptake of radioactive phosphorus by loss of calcium from enamel.[26,27] This factor may be responsible for the erosive pattern seen on the surface of PES in the present study.

Since the erosion in this study was induced under in-vitro conditions, the results cannot be completely extrapolated to in-vivo situations. Presence of pellicle is one factor which protects the teeth from acidic challenges. The amount and quality of saliva, in particular its buffering capacity, are also important factors in the occurrence of dental erosion.[3] It has been seen that children aged 3-7 years have larger variations and slower salivary sugar clearances and also lower salivary flow rates than older children and adults.[28] From the standpoints of both hard tissue quality and salivary conditions, deciduous teeth seem to be at greater risk from erosive challenges than are permanent teeth.[3]

Another aspect of medication-induced erosion is that most syrups prescribed to children are given in 2 to 3 divided doses.[29] The night doses usually have a deleterious effect on enamel due to the following reasons- (1) at night, flow rate of saliva is diminished; some medications, such as anticonvulsants, sedatives or antihistamines also lower the salivary flow,[18] (2) in young children, the oral clearance process is less effective than adults due to lower salivary flow[28] and less pronounced oral muscular co-ordination ability[30] and (3) sugar containing analgesics are given last thing at night to relieve pain; a night-time 'tickly cough' is soothed by a sugary cough syrup to help children go to

sleep; the last daily dose of antibiotic syrup is given at bedtime.[18]

A number of steps should taken by physicians and parents of children who need to take oral liquid medications during early years. Physicians can arrange an early parental consultation with a pediatric dentist or general dentist. This will get oral hygiene measures underway as soon as the first incisors erupt. When the child is awake, the teeth should be brushed before the medication is given and a clearing drink of water offered after the medication. A topical fluoride gel may be used twice a week under the direction of the dentist, as total fluoride from all sources must be considered before supplementary fluoride is prescribed.

Prevention of dental erosion caused by PLMs can be done only by a group effort. The Pedodontist has a major role in educating the people at various levels of the society about the ill effects of using certain PLMs. Availability of children's medicines in sugar-free form would enhance the prescribing of sugar-free medicines by dental and medical professionals. Further studies are required to establish the direct relationship between the various components of the sugared liquid medications and its effect on enamel surface, which is mandatory before establishing any definitive protocols in the prevention of dental erosion caused by PLMs.

Conclusion

The findings of the present study can be summarized as follows- (1) pH values of the PLMs used in the study, i.e. Crocin, Ibugesic Plus, MoxRedimix, Althrocin, Gardenal, Valparin 200, ViSyneral, Delices, Benylin and Benadryl were found to be 6.4, 6.8, 6.5, 6.4, 6.9, 7.3, 4.3, 4.5, 7.2 and 6.7 respectively, (2)all the PLMs used in the study showed an erosive effect on the primary enamel surface when viewed under SEM; majority of the medications caused etched prism pattern followed by crater formation and sporadic rod ends in that order on PES and (3) there is a need to educate parents and professionals about the association between dental erosion and PLMs, which predisposes to dental caries.

The following recommendations can be made at various levels of the society in order to decrease the dental erosion caused by PLMs-[9,18]

1. Parents should know the importance of primary dentition.
2. Parents should be aware that sugar is present not only in foods, beverages and fruits, but also in medicines, and that sugar containing medications are better taken at meal times rather than before meals or in between meals.
3. Doctors (Pedodontists and Pediatricians) must prescribe medicines in non-cariogenic forms like tablets and capsules, and if a sweetened medication has to be given, prescribe the ones containing non-cariogenic sugars like saccharin, aspartame and sorbitol.
4. Pharmaceutical Companies must display labels on all medications which indicate the type and amount of sweetener added, along with warning and possible negative effects on teeth.
5. Manufactures can come out with medicines having non-cariogenic sweeteners and "tooth friendly" symbols can be placed on these packs.

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