AN IN VITRO EVALUATION OF EROSIVE EFFECT OF SOME COMMONLY PRESCRIBED ANTIBIOTICS ON PRIMARY ENAMEL INTEGRITY

Radwa M. Fathy[1]* *BDS*, Azza G. Hanno[2] *PhD,* Nadia A. Wahba[2] *PhD,* Sawsan H. Mahmoud[3] *PhD*

ABSTRACT

INTRODUCTION: Children are frequently subjected to liquid medications, especially antibiotics. They are acidic, have low pH and high titratable acidity. This can erode enamel.

AIM: This in vitro study aim to determine the correlation between antibiotics as regards their erosive effect and frequency of intake on primary enamel integrity.

MATERIALS AND METHODS: Three commonly prescribed pediatric antibiotics groups: macrolides, cephalosporins and mixed composition were chosen. pH and titratable acidity of the selected antibiotics and artificial saliva were determined.
Seventy seven human primary teeth, exfoliated or extracted for orthodontic reasons
were randomly assigned to three antibiotics groups and a control group, 11specimens for each group. Specimens were immersed in fresh solutions of antibiotics for 1 minute over 3, 5and 10 days, depending on the type of antibiotic. All samples were preserved in artificial saliva in between immersion cycles. Enamel micro hardness was evaluated at baseline, 3& 5&10 days.

RESULTS: Highest percent reduction was recorded for the mixed antibiotic (24.39 ±4.65) P<0.0001, followed by cephalosporin (13.79 ±4.37) P<0.0001 and macrolides (7.99 ±2.82) P<0.0001. Mixed type immersed for 10 days showed the highest reduction in microhardness (37.00 ±4.71). Macrolides for 3 days showed the lowest reduction (12.22 ±3.20). All the experimental groups recorded loss in microhardness with high significant difference P<0.0001.

CONCLUSION: Tested antibiotics could erode enamel even when pH is above critical and low titratable acidity. Increasing duration and frequency of prescription, increases the erosive potential.

KEYWORDS: Antibiotics, Enamel erosion, Microhardness.

RUNNING TITLE: Erosive effect of antibiotics on primary enamel.

1 Post graduate student of Pediatric Dentistry and Dental Public Health, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

2 Professor of Pediatric Dentistry and Dental Public Health, Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

3 Assistant Professor in Pediatric Dentistry and Dental Public Health, Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University, Alexandria, Egypt

* Corresponding Author:

E-mail: *drradwa303@gmail.com*

INTRODUCTION

Dental erosion is a chronic and localized pathological chemical process that causes irreparable and progressive loss of hard tooth structure due to acid dissolution without bacterial causes (1,2). It starts with softening of the enamel surface. When contact with acid continues, it progresses to deeper tooth structure (3).

Both primary and permanent dentitions are affected by dental erosion but in different patterns, where deciduous enamel histologically differs slightly from permanent enamel (4,5).

Primary enamel is more susceptible to development and progression of dental erosion as it is thinner and less mineralized than permanent enamel. When children experience erosion in their primary dentition, they run a higher risk of developing erosion in their permanent dentition (3). Dental erosion is a multifactorial process, caused by intrinsic and extrinsic factors. The main intrinsic etiological cause of dental erosion is the gastric fluid that, sometimes is present in the oral cavity in various conditions as eating disorders, gastro-esophageal reflux disease (GORD), Bulimia nervosa, Chronic vomiting, Rumination and Persistent regurgitation (6).

Extrinsic etiological factors of dental erosion come from different sources mainly medicaments, drinks, foods and acidic hygiene products (7). Changing

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life style and dietary habits, especially in adolescents and children, witnessed a shift towards junk food, sweets, snacks and acidic drinks with low pH, low buffering capacity and more sugar content. This shift is among the most common causes that increase dental erosion (8).

Saliva is considered the most important protector biological factor included in dental erosion, where it provides the teeth with calcium, phosphate and fluoride necessary for remineralization (6). It also helps the formation of acquired salivary pellicle, which can be formed on primary teeth over 24 hours, it prevents surface mineral loss and reduces surface roughness of enamel when exposed to acid. Saliva cannot protect the teeth when exposed to severe erosive factors. (6, 9). Any decrease of pH or salivary flow increases the risk of erosion (10).

Accurate diagnosis of dental erosion can be obtained by taking full clinical history including patient's habits, diet, general health, medication and proper oral examination (11).

Once practitioners are acquainted with etiological factors of erosion, they should focus on prevention and reduction of erosion; by informing their patients with recommendations followed by definitive treatment (11).

Children are subjected to different forms of oral liquid medications. They are all supplied in the form of solutions, syrups and suspensions, to avoid difficulty of swallowing tablets or capsules. They are mostly acidic preparations (7). Acidity is meant to enhance chemical stability, drug distribution, physiological compatibility and improve flavor (12). Unfortunately, prolonged exposure to liquid medications has harmful effects on dental health (13).

Other provocative factors include flavoring and coloring agents, preservatives and fructose or sucrose or a combination, which are added to make them more sweet. These ingredients increase acidity and drop in pH of the oral cavity, which eventually leads to more demineralization and tissue loss (14). Frequency, timing and behavior towards consumption of these medications can aggravate the erosive potential. They may be prescribed twice or more daily, between meals and at bed time where salivary flow is reduced and time of clearance from oral cavity is increased (7 ,12). A significant relation between dental tissue loss and viscosity of drug is also an important issue. Drugs with high viscosity need large amount of saliva to neutralize their effect (12).

Antibiotics are prescribed frequently for children, either prophylactic or therapeutic in different clinical conditions. Oro-facial infection is the most common condition for therapeutic use of antibiotics in dental practice (15).

The aim of this study was to evaluate the correlation between erosive effect and frequency of prescription/day of three types of the most commonly prescribed antibiotics on microhardness of primary enamel structure.

The null hypothesis proposed was that there is no statistically significant difference between the enamel micro hardness of deciduous teeth before and after application of different types of antibiotics with different frequency of intake as well as length of prescription.

MATERIAL AND METHOD

Ethical approval:

The ethical approval for this research was obtained from the ethical committee of the Faculty of Dentistry, Alexandria University. The approval number was: IORG0008839.

This study was an in -vitro experimental study, that was conducted at the Department of Pediatric Dentistry and Dental Public Health, Faculty of Dentistry, Analytical Chemistry Department, Faculty of Pharmacy and Department of Production at Faculty of Engineering, Alexandria University.

Sample size estimation

Sample size was estimated assuming 5% alpha error and 80% study power. The mean (SD) percent change in microhardness was 3.49 (14.44) % for teeth immersed in artificial saliva and -27.92 (28.16) % for pediatric syrup with different pH level of pediatric antibiotics (12). Based on difference between independent means, a sample of 10 per group is required, increased to 11 samples to make up for processing errors, yielding an effect size of 1.404. Total sample = Number per group x Number of subgroups = 11 x 7 = 77 samples. Sample size was based on Rosner's method (16) calculated by G*Power 3.1.9.7 (17).

Study sample

Freshly exfoliated sound human primary teeth in addition to those extracted for orthodontic purposes. Teeth with cracks, enamel defects or developmental anomalies were excluded from the study.

Medication selection

The three main groups of pediatric antibiotics, used in this study were selected after performing a pilot study among different health care providers to determine the most commonly prescribed formulae. This was done by performing an online survey. According to results of pilot study, the selected medications were Macrolides, Cephalosporins and mixed group (Amoxicillin +Clavulanic acid). The frequency of dosage was determined according to manufacturer's instructions and the results of the pilot study. The most participants followed the recommended manufacturing instructions of 3-5 days regimen. A small proportion of participants reported to prescribe a 5-10-days regimen.

Randomization

Teeth fulfilling the inclusion criteria were randomly assigned using a computer-generated list of random anumbers and equally allocated to one of the experimental groups or the control group (18).

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Grouping

Experimental group1 "Macrolides" represented by Azithromycin (amoun Reg.no:20694/2015.)

Teeth in this group were immersed in Azithromycin 200 mg, administered once per day. It was further subdivided into 2 subgroups:

IA: 11 specimens were immersed for 3 days.

IB: 11 specimens were immersed for 5 days.

Experimental group II "Cephalosorins" represented by Duricef (rxlist:Reg .no.19077/2007)

This group was immersed in Duricef 500mg, administered twice per day. It was further subdivided into 2 subgroups:

IIA: 11 specimens were immersed for 5 days

IIB: 11 specimens were immersed for 10 days

Experimental group III "Mixed compositions of "Amoxicillin +Clavulanic acid" represented by Hibiotic (amoun :Reg.no:23402/2016)

This group was immersed in Hibiotic 457 mg, administrated twice per day. It was further subdivided into 2 subgroups:

IIIA: 11 specimens were immersed for 5 days

IIIB: 11 specimens were immersed for 10 days

Group IV (control group)

11 specimens were immersed in artificial saliva throughout the experimental period.

Artificial saliva was prepared in the pharmaceutical science park of Analytical Chemistry Department at Faculty of Pharmacy, Alexandria University.

Equipment

- Vickers hardness tester (Leco corporation. Michigan USA. Model LM-100).
- Optical microscope (XCAM1080PHB,TOUP CAM, JAPAN (2018)).

METHODS

Measurement of pH and titratable acidity

Measurement of pH

The pH of selected antibiotics and artificial saliva was measured using a digital pH meter (Model: pH-MV temp meter-pH-206., Ltd. China).

Twenty ml of each medicated syrup that was poured in a glass beaker, was placed in a thermostatically controlled water bath at 37°C and a glass electrode was inserted into the syrup which displayed pH on the meter. Each sample was tested three times to record a mean measurement.

Measurement of Titratable acidity

The titratable acidity of syrups and artificial saliva was measured by placing 20ml of each syrup in a glass beaker, placed in a thermostatically controlled water bath at 37°C. 0.1M sodium hydroxide solution was gradually pipetted into the beaker. The samples were stirred continuously until the pH became neutral. The volume of sodium hydroxide required to increase the pH of the sample to neutrality was recorded; and the process was repeated three times for each sample to record a mean measurement. Both pH and titratable acidity were measured at the Analytical Chemistry Department, Faculty of Pharmacy, Alexandria University.

Samples cleaning and preparation

The selected freshly extracted teeth were cleaned with water and hand scaled to remove any debris, then immersed in 5% sodium hypochlorite for 5 seconds to remove any stains. They were then rinsed with distilled water to remove any remaining hypochlorite. Teeth were kept in artificial saliva at room temperature to avoid dehydration till the time of experiment (2).

The teeth were cut from the CEJ to separate roots from the crowns using abrasive disc mounted on low-speed hand piece with copious water irrigation. Each specimen was embedded in the middle of a rubber mold filled with acrylic resin with buccal surface facing upwards. After curing of the acrylic resin, the specimens were removed from the molds and the convex buccal surface of the crown was mechanically ground with water cooled silicon carbide abrasive papers to obtain flat enamel surface. The test site was demarcated by attaching a piece of insulating tape with a 4x4mm diameter. The tooth was coated with 2 layers of acid resistant nail polish, leaving the flat surface uncoated. Finally, the tape was removed, exposing the area to be tested. All samples were maintained in artificial saliva until time of immersion (2,19).

Immersion cycles

Each sample was exposed to 10ml of each medicine for 1 min once or twice daily according to the designated group, after which samples were washed with distilled water. They were then kept in 10 ml of artificial saliva to the next cycle. All solutions were renewed before each cycle and refreshed daily (2). Duration and frequency were determined for each group according to manufacturer's instructions, in addition to results of pilot study. Enamel micro hardness was evaluated at baseline for the control group. This was used as a reference for baseline values for all groups. Micro hardness was evaluated at 3,5 and 10 days for experimental groups according to type of antibiotic.

Vickers hardness test

A diamond indenter (Vickers) produced 50 g for 10 seconds to make3 indentations on the enamel surface, then the average was obtained for each sample. After load removal, an optical microscope was used to measure the diagonals of indentation (12).

Statistical Analysis

Normality of microhardness values was checked using the Shapiro Wilk test and Q-Q plots. Data were presented using mean and standard deviation mainly, in addition to, median, minimum, and maximum values. Immersion time was categorized according to its prescription dose for each antibiotic into short and long intervals. For the Azithromycin "three days" was considered short and "5 days" considered long, whereas, for the Duricef and Hibiotic "five days" was considered short and "10 days" considered long. Percent reduction in microhardness was calculated according to the following formula: [(Long interval values – short

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interval values or artificial saliva) / short interval values or artificial saliva) x 100].

Comparison between artificial saliva, short and long interval values in each antibiotic type was done using One Way ANOVA followed by Tukey's post hoc test with Bonferroni correction while percent reduction was compared between different antibiotics using Mann Whiteny U test and Kruskal Wallis test followed by Dunn's post hoc test with Bonferroni correction. To detect the effect of antibiotic type, prescription dose, and the interaction between them, Two Way ANOVA was employed. All tests were two tailed and the significance level was set at p value≤0.05. Data were analyzed using IBM SPSS, version 23 for windows, Armonk, NY, USA.

RESULTS

I. pH and titratable acidity

Table 1 shows the pH and titratable acidity for the three antibiotics and artificial saliva. Hibiotic syrup had the lowest pH and highest titratable acidity, followed by Duricef, then azithromycin whose pH was above critical pH and very low titratable acidity, while artificial saliva had almost neutral pH and the lowest titratable acidity.

II. Assessment of microhardness

Mean and standard deviation (SD) were used for inter-group and intra-group comparison of microhardness reduction after different periods of drug immersion. Microhardness of the control group was used as baseline reference.

Table 2 shows that reduction of enamel microhardness was noticed in all experimental groups by different percentages, also shows the effect of duration of prescription. Subgroup IIIB (Hibiotic for 10 days), which represent the long duration showed the highest percent reduction in microhardness (37.00 ±4.71). While subgroup IA (Azithromycin for 3 days) showed the lowest percent reduction in microhardness(12.22 ±3.20). Also the greatest difference in percent reduction in microhardness between short and long duration was noticed in group III (Hibiotic) (24.39 ±4.65), the lowest difference was in group I(Azithromycin) (7.99 ±2.82), where statistical significant difference between short and long duration in different groups was recorded (P≤0.0001), while statistical significant difference in long duration between sub group IIB(Duricef for 10 days) and sub group IIIB (Hibiotic for 10 days) was(P≤0.010)

Table 3 revealed a strong relation between duration of prescription and loss of microhardness, where a longer duration was directly associated with reduced microhardness among the three study groups, P <0.0001.

Table 1: pH and titratable acidity of the three antibiotics and artificial saliva

Solution	pH Mean (±SD)	Titritable Acidity mean (ml) (±SD)
Azithromycin	5.85±0.09	1.02±0.56
Duricef	4.87±0.01	1,47±0,15
Hibiotic	4,43±0.01	5.55±0.21
Artificial Saliva	6.8±0.1	0.20±0.10

Table 2: Comparison of percent reduction in microhardness after immersion in different antibiotics as compared to artificial saliva

Immersion intervals		Group I Azithromycin (n=11)	Group II Duricef (n=11)	Group III Hibiotoc (n=11)	H test (P value)
3 days	Mean ±SD	12.22 ±3.20	-	-	-
	Median	12.33	-	-	
	Min – Max	8.49 – 18.23	-	-	
5 days	Mean ±SD	19.25 ±3.36	20.00 ±3.44	16.66 ±4.16	3.485 (0.175)
	Median	19.56	19.45	16.14	
	Min – Max	13.82 – 25.42	15.84 – 26.25	9.37 – 22.13	
10 days	Mean ±SD	-	31.06 ±4.08	37.00 ±4.71	2.528 (0.010*)
	Median	-	30.69	37.15	
	Min – Max	-	24.59 – 37.97	29.13 – 45.64	
Short – long	Mean ±SD	7.99 ±2.82	13.79 ±4.37	24.39 ±4.65	23.314 (<0.0001*)
	Median	8.63	13.08	24.54	
	Min – Max	3.54 – 12.10	7,73 – 20.55	17.12 – 32.03	

*Statistically significant difference at $p \leq 0.05$
H test: Kruskal wallis test

Table 3: Two Way ANOVA assessing the effect of type of antibiotic and prescription dose on enamel microhardness

Variables	Mean Square	F test	P value	Partial Eta Squared
Antibiotic	6143.83	134.29	<0.0001*	0.817
Prescription dose	20479.38	447.65	<0.0001*	0.882
Interaction	1930.10	42.19	<0.0001*	0.584
Corrected Model	7325.45	160.12	<0.0001*	0.930

*Statistically significant difference at p≤0.05
F test: Anova test

DISCUSSION

The present study was designed to evaluate the correlation between erosive effect as well as the impact of frequency of prescription/day of three types of commonly prescribed antibiotics on primary enamel structure by evaluation of its micro hardness.

In order to determine the commonly prescribed antibiotics for children, a pilot study was performed among different health care providers, to define their preferences.

This was implemented by performing an online survey.

Accordingly, selected medications, were three main groups, namely: Macrolides (8%), Cephalosporins (15,86%), and mixed group (Clavulanic acid +Amoxicillin) 31,28%. (Azithromycin, Duricef and

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Hibiotic respectively).

The frequency of dosage was determined according to manufacturer's instructions. Most of the doctors followed the recommended duration which was 3 and 5 days of prescription. A small proportion of those who responded to the survey, reported prescribing a 5–10 days regimen.

Seventy-seven sound, freshly shed or extracted primary teeth were prepared for immersion in the selected antibiotic solutions, for assessment of enamel microhardness. Microhardness is one of the most suitable tests to determine the erosive potential of a drug (20-22).

Samples were randomly divided into four groups: three experimental groups and a control group. In the current study, artificial saliva was used as a medium for tooth immersion of the control group and as an immersion medium between immersion cycles of the experimental groups, to simulate oral environment as adopted by previous studies (2,19,20).

The experimental groups were further subdivided into two subgroups for each group, to represent different immersion periods (short and long prescription), depending on the manufacturer's instructions, in addition to the results of the pilot study. Each subgroup comprised 11 samples.

Titratable acidity is the property of an acid solution to keep its pH when neutralizing agents are added, in other words, it is a measure of its buffering capacity. Consequently, a substance with low titratable acidity is readily neutralized by oral fluids. For this reason, this experimental study tested the pH and titratable acidity of the selected antibiotics, to determine their erosive potential.

In this respect, Hara and Zero (23) reported pH to be the most important predictor of dental erosion, whereas titratable acidity was less correlated with erosion.

In view of the results of the current study, the proposed null hypothesis was rejected.

Results of the present study revealed that, the mixed type of antibiotic (Hibiotic) showed the lowest PH and the highest titratable acidity. Therefore, it was the most acidic among the three tested groups. It was followed by the cephalosporin (Duricef) and finally the macrolide (Azithromycin) that proved to score the highest pH and lowest titratable acidity.

Microhardness was measured for the control group as a baseline reference for the three experimental groups. After different immersion cycles were completed, microhardness was measured for each group using Vickers micro hardness tester.

The results of the current study showed that all experimental groups showed decrease in microhardness. This is coincident with the work of Valinoti et al (24), who studied 29 antibiotics, among which the three main groups of the present study were included. They concluded that

antibiotics with low pH, high titratable acidity, sugar content and high viscosity are risk factors in dental erosion. Another confirming study, was that of Gado et al, (7) who reported that three similar analyzed antibiotics had an erosive potential.

Results of the present study, showed that the mixed group (Hibiotic for10 days) representing the long prescription, showed the greatest reduction in microhardness, whereas, macrolides (azithromycin for 3 days) representing the short prescription, showed the lowest reduction of microhardness. This could be attributed to the lowest pH and the highest titratable acidity, that was reported for this type of antibiotic, which is a combination of amoxicillin + clavulinic acid. This apparently tended to increase its acidity. In comparison, azithromycin had the highest pH and the lowest titratable acidity.

The results of the present study are also similar to those reported by Gado et al (7) who stated that Hibiotic had a more erosive effect than Duricef. Although this study, showed that the macrolide "Azithromycin" had a pH above the critical pH of 5.5 and very low titratable acidity, in comparison to the other two tested types, an erosive effect was yet observed. In accordance, Valinoti et al (24) reported that although azithromycin had quite an acceptable performance, it still had an erosive potential. This result also confirmed that of Mahmoud et al (12), who reported that medicines could erode the teeth even when the pH is above critical value. They attributed their statement to an increase in viscosity and sugar content.

An interesting finding was that although Azithromycin in this study, recorded the lowest reduction in microhardness in the short duration prescription (3 days), the long duration (5days) had almost the same effect as that of Duricef in the 5-day group, despite its lower pH and higher titratable acidity. In the same context, Kulkarni et al (2) and Gado et al (7), measured erosion after different immersion periods of 7,14 & 21 days, and showed highly significant decrease in enamel microhardness which increased with increasing duration of immersion.

The present study was a trial to cast light on the undesirable effects of different antibiotics if strict oral health measures are not undertaken.

A possible limitation of this study is that the erosive potential was only studied in relation to the pH and titratable acidity of antibiotics, but did not put into consideration other factors, such as viscosity, sugar content, acid type, and presence of buffering agents

CLINICAL SIGNIFICANCE

1- Necessary preventive measures should be taken in children who use antibiotics routinely.

2-Pediatricians should encourage parents to schedule periodic follow up appointments with pediatric dentists

3- Search for alternative compositions to decrease

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detrimental effects.

Future direction

Further clinical research is required to elaborate the findings of the present study and depict the effect of various types of antibiotics on primary tooth enamel.

CONCLUSION

Based on the limitation of this study it is concluded that

1- All three types of antibiotics analyzed in the current study had an erosive effect.
2- Antibiotics could erode the primary teeth enamel even with a pH above critical pH and low titratable acidity.
3- Increasing duration and frequency of prescription increases the erosive potential of an antibiotic.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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