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ORIGINAL ARTICLE

Erosive Effect of Analgesics on Primary Tooth Enamel - An *in Vitro* Study

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ABSTRACT

Objective: To evaluate *in vitro* erosive effect of analgesics on primary tooth enamel. **Material and Methods:** The pH and the titratable acidity measurements of the medicines were performed in triplicate using a digital pH meter. Enamel slabs of primary teeth flat and polished were selected by initial surface microhardness analysis. Medications were selected and specimens were assigned into five groups (n=12): Dalsy; Magnopyrol; Paracetamol; Tylenol; and distilled water (negative control). Specimens were immersed in 5 ml of each group solution for 30 min, 4x/day for three days and stored in artificial saliva at 37 °C between immersions and at night. Final microhardness was determined. The data were submitted to One-way ANOVA and Tukey's test. Scanning electron microscopy (SEM) analysis was performed in three specimens of each group. **Results:** Medicines showed acidic pH and mean values of titratable acidity ranged from 1.46 to 11.66 ml of 0.1N NaOH. The mineral loss of Magnopyrol was statistically significant in relation to the control group ($p<0.01$). Magnopyrol showed higher values when compared to Tylenol ($p<0.05$). SEM images displayed microstructure alterations in the Paracetamol group. **Conclusion:** Despite the low pH values, only Magnopyrol showed greater enamel softening. Paracetamol demonstrated morphological changes in primary tooth enamel.

Keywords: Tooth Erosion; Analgesics; Dental Enamel; Tooth, Deciduous; Child.

Introduction

Dental erosion is the chemical loss of mineralized tooth substance caused by repeated contact with acids of non-bacterial origin [1]. In preschool children, the prevalence was 47%, 10%, and 4% of low, moderate and severe cases, respectively [2]. Its etiology is multifactorial and related to intrinsic factors, such as eating disorders and gastroesophageal reflux [3], and also related to extrinsic factors, such as intake of acidic beverages, medicines, and food [4].

The erosive potential of acidic substances can be influenced by chemical parameters such as pH, buffer capacity, titratable acidity, viscosity, as well as calcium, phosphate and fluoride concentrations [5]. Pediatric liquid medicines, for instance, may present low endogenous pH and high titratable acidity, promoting a rapid decrease in oral pH, which remains acid for an extended period of time [6]. On the other hand, pharmaceutical industries add acids to enhance flavor and some properties of the formulation, such as maintenance of chemical stability, control tonicity, and physiological compatibility [7]. In addition, other factors such as higher intake frequency, high viscosity, and, in the case of antihistamines, the side effect of reduced salivary flow may contribute to increasing the erosion risk [8].

Several studies have shown that primary teeth have more susceptibility to dental erosion in comparison to permanent teeth [9-11]. In addition, it has been demonstrated that acidic medicines were able to reduce the hardness of primary teeth [6,12] and promote morphological changes in the enamel [13]. In previous *in vitro* studies, acidic antihistamines contributed to dental erosion [7,12,14-17], as well as respiratory disease medications [7,13-20]. Antibiotics for pediatric use have also been related to dental erosion [7,13,16,17,19-22]; however, more studies are still needed to evaluate the erosive potential of analgesics on primary enamel [6,7,13,17,19,22,23]. Furthermore, since some children may require frequent use of oral liquid medicines, evaluation of the primary enamel behavior exposed to these products becomes necessary. Thus, the aim of this study was to evaluate *in vitro* the erosive effect of analgesics for children's use on primary tooth enamel.

Material and Methods

Ethical Aspects

This research protocol was approved by the Research Ethics Committee of the School of Medicine of the Federal University of Ceará (Process number 27279914.4.0000.5054).

Medicine Selection

A pilot study was performed under similar conditions of this *in vitro* study. The pH, titratable acidity and surface hardness analysis were considered for medicine selection. Four analgesics (Dalsy®, Magnopyrol®, Paracetamol and Tylenol®), in the form of liquid preparations for pediatric use, available in the Brazilian market were selected and tested in this study. A negative control (distilled water) was also included (Table 1).

Table 1. Brand names, manufacturers, active principles and batches of all medicines.

Brand Names	Manufacturers	Active Principles	Batch
Dalsy®	Abbott Laboratorios do Brasil Ltda. (São Paulo, SP, Brazil)	Ibuprofen	040848F01
Magnopyrol®	Mantecorp Farmasa (São Paulo, SP, Brazil)	Dipyrone	LB12CO289
Paracetamol *Criança*	EMS Pharma (Hortolândia, SP, Brazil)	Acetaminophen	502324
Tylenol® *Criança*	Janssen-Cilag Farmacêutica Ltda. (São Paulo, SP, Brazil)	Acetaminophen	RLL089

pH Analysis

The endogenous pH of each medicine was determined using the digital pH meter DLA-PH (Del Lab, Araraquara, SP, Brazil) at room temperature. The calibration was performed using pH 4.01 and 7.00 buffer solutions (Orion Standard All-in-One pH Buffer Kit, Thermo Electron Corporation, Marietta, OH, EUA). Initially, samples underwent dilutions on distilled water, so that 10 mL of each medicine were transferred to a 100 mL volumetric flask, and the total volume was reached by adding 90 mL of distilled water. Then, 50 mL of the solution was transferred to a beaker. The pH measurements for each selected medicine were performed in triplicate. An average of the three obtained values was calculated for each drug.

Titratable Acidity Analysis

The titratable acidity of each medicine was measured by the gradual addition of a 0.1N sodium hydroxide solution (NaOH), previously standardized, to the samples until a neutral pH of 7 was reached, using a digital pH meter (TEC-3MP, Tecnal Equipamentos Científicos, Piracicaba, SP, Brazil). The evaluation was performed in a volume of 10 ml of each medication diluted in 50 ml of distilled water in a beaker. These analyzes were performed in triplicate for each medicine. The titratable acidity value corresponds to the total amount of base required to raise to a neutral pH. An average of the three obtained values was calculated for each drug. This protocol was based on a previous study [17].

Selection and Preparation of Specimens

Healthy human primary molars extracted and/or exfoliated were donated and previously stored in 0.1% thymol at 4ºC. These teeth were hand scaled and cleaned with water/pumice slurry in rotating bristle brushes at low speed (N270, Dabi Atlante Equipamentos Odontológicos, Ribeirão Preto, SP, Brazil) to remove calculus and surface-adhered debris. Afterwards, the selected teeth were sectioned in the cement-enamel junction with a water-cooled diamond saw of a precision sectioning machine (Isomet 1000, Buehler Ltd., Lake Bluff, IL, USA), to separate the coronal and root portions, when present. Finally, the buccal surface of each tooth was sectioned to obtain a fragment of enamel measuring 3 x 3 x 2mm.

Subsequently, all enamel blocks were embedded in Pre-30 self-polymerized acrylic resin cylinders to facilitate handling (Arotec PRE 30®, Arotec S.A. Indústria e Comércio, Cotia, SP, Brazil), with the buccal surfaces exposed. The enamel surfaces were then flattened with No. 1200, 2400-, and 4000-grit Al_2O_3 grinding papers under water cooling (Rotoforce 4, Struers A/S, Ballerup, Denmark) and polished with 1-µm diamond paste (DP suspension, Struers A/S, Ballerup, Denmark) on a polishing cloth. After each grinding and polishing procedure, the specimens were sonicated for 10 min (Ultra Cleaner 1400, Unique Indústria e Comércio de Produtos Eletrônicos Ltda., Indaiatuba, SP, Brazil) in deionized distilled water.

The absence of cracks, hypomineralization, and hypoplasia was confirmed under an ×20 magnifier (Leica S6 D Stereozoom, Leica Microsystems AG, Heerbrugg, Switzerland) and polished surfaces with structural defects were discarded.

Initial Surface Microhardness Analysis

A baseline surface microhardness test was performed for the initial screening of the specimens with a Knoop diamond under a 25-g load for 5s (FM100; Future Tech., Tokyo, Japan). Five indentations spaced 100 µm apart were made at the center of the slabs. An average microhardness value was calculated for each slab. Specimens that presented microhardness values higher or lower than 20% of the mean value of all specimens

(360 KNH) were discarded. Based on these criteria, 60 specimens were selected for the *in vitro* pH cycling model. Thus, the obtained microhardness averages were used as the initial surface microhardness values. Subsequently, the fragments were stored in a 100% humidity environment until the initiation of the experimental phase.

After the initial microhardness measurements, the selected enamel slabs were randomly assigned according to the immersion media into 5 groups (n=12), as follows: Dalsy®; Magnopyrol®; Paracetamol *Criança*; Tylenol® *Criança* and distilled water – negative control group.

Experimental Protocol

The specimens were immersed in 5 ml of each medicine according to each group and stirred in a mechanical stirrer (TE-141, Tecnal Equipamentos Científicos, Piracicaba, SP, Brazil) for 30 minutes at room temperature as previous used during this immersion period [16]. The ratio of liquid volume to the exposed surface area (buccal) of enamel consisted of 5 ml to an area of 3x3 mm. The established protocol was similar to the dosage recommended by the manufacturer (4x/day) for 3 days, totalizing 120 minutes of daily exposition to each drug group. After immersion, the specimens were rinsed with distilled water for 10 seconds. Between the immersion, the specimens were kept in 5 ml artificial saliva proposed by Amaechi and Higham [24] at 37°C for a period of 2 hours under a mechanical stirrer. At the end of each daily cycle, the specimens remained overnight in artificial saliva. All solutions were changed daily. The experiment was conducted for three days, totalizing 6 hours of exposure to the tested solutions.

Final Surface Microhardness Analysis

After three days of erosive challenge, the final surface microhardness was assessed as previously described.

Statistical Analysis

Data were expressed as the mean and standard deviation and tabulated in an Excel spreadsheet (Microsoft, Inc, Redmond, Washington, USA) and exported to a statistical software GraphPad Prism 5.0 for Windows (GraphPad Software Inc., San Diego, California, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. The experimental groups were compared by a One-way ANOVA test for repeated measures followed by a Tukey post-test (parametric data). All analyses were performed, considering a confidence level of 5%.

Scanning Electron Microscopy Analysis

SEM analysis was performed on the last day of the experiment in three specimens of each group. The following protocol was undertaken: the specimens were dehydrated in an increasing ethanol series (70, 95 and 100%), each solution was changed at 15-min intervals for 1 h per concentration, mounted on stubs, sputter-coated with gold and analyzed in a scanning electron microscope (Evo50, Carl Zeiss AG, Oberkochen, Germany) at 20 kV. The entire surface of each tooth was scanned, and the most representative images were recorded at 150 and 1500X magnifications to identify the presence of areas of erosion. The SEM analysis was intended to provide a visual and illustrative comparison of the specimens, and hence no statistical analysis was performed.

Results

pH and Titratable Acidity

Table 2 presents the pH and titratable acidity mean values of the tested analgesics. All selected medicines showed an acidic pH less than the critical pH of dental enamel. The results of the pH measurements ranged from 3.89 (Dalsy®) to 5.29 (Magnopyrol®). Dalsy® exhibited the highest titratable acidity (11.66 mL) compared with other analgesics.

Table 2. Mean values and standard deviation of pH and titratable acidity of tested analgesics.

Medicines	pH	0.1N NaOH (mL)
Dalsy®	3.89 ± 0.01	11.66 ± 0.20
Magnopyrol®	5.29 ± 0.06	1.43 ± 0.05
Paracetamol	4.40 ± 0.09	1.93 ± 0.20
Tylenol®	4.30 ± 0.07	1.73 ± 0.05

Surface Microhardness

Evaluation of the initial and final hardness (mean and standard deviation values in Knoop Hardness Number - KHN) of the tested groups are shown in Figure 1. Magnopyrol® was the only analgesic that presented a statistically significant loss in surface microhardness in relation to the control group ($p<0.01$). Also, Magnopyrol® presented a statistically significant greater loss of microhardness when compared to Tylenol® ($p<0.05$). Paracetamol, Dalsy® and Magnopyrol® demonstrated lower final microhardness values compared to their initial ones; however, these differences were not statistically significant ($p>0.05$).

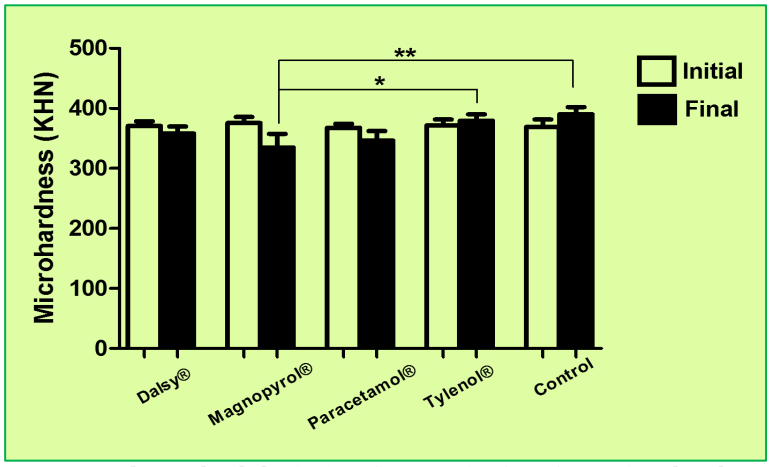

Figure 1. Mean and standard deviation (in KHN) of surface microhardness values.

Scanning Electron Microscopy Analysis (SEM)

After 3 days of the erosion cycling model, the SEM photomicrographs exhibited microstructure alterations with crater formation in specimens exposed to Paracetamol. These specimens clearly showed an evidenced structural loss. The enamel surface was irregular, rough, and damaged, with depressions and etched prism pattern (Figure 2 - C).

The other groups (Dalsy®, Magnopyrol®, and Tylenol®) showed a smooth enamel surface with little porosity and minimal surface loss, with no evidence of erosion (Figure 2 – A, B, and D, respectively). The distilled water group presented deposition of material on the enamel surface (Figure 2 - E and F).

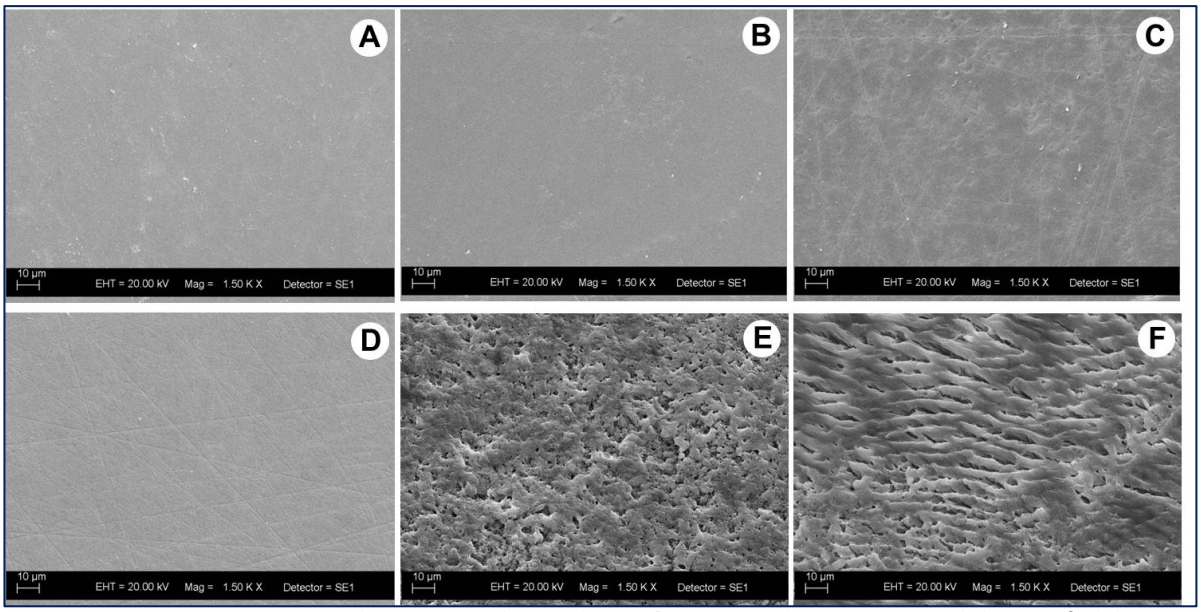

Figure 2. SEM images of enamel surfaces after 3-day pH cycling at 1.500X. (A) Dalsy®, (B) Magnopyrol®, (C) Paracetamol, (D) Tylenol®, (E and F) Distilled water (negative control).

Discussion

In the present study, the erosive potential of analgesics for children was evaluated *in vitro* in primary tooth enamel. There are a limited number of studies in the literature regarding this topic. In this experiment, all evaluated medicines presented acidic pH. Dalsy® exhibited the lowest mean pH values and the highest titratable acidity of all medications. Magnopyrol® was the only one that presented enamel loss of surface microhardness under the studied conditions.

Pediatric medicines can present erosive potential due to the presence of acids in their formulations, low pH, high titratable acidity, absence of buffering agents and low concentrations of calcium, fluoride, and phosphate in their composition [14,16]. Therefore, analgesics are the most used type of medicines in children, according to parents' perceptions [25].

Acidic substances with low pH values can exacerbate erosive dissolution and lead to further demineralization [26]. Previous studies have found that medications for children's use presented low pH, as antibiotics [12,13,16,19], antihistamines [7,12,14,16-18], mucolytics and bronchodilators [12,14], as well as analgesics [19,23]. This is in line with our results, which showed that all evaluated medicines were acidic with a pH ranging from 3.89 to 5.29, below the critical pH value of 5.5 for enamel dissolution.

However, not only the pH value is important, but also the titratable acidity, which is the total acid content and, thus, an indication of the erosive potential [26]. Lussi and Carvalho [8] verified that pH and titratable acidity can significantly influence erosion in deciduous enamel. It can be assumed that medicines with low pH and high titratable acidity are those with the greatest erosive potential [4]. Interestingly, in this study, Dalsy® presented the lowest pH and the highest titratable acidity among the evaluated medicines, however, this medicine did not show a significant enamel loss. Erosive dissolution can also be influenced by Ca^{2+} concentration and, to a lesser extent phosphorus concentration of the substances [8]. In this study, however, pH and titratable acidity were the only physicochemical parameters analyzed.

It has been assumed that microhardness is the most useful method to assess enamel "softening" [27]. Among the tested groups, Magnopyrol® was the only one that showed statistically different hardness loss compared to the control group, thus presenting an erosive effect in this experimental protocol. This medicine

presented an acidic pH (5.29), but the titratable acidity was lower compared to the other drugs. It can be suggested that this result might have been also influenced by the action of one of its components, disodium edetate (EDTA), which is a specific chelating agent for calcium ions and, consequently, for dentin.

One factor that may contribute to the divergence between the pH and the hardness values found of some medications group (Dalsy®, Paracetamol and Tylenol®) is that some medicines with lower pH can cause an outermost surface "softening" and lead to an enamel loss after an acid challenge. However, considering these findings, it can be suggested that minerals from artificial saliva storage may have been deposited on the enamel surface after the erosive challenge.

By scanning electron microscopy, morphological changes in primary tooth enamel indicate an erosive potential of these drugs [13]. According to the SEM assessments of this study, only Paracetamol clearly exhibited structural enamel loss with an irregular and etched prism pattern enamel surface. The SEM results can be explained by the short time of exposure to the medicines in this *in vitro* experiment. Other studies observed higher dissolution on the enamel surface after 5 and 8 days [28]. Similar results were obtained in other studies [12,13,28-30].

It is important to note that the chosen protocol of 3 days for the erosive challenge of this study was based on the manufacturer's recommended dosage, simulating the conditions of use of these drugs. Also, as pointed out that the administration of analgesics should be limited to the first few days after the procedure. [31]. Therefore, different results can be found in other studies [12,18], in which the experimental protocol was more erosive with a greater immersion time in medicines and more days of the erosive challenge. The 30-min exposure time may have been overestimated; however, future experimental designs on this topic will consider more groups with different time intervals so that the differences and impact on dental erosion can be better analyzed.

It has been shown that children who initially presented erosive lesions in deciduous teeth had a significantly greater risk of having erosive lesions in their permanent teeth [32]. Moreover, primary teeth have more susceptibility to dental erosion in comparison to permanent teeth [9-11]. Children using these drugs will most probably experience a deleterious accumulative effect that might lead to erosive lesions on the tooth enamel surface [28]. The findings of the current study indicate that the use of liquid medicines in a daily routine of children may place them at risk for dental erosion, especially when used for the treatment of chronic diseases or over a long period.

This study has some important limitations. First, the absence of a daily assessment of the surface microhardness; thus, enamel softening was not monitored during each day of the erosive cycling model. Second, the pH of the water used was not measured. Finally, the ideal situation is to apply different assessment methods, such as performing a profilometry analysis in dental erosion studies. Profilometry is a method that may be adopted for surface loss with high precision provided that material loss exceeds about 0.4 μm [33]. Thus, this reflects another limitation of this study. Moreover, it can be suggested that further studies are required using other methods, such as calcium/phosphate release or optical profilometry, to check the erosion provided by these medicines.

As dental erosion in primary teeth could predict wear in permanent teeth, dental professionals should be fully aware of the erosive effect of some medicines on primary enamel to avoid oral hygiene instructions soon after intake of liquid medicaments.

Conclusion

When used according to the recommended dosage, under these experimental *in vitro* conditions, Magnopyrol® presented greater enamel softening in primary teeth, and Paracetamol showed morphological surface alterations, suggesting that these medicines may have an erosive effect.

Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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