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ELLAGIC ACID ON THE QUALITY OF THE ADHESIVE INTERFACE OF CLASS I COMPOSITE RESIN RESTORATIONS AFTER AGING

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Abstract

To evaluate the effect of ellagic acid on the inhibition of matrix metalloproteinase by analyzing the quality of the adhesive interface with bond strength measures in periods of 24 hours and six months of storage. 40 healthy human third molars were prepared with class I cavities (5x4x3mm). The teeth were divided into four experimental groups: Group 1- without application of ellagic acid and storage time of 24 hours; Group 2- with ellagic acid/24 hours; G3- without ellagic acid/six months; Group 4- with ellagic acid/six months. Then, the cavities were restored with 3M[™] Adper[™] Easy One used as Self-Etch Adhesive and Z250 composite resin, with and without the previous application of ellagic acid. Subsequently, hourglass-shaped specimens were obtained and subjected to the bond strength (BS) test (n = 10) in a universal testing machine. The bond test was performed after 24 hours and six months of storage. For the standard evaluation, the samples were infiltrated with silver nitrate and placed in a developing solution for analysis in a Scanning Electron Microscope (SEM). The data obtained were analyzed with the Kruskal-Wallis non-parametric test, showing a statistically significant difference. The highest bond strength values were found for the 24-hour groups followed by the groups with six months of storage. For nano-infiltration, groups G1 and G2 showed lower infiltration than groups G3 and G4. The previous application of ellagic acid did not affect the BS of the adhesive interface of the adhesive system analyzed, regardless of storage time.

Keywords: Dental adhesives. Ellagic acid. Microscopy, Electron, Scanning Transmission.

1. Introduction

The use of the conventional two-step adhesive system requires prior acid etching, followed by the application of hydrophilic and hydrophobic monomers contained in the same bottle (Kong et al. 2020). This implies reducing the diffusion of monomers in the hybrid layer (Trevelin et al. 2020), which results in an incomplete adhesive infiltration, thus leaving some collagen fibrils naked (Osorio et al. 2011).

Collagen fibrils that have not been completely enveloped by resinous monomers can be degraded hydrolytically through the absorption of water by hydrophilic monomers within the hybrid layer or the action of proteolytic enzymes known as matrix metalloproteinases (MMPs). Proteolytic enzymes are

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secreted by odontoblasts during dentinogenesis and remain inactive within the dentin cell matrix (Tjäderhane et al. 2012). These metalloproteinases regulate the organization of collagen fibers and mineralization (Boushell et al. 2008).

In demineralized dentin, it is possible to find the presence of MMP-2 or gelatinase A, which degrades the main collagen found in dentin (type I collagen), as well as active MMP-9 or gelatinase B, which degrades type IV collagen - the main component of denatured collagen (Mazzoni et al. 2013; Hass et al. 2021; Perdigão et al. 2021).

The MMPs are secreted in the form of inactive proenzymes (zymogens), which are activated with the segmentation of the zymogen called propeptide that occurs by breaking a bond of cysteine and Zn⁺⁺ ions, blocking the reactivity of the active site (Mazzoni et al. 2012; Boelen et al. 2019;). Thus, in this process, inactive zymogens become active MMPs and this activation is the result of the interaction in the sulfhydryl group of cysteine, which is found in the propeptide domain and the catalytic domain that contains the zinc ion. This process can be directly controlled by the local pH in which these proteases are found (Ou et al. 2018). The low pH stimulates the activation of MMPs, promoting the degradation of the extracellular matrix. However, the transformation of insoluble collagen fibrils into soluble peptides discontinues the hybrid layer inside the dentin, resulting in loss of retention in the tooth/restoration interface (Bedran-Russo et al. 2014; Breschi et al. 2018).

The most studied MMP inhibitor in adhesive dentistry is chlorhexidine digluconate, which presented satisfactory results when evaluated for long-term bond strength (Kong et al. 2020). However, MMP inhibitors based on other substances have been researched in the biomedical field, showing medicinal properties such as some polyphenols found in plants, seeds, and fruits (Zhang et al. 2009).

Ellagic acid, extracted from the fruit Punica Granatum L., known as pomegranate, is a biphenol from the group of hydrolyzable tannins and it can inhibit the expression and action of collagenases (MMP-1), gelatinase (MMP-2, MMP- 9), stromelysin (MMP-3), and elastase (MMP-12) (Zhang et al. 2009). Thus, studies show that ellagic acid in adhesive dentistry may contribute to greater longevity of the adhesive interface due to the potential inhibition of endogenous enzymes, thus reducing the degradation of collagen fibers. Therefore, this *in vitro* study aimed to evaluate the effect of ellagic acid as an MMP inhibitor on the integrity of the adhesive interface during periods of 24 hours and six months, using 3M[™] Adper[™] Easy One used as Self-Etch Adhesive. The null hypothesis is that the previous application of ellagic acid did not affect the bond strength of the adhesive interface of the adhesive system.

2. Material and Methods

Ethical aspects

The project was approved by the Research Ethics Committee of FOP-UNICAMP, affiliated with the National Research Ethics Commission - CONEP. The teeth came from dental surgeons in the city of Piracicaba by the donation of teeth signed for the project, following resolution No. 466/2012 of the National Health Council.

Materials

Table 1 describes the composition and manufacturers of the materials used in the study.

Experimental groups

Forty human teeth (n = 10/group) were used and randomly divided into the following experimental groups: Group 1 - Without the application of ellagic acid and storage of 24 hours; Group 2 - With the application of ellagic acid and storage of 24 hours; Group 3 - Without ellagic acid and storage of six months, and Group 4 - With ellagic acid and storage of six months.

Trademark	Composition	Manufacturer
35% phosphoric acid	-35% phosphoric acid	Ultradent, Jordan, UT, USA
Single Bond 2	-Water	
	-HEMA	
	-Bis-Gma	
	-Ethanol	3M ESPE, St. Paul, MN, USA
	-Copolymer of polyalkenoic acid	
	- Camphorquinone	
	- Silica nanoparticles	
	- Dimethacrylates	
	-Bis-Gma	
	-TEGDMA	
Filtek Z250 composite resin	-UDMA	3M ESPE, St. Paul, MN, USA
	-Bis-Ema	
	-Camphorquinone	
	-Colloidal silica	
Ellagic acid	- Ellagic acid ≥95%	Sigma–Aldrich, St.
		Louis, MO, USA

Table 1. Description of the products, their composition and manufacturers.

Teeth preparation

In the study, 40 freshly extracted human third molars were used, stored for a maximum period of 24 hours in a buffered 0.1% thymol solution, and maintained in a stove at 37°C. The external surfaces were cleaned with a 5-6 periodontal curette (Duflex, SSWhite, Rio de Janeiro, RJ, Brazil) through root scraping, followed by blasting with sodium bicarbonate and water. After cleaning, the teeth were stored in distilled water in a stove at 37°C until the beginning of cavity preparation.

The teeth were embedded in polystyrene resin to facilitate the standardization of cavity preparations. Then, the occlusal surface was flattened in a polishing machine (Arotec Ind. Com., São Paulo, Brazil) with 400, 800, and 1200 sandpapers, respectively (3M - 411Q 3M do Brasil- Sumaré, SP, Brazil), maintaining the occlusal surface of the enamel.

After planning the occlusal surface, the teeth were taken to the standardizing machine for cavity preparations, in which the class I preparation was performed with the following dimensions: 5 mm in the mesiodistal direction, 4 mm in the buccolingual direction, and 3 mm of depth with the cavosurface angle in the enamel. The preparations were performed with a #56 carbide drill (KG Sorensen Ind. E Com. Ltda, Barueri, SP, Brazil) at high speed and under constant irrigation. The drill was replaced every five cavity preparations.

Restorative procedures

The adhesive protocol was performed according to the manufacturer's recommendation. A drop of ellagic acid was applied with an automatic pipette and actively spread with a microbrush (KG Sorensen Ind. E Com. Ltda, Barueri, SP, Brazil) on the entire surface of the preparation for 60 seconds on G2 and G4, then, excess solution was removed with an absorbent paper. Subsequently, two layers of the adhesive (3M[™] Adper[™] Easy One used as Self-Etch Adhesive) system were spread over the dentin surface with a microbrush for 20 seconds and dried for 5 seconds. Then, photoactivation was performed for 10 seconds with the active tip of the device juxtaposed to the occlusal surface. The crowns were restored using the incremental technique with the Filtek Z 250 microhybrid composite in six increments. Each increment was photoactivated for 25 seconds with a Radii Cal light-curing device (SDI, São Paulo, SP, Brazil) with 1200 mw/cm² of irradiance, which was measured before each photoactivation.

In the microtensile test, the dental crowns were separated from the root portion at the height of the cemento-enamel limit by sectioning the dental element perpendicularly to its long axis using a double-sided diamond disc (KG Sorensen Ind. E Com. Ltda, Barueri, SP, Brazil) under constant refrigeration. Then, the crowns were fixed on acrylic plates with sticky wax (New Wax, Thechnew Com. e Ind. Ltda, Rio de Janeiro,

RJ, Brazil). The set was fixed in a precision metallographic cutter (Isomet 1000, BUEHLER Ltda. Lake Buff, IL, USA) in which a high-concentration diamond disc (Extec Corp., Enfield, CT, USA) was adapted. It rotated at low speed under constant irrigation with distilled water and made serial sections in the mesiodistal direction to obtain 1-mm-thick slices. Next, the tooth was repositioned and cuts were made in the buccolingual direction to obtain toothpicks of approximately 1 x 1 mm. Half of the sticks obtained for the microtensile test were analyzed after 24 hours and the other half was stored in distilled water and replaced weekly. New tests were performed after six months of storage.

Bond strength (BS) test

The toothpicks were attached to the microtensile device (Geraldeli), with cyanoacrylate-based adhesive (Super Bonder Gel, Loctite, Henkel Ltda., Itapevi, SP, Brazil), by the ends to place them parallel to the traction loading, and then taken to the universal testing machine (EZ Test L Shimadzu, Japan). The test was conducted with a 500-kgf load cell at a speed of 0.5 mm/min, until rupture. The force required to rupture the specimens, in kilogram-force (kgf), was noted and the dimensions of the adhesive interface of the specimens were measured with a digital caliper (Mitutoyo Corporation, Tokyo, Japan). The fracture strength in MegaPascal (MPa) was calculated according to the mathematical formula: R = F (kgf) x 9.8 / A (R = bond strength in MPa, F = force in kilogram-force (kgf), and A = area in mm².

Preparation of test specimens for nano-infiltration analysis

Ten toothpicks from each group were randomly selected and immersed in a silver nitrate solution containing 10 grams of nitrate crystals added to 10 mL of deionized water. Later, 28% ammonium hydroxide drops were applied for eight hours, then, the toothpicks were inserted in polystyrene resin.

After the inlay, the toothpicks were worn in a polishing machine with 600, 1200, and 2000 sandpapers, respectively, and polished with felt discs and diamond pastes in decreasing granulations of 3, 0.5, and 0.25 μ m. Between each sanding and paste granulation, the samples were taken to an ultrasound vat for 10 minutes to remove debris.

The samples were dried with absorbent paper and then an 85% phosphoric acid solution was applied for 30 seconds for demineralization, followed by washing with distilled water. For deproteinization, a 10% sodium hypochlorite solution was used for 10 minutes. Then, they were washed with distilled water and dried at room temperature. Subsequently, the samples were dehydrated in ethyl alcohol in increasing concentrations (25%, 50%, 75%, 90%, and 100%) for 10 minutes at each concentration.

Scanning Electron Microscopy analysis

Fracture pattern analysis

The toothpicks obtained from the microtensile test were mounted in aluminum stubs and covered with gold (Baltec Sputter Coater - SCD - 050) to be evaluated in SEM and the failure mode was classified as 1) cohesive in dentin, 2) resin cohesive, 3) adhesive, or 4) mixed.

Nano-infiltration analysis

The samples were coated with carbon (BalTec-SCD 050-SputterCoater) to be observed in SEM, operating in a high vacuum at a power of 20 KV, in which images were obtained in backscattered electrons.

Statistical analysis

Initially, an exploratory analysis of the data was performed using the Proc lab from the SAS ESTAT software. The data were tabulated and submitted to the Kruskal-Wallis non-parametric statistical test, at a minimum confidence level of 95%.

3. Results

Table 2 shows that the bond strength value was statistically similar between groups G1 and G2. Fewer microtensile values were reported in groups G3 and G4, which were statistically similar.

Treatment	Microtensile values
Without ellagic acid 24 hours	160.72 (112.97-566.42) A
With ellagic acid 24 hours	126.18 (30.57-758.43) AB
Without ellagic acid 6 months	100.10 (4.33-203.68) BC
With ellagic acid 6 months	59.20 (3.65- 135.11) C

The nano-infiltration evaluation required a qualitative test to evaluate the infiltration of silver nitrate in the adhesive interface of the specimens.

Group 1, without the presence of ellagic acid and storage of 24 hours, showed little infiltration at the adhesive interface (Figure 1A and 2A) as well as group 2, with the presence of ellagic acid and storage of 24 hours (Figure 1B and 2B).

Group 3, without the presence of ellagic acid and storage of six months, showed a greater amount of infiltration at the adhesive interface (Figure 1C and 2C) as well as group 4, with the presence of ellagic acid and storage of six months (Figure 1D and 2D).



Figure 1. Scanning electron microscopy images at 50x magnitude. A) The small presence of infiltration for the group without ellagic acid stored for 24 hours; B) The small presence of infiltration for the group with ellagic acid stored for 24 hours; C) A large amount of infiltration for the group without ellagic acid stored for six months; D) A large amount of infiltration for the group with ellagic acid stored for six months.

4. Discussion

According to the results of the present research, the null hypothesis was confirmed. The application of ellagic acid on the dental structure did not decrease the bond strength values from the adhesive interface of the adhesive system analyzed, regardless of storage time. However, there was a reduction in the bonding values for specimens with and without application of ellagic acid after six months of storage in distilled water.

The dentin structure contains a variety of enzymes that can impair the adhesion to restorative materials, among which metalloproteinases, known as MMPs, stand out (Zhou et al. 2019). The MMPs play an important role in biological mechanisms, such as in the growth process (dentinogenesis) and several pathological processes (Nishitani et al. 2006), such as the degradation of extracellular dentin components after a wide variation in tissue pH. It is reported that after the mineralization process of the collagen matrix, inactive forms of MMPs remain trapped within the calcified matrix (Nishitani et al. 2006). However, they can be re-exposed and potentially activated during the carious process or acid attack during restorative procedures. The acidic environment created by these situations favors the proliferation of bacteria and can promote the activation of endogenous MMPs.



Figure 2. Scanning electron microscopy images at 500x magnitude. A) Presence of infiltration for the group without ellagic acid stored for 24 hours; B) Presence of infiltration for the group with ellagic acid stored for 24 hours; C) A large amount of infiltration for the group without ellagic acid stored for six months; D) A large amount of infiltration for the group with ellagic acid stored for six months.

Even after applying the adhesive systems, the MMPs that were activated can degrade the collagen matrix of the demineralized dentin. This is because adhesive systems, whether conventional or selfadhesive, can reactivate gelatinase enzymes (MMP-9 and MMP-2) and collagenases (Mazzoni et al. 2007). The decrease in bonding values after six months of storage might be explained because self-etching mode, such as the one used in the present study, increase the enzymatic activity of dentin and demineralize dentin even after photopolymerizing the material, through a mechanism named "acid activation". This biodegradation of the hybrid layer occurs through the sorption of water by the polymer, promoting hydrolysis, which increases the diameter of the dentinal tubules by the acid (Maravic et al. 2017; Scafa et al. 2017) and it may justify the reduction of the BS values within six months of storage when compared to 24 hours.

During the formation of the hybrid layer, the removal of the mineral portion of the most superficial part of the dentin not only exposes collagen fibrils but also releases and activates metalloproteinases trapped in the dental tissue, such as MMPs. These metalloproteinase enzymes are responsible for hydrolyzing collagen that was not infiltrated by the adhesive system, leading to a possible reduction of bond strength between the dental structure and the adhesive restoration (Mazzoni et al. 2007; Tjäderhane et al. 2013).

The degradation of collagen matrices can occur after restorative procedures, but it may be prevented by applying MMP inhibitors. Ellagic acid can be extracted from many fruits such as persimmons, raspberries, wild strawberries, peaches, plums, and pomegranates; from seeds such as nuts and almonds; and some vegetables. It is a biphenol from the group of hydrolyzable tannins that can inhibit the expression and action of collagenases (MMP-1), gelatinase (MMP-2, MMP-9), stromelysin (MMP-3), and elastase (MMP-12) (Breschi et al. 2018).

This inhibitory property can contribute to greater longevity of the adhesive interface due to the potential inhibition of endogenous enzymes, thus reducing the degradation of collagen fibers (Fischer et al. 2019).

The alcohol contained in the adhesive does not dissolve ellagic acid, which in turn, does not impair the bonding properties of the tooth-restoration interface, allowing the formation of a regular hybrid layer (Ferdosian et al. 2017; Shavandi et al. 2018). From the results obtained in the present study, the adhesive bond strength with 24-hour storage was not affected by the previous application of ellagic acid, but this adhesive bond does not last for a longer period, as there is a reduction in bonding values and an increase in the amount of nano-infiltration for the six-month storage groups. It is worth noting that the maximum evaluation time for ellagic acid is not yet available in the literature and further studies are required to elucidate this question.

5. Conclusions

The previous application of ellagic acid did not affect the BS of the adhesive interface of the adhesive system analyzed (3M[™] Adper[™] Easy One used as Self-Etch Adhesive), regardless of storage time.

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