

Effect of Dentin-Pretreatment using Arginine, Polyamidoamine Dendrimer and their Combination on Bond Durability and Micromorphology

Keywords

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ABSTRACT

Objectives To analyze the impact of dentin pretreatment using arginine (L.arg), amine-terminated polyamidoamine dendrimer (PAMAM-NH₂), and their combination on microtensile bond strength (μTBS) and resin-dentin micromorphology. *Methods* Demineralized middle-coronal dentin surfaces of eighty sound molars were randomly distributed among four groups depending on the implemented surface pretreatment (n=20): (1) 8% L.arg, (2) PAMAM, (3) PAMAM + L.arg, and (4) untreated dentin (control group). Following bonding and composite build-up procedures, each group was subdivided into: the non-aged subgroup, where the μTBS was measured immediately, and the aged subgroup, where the specimens were thermo-cycled before μTBS. Resin-dentin sticks were prepared for μTBS testing. The failure mode distribution was analyzed. The resin-dentin interface was investigated using Field-emission scanning electron microscopy. A two-way ANOVA was utilized, followed by Tukey's post hoc test. Results before thermo-cycling, group 1 had the highest μTBS mean value followed by groups 2 and 4 without a significant difference. While group 3 showed the statistically least μTBS (P <0.001). After thermo-cycling, PAMAM pretreatment significantly increased the μTBS. *Conclusions* PAMAM pretreatment possessed a favorable impact on the dentin- resin bonding durability. Clinical relevance PAMAM -NH₂ and L.arg surface treatment could improve immediate and long-term stability of the dentin-resin bonding.

INTRODUCTION

The durability of the adhesion between resin-based composite (RBC) restorations and tooth structures is now one of the crucial issues¹. Dental adhesion is a complicated process that is influenced by the properties of hard tissue substrates, particularly dentin, which has facilitated the evolution of many adhesive systems throughout time². Matrix metalloproteinases (MMPs) cysteine cathepsins are enzymes, which are when activated, able to degrade dentin extracellular matrix proteins³. They cause damage to non- resin-penetrated collagen type 1 which negatively affects the restoration lifetime³⁻⁵.

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Since bond durability is limited by the stability of the hybrid layer, several approaches were developed to prolong the resin–dentin interfacial bonding durability. Chlorhexidine is one of the examples, which was used to inhibit MMPs or using cross-linkers as primers. However, those affect only the strength of adhesion by timing while improvement an immediate adhesive strength was not distinguished⁶.

Arginine (L.arg) as an alkaline amino acid, has stability in a water-based solution. It can protect tooth structures against mineral loss and help in reversing erosive⁷ or demineralization procedures⁸. The bonding effectiveness of 4-MET self –etch adhesive improved following Arg-CaCO₃ dentin pretreatment⁹. Moreover, it was shown that 8% L.arg and calcium carbonate dentin pretreatment didn't negatively influence the shear bond strength resin composites and optimal bonding could be attained through the use of these materials in conjunction with desensitizing agents¹⁰. Arg-CaCO₃, when dissolved in residual water has the potential to diminish the liquid / vapor surface tension and enhance the wettability of dentin surfaces creating an elevated-energy surface characterized by reduced contact angles that typically favors mechanical locking and adhesion¹¹.

PAMAM dendrimer, also known as “artificial protein”, has tree-like structures featuring “branches” spreading around a main axis. It imitates natural non- collagenous proteins owing its regular spatial construction, numerous reactive external groups and its distinct size. PAMAM-NH₂ has several amine groups on its external surface and amide groups on its branches. These reactive groups can draw calcium ions during remineralization, so it supposed to be an efficient template to boost remineralization. PAMAM-NH₂'s mono-dispersed molecular weight within the size retention region of collagen also, maintain it on the dentin surface¹². PAMAM-NH₂ has a promising antimicrobial potential through the large number of positive charges that

damage the bacterial cell wall. As a cavity disinfectant, PAMAM-NH₂ did not influence the bonding or adhesive permeability¹³. Additionally, it was determined that exposed collagen fibrils proteolysis within the hybrid layer was precluded by PAMAM-OH dentin pretreatment. Beside it promoted a substantial resin-dentin bond following thermo-cycling and facilitated the remineralization process within the hybrid layer¹⁴. Accordingly, the current study aimed to assess the impact of demineralized dentin pretreatment with 8% wt L.arg solution, amine-terminated polyamidoamine dendrimer third generation (G3-PAMAM-NH₂), and their combination on the microtensile bond strength and resin-dentin micromorphology. The null hypotheses was that; - 1) Resin-dentin bond strength of demineralized dentin will not be impacted by the proposed various dentin pretreatment, 2) The demineralized dentin pretreatment using L.arg, G3-PAMAM-NH₂, and their combination would not enhance the microtensile bond strength immediately and following thermo-cycling, 3) The proposed dentin pretreatment would not affect the adhesive interface.

METHODS

Materials applied in the current study, their description, manufacturer, and composition are demonstrated in Table 1.

SAMPLE SIZE ESTIMATION

Sample size was calculated via G*Power version 3.1.9.7. Considering the results of previous research⁹, the statistical calculation according to power 80%, an effect size (d) of (0.405), and with a error 5% revealed that the predicted sample size was 72 samples, but has been increased to 80 samples to provide appropriate results.

Table 1. Showing the materials used in the study.

Name of materials	Composition/specification	Manufacturer
Polyamidoamine dendrimer (PAMAM G3)	Dendrimer with ethylenediamine core (2 carbon core) and 32 amino surface groups 20% in methanol	Dendritech®, Inc. Sigma-Aldrich corporation, Germany
L. Arginine	8wt % L.Arginine	Nano Gate Company (Cairo, Egypt)
All Bond universal adhesive	10-MDP, Dimethacrylate resins, HEMA, Ethanol, Water, Initiators. Colloidal silica.	BISCO Inc., USA.
Nova Compo C (Resin composite)	Nano-hybrid resin composite, Different dimethacrylates (18-22%wt.), USL (ultra-low shrinkage monomer), 83-78 fillers (barium glasses, ytterbium and prepolymer), additives, catalysts, stabilizers and pigments	IMICRYL, Turkey.
Etchant gel	Phosphoric acid (H ₃ PO ₄) 37%	Spident, Korea

SPECIMEN PREPARATION AND BONDING PROCEDURES

Before the study begun, the Ethical Research Committee, Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt approved this study (Final code: REC-PD-24-14). Anonymous eighty human permanent carious-free molars extracted due to periodontal or orthodontic reasons were collected. Teeth were thoroughly cleaned from blood, debris, and plaque using streaming water and a brush with soft bristles. After that, the teeth were kept in a fresh thymol solution at 4 °C until further use. Teeth were embedded in 2 cm diameter cylindrical plastic molds pre-filled with soft acrylic resin. Then, occlusal enamel was removed under water cooling by a diamond saw (Isomet 4000, Buehler, Lake Bluff, IL, USA) till reaching the mid-coronal dentin. Then, water-cooled sandpapers (600 grit) were used for smear layer formation. The dentin surface of teeth was demineralized for 2 minutes of applying phosphoric acid gel 37% (Etch fine Spident, Korea) followed by rinsing with deionized water for an additional 2 minutes¹⁵. The teeth were then randomly distributed among 4 groups (n=20) according to the specified pretreatment:

Group 1: Demineralized dentin was pretreated with 8% L. arg solution for 5 minutes¹⁶. It was freshly prepared by dissolving 0.8 gram of L. arg powder in 10 ml of deionized water. Each specimen was immersed in 1ml of % L. arg solution in a plastic container. **Group 2:** Demineralized dentin was pretreated with PAMAM solution. It was applied on the demineralized dentin surfaces for 60 seconds utilizing a micro brush accompanied with a rubbing action for proper infiltration then rinsed with deionized water for 30 seconds¹⁴. **Group 3:** (PAMAM + L. arg) pretreated group where PAMAM solution was first applied over the demineralized dentin surfaces as in group 2. After that, the specimens were treated by 8% L. arg solution as in group 1. **Group 4** (control group): demineralized dentin surfaces left untreated.

Following the application of different pretreatment solutions, absorbent papers and gentle air were used to remove any excess from the dentin. The universal adhesive (All Bond universal BISCO, USA) was applied depending on the manufacturer's instructions and cured by a light-emitting diode light unit (LED, RTA; MiniS Curing Light – China) device with 1000 mW/cm² intensity and a 420-480 nm wavelength for 15 seconds. 4 mm resin composite build up were performed (Nano-hybrid resin composite, B&E, Korea) and cured for 40 seconds individually. Then the specimens were submerged in distilled water at 37 °C for 24 hour.

BEAM PREPARATION AND MICROTENSILE BOND STRENGTH MEASUREMENTS

In each group, specimens were randomly distributed among two subgroups (n=10); Non-aged subgroup in which the specimens were submitted to μ BS testing immediately while the

aged subgroup underwent thermocycling before bond strength testing. Longitudinal sectioning of the bonded specimens was performed to obtain beams with 1 mm² thickness. They were obtained by mounting pretreated tooth in the gripping attachment which was serially sectioned using a cutting machine (IsoMet 4000 Buehler, Germany) under copious coolant¹⁷. Later these beams were stored in distilled water in tight-seal plastic labelled tubes for 24 hours. In aged subgroup, 10000 cycles were applied on beams between 5 and 55 °C with a duration of 30 seconds in each cycle. This was performed in a thermocycling device (SD mechatronic thermocycler, Germany). At least 10 beams per tooth, from the central area, were tried to test μ BS. Beams were fixed using cyanoacrylate-based adhesive and tested by employing a universal machine (Instron, Model 3345-England). The beams were stressed in tension while the crosshead speed was 0.5 mm/min till failure occurrence. Then, bond strength was calculated in Megapascal (MPa).

FAILURE PATTERN ANALYSIS

Failure pattern was analyzed quantitatively using a stereomicroscope (MA 100 Nikon, Tokyo, Japan) with 30 x magnification. Failure at de-bonded interfaces was categorized into cohesive (that occurs entirely inside the resin composite or dentin), adhesive (that occurs at the junction between dentin and resin), and mixed (includes both adhesive and cohesive failures)^{15,18}.

SCANNING ELECTRON MICROSCOPE EXAMINATION (SEM)

Scanning electron microscopy (FESEM, Quattro S, Thermo Scientific) was utilized to examine two representative specimens from each subgroup at resin dentin interface before and after thermocycling. Buccal and lingual halves were obtained by sectioning tooth mesiodistally to be examined at adhesive-dentin interface under coolant with a concentration of lubricant: water 1:33 respectively. The disc used for sectioning was fixed into a hard tissue microtome device cutting (FEI Company, Netherlands). Demineralization of sections was done for 30 s with 6N HCl, followed by rinsing then, 2.5% NaOCl was used to eradicate protein for 10 min, and dehydrated using 25, 50, 75, 95 and 100% ethanol respectively for 15 min. Finally, the specimens were set on aluminum stubs and observed under a field emission gun (accelerating voltage 30 K.V., and resolution for Gun.1n.) at magnification 14 x up to 1000000¹⁹.

STATISTICAL ANALYSIS

Mean and standard deviation (SD) values were represented numerically. P-value put below 0.05 to get significance within all tests. Shapiro-Wilk's test was utilized to test normality. Levene's test was used to check homogeneity of variances. Data showed homogeneity and parametric distribution were studied using two-way (ANOVA) test complemented by Tukey's

post hoc test. Simple main effects comparisons were accomplished using the two-way model error term with p-values adjusted through Bonferroni correction. Statistical analysis was accomplished via R statistical analysis software version (4.3.2) for Windows (R Core Team (2024)).

RESULTS

MICROTENSILE BOND STRENGTH (μ TBS)

Two-way ANOVA showed that the type of dentin pretreatment protocol and thermocycling possessed a considerable impact on the bond strength ($p < 0.001$), while the effect of their combination wasn't statistically significant ($p > 0.05$), as shown in Table 2. Table 3 illustrates the mean and standard deviation values for the tensile bond strength of various variables, along with a comparison of the main effects. The results revealed that prior to thermocycling, the PAMAM group had the highest μ TBS mean value (39.26 \pm 3.55 MPa) followed by the L.arg group (36.51 \pm 5.49 MPa) and the control group (34.73 \pm 5.41 MPa) without significant difference among these groups. However the PAMAM + L. arg group showed statistically the least μ TBS mean value (28.66 \pm 3.47 MPa) ($P < 0.001$). While after thermocycling, PAMAM group exhibited the highest μ TBS mean value (32.39 \pm 2.44 MPa) among all groups with significant difference followed by L. arg group (25.94 \pm 3.21 MPa), the control group (22.23 \pm 3.28 MPa) and the PAMAM + L.arg group (17.63 \pm 4.25 MPa). Regarding the failure mode distribution, 50% of the PAMAM non-aged samples revealed mixed

failure and 20% showed cohesive failure (in dentin). While for the PAMAM + L.arg group, adhesive and mixed failures were equally represented, additionally for the other groups most of the samples had adhesive failures (Figure 1). However, most of the aged samples in all groups had adhesive failures, and the difference did not reveal statistical significance ($p = 0.124$).

SCANNING ELECTRON MICROSCOPY ASSESSMENT

Representative SEM micrographs for the resin-dentin bond analysis from each group are shown in (Figure 2 and 3). Before thermo-cycling, L.arg group specimens demonstrated a consistent hybrid layer with several, well-defined elongated resin tags that exhibited little lateral branching (Figure 2A). While specimens of PAMAM group revealed a thick, uniform hybrid layer with dense resin tags that appeared shorter in length (Figure 2C). Whereas the hybrid layer in the (PAMAM + L.arg) group specimens weren't uniform in addition there were less numerous elongated resin tags extended inside the dentinal tubules (Figure 3E). For the control group, the hybrid layer was homogenous, and the resin tags were deeply extended, which demonstrated several lateral branching (Figure 3G). After thermo-cycling, the hybrid layer in PAMAM specimens was not greatly affected (Figure 2D). While specimens of the L.arg. and control groups revealed some areas of hybrid layer separation from the adhesive layer (Figure 2B and 3H), furthermore in the (PAMAM + L.arg) examined specimens, areas of hybrid layer and resin tags degradation were clearly noticed (Figure 3F).

Table 2. Two-way ANOVA test results.

Parameter	Sum of squares (II)	df	Mean square	f-value	p-value
Material	1686.15	3	562.05	34.82	<0.001*
Thermocycling	2098.08	1	2098.08	129.99	<0.001*
Material*Thermocycling	85.79	3	28.60	1.77	0.160

*Significant ($p < 0.05$)

Table 3. Summary statistics and the main effect of materials.

Material	Tensile bond strength (MPa) (Mean \pm SD)				f-value	p-value
	L. arg	PAMAM-NH2	PAMAM and L. arg	Control		
Thermocycling						
Non aged	36.51 \pm 5.49A	39.26 \pm 3.55A	28.66 \pm 3.47B	34.73 \pm 5.41A	12.50	<0.001*
Aged	25.94 \pm 3.21B	32.39 \pm 2.44A	17.63 \pm 4.25C	22.23 \pm 3.28BC	24.09	<0.001*
f-value	34.55	14.64	37.71	48.41		
p-value	<0.001*	<0.001*	<0.001*	<0.001*		

Values with different superscripts within the same horizontal row are significantly different *Significant ($p < 0.05$)

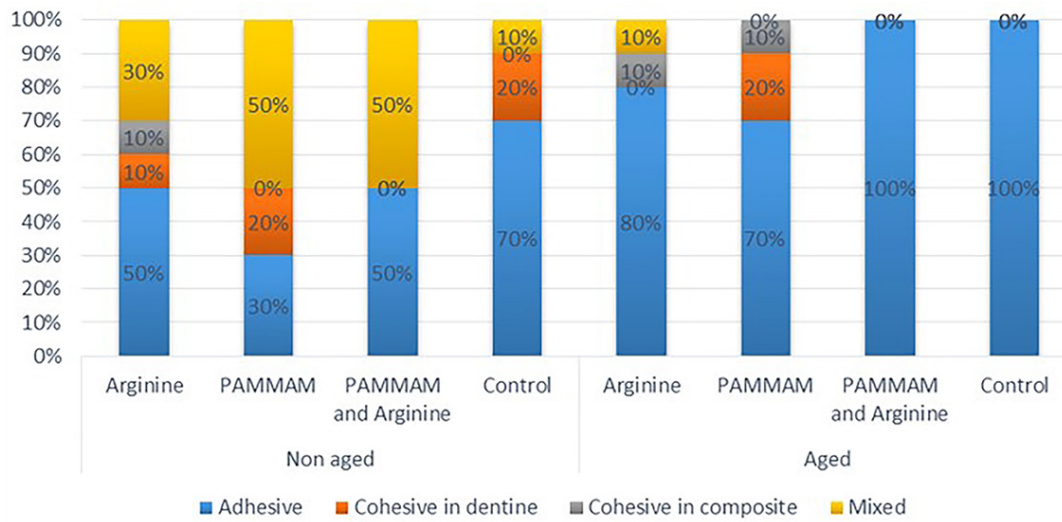


Figure 1: Stacked bar chart showing failure mode distribution.

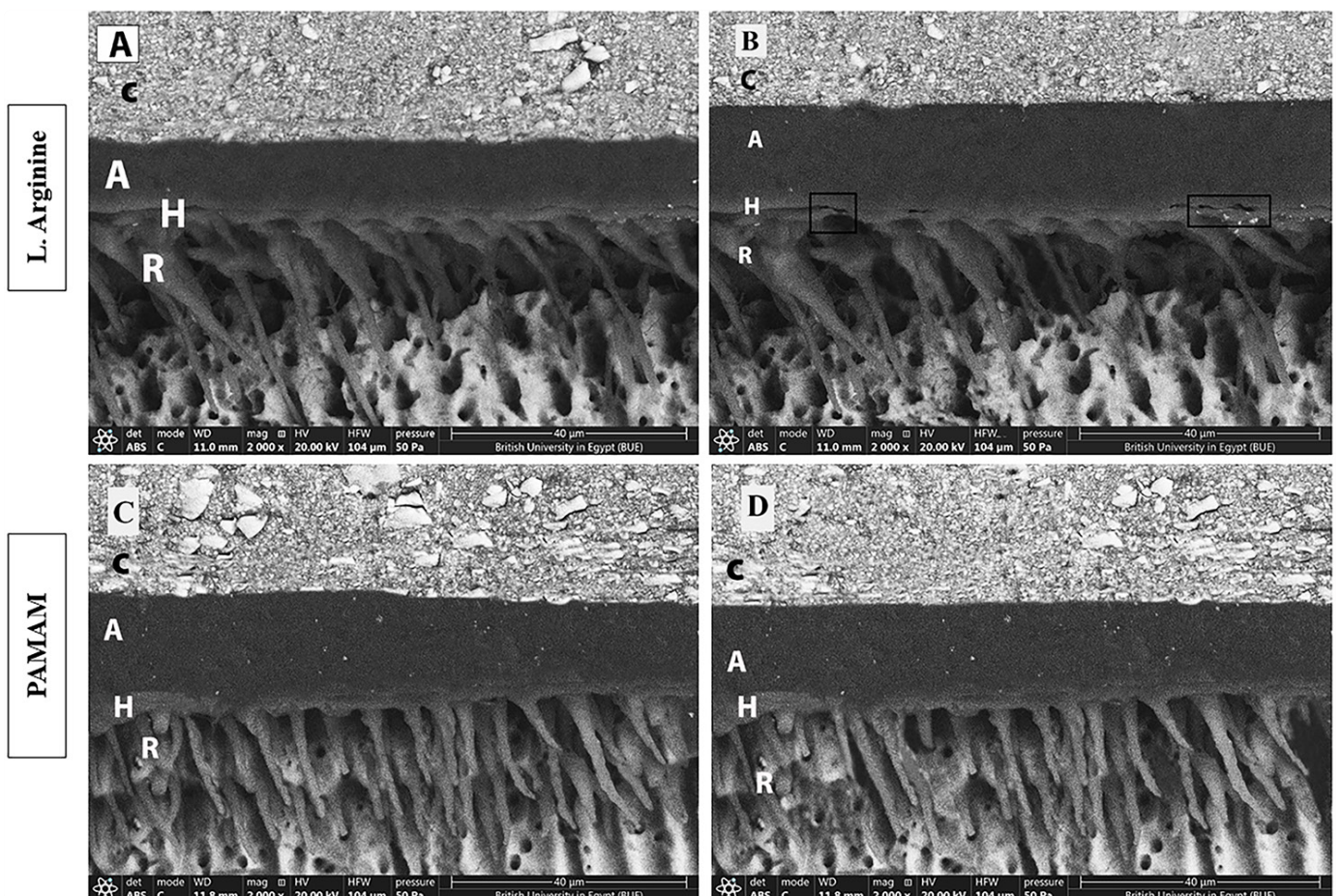


Figure 2: Representative SEM images at magnification 2000X of the resin-dentin interface of the different groups. The images (A and C) represent specimens before thermocycling while (B and D) images represent specimen after thermocycling aging. Abbreviations: A= adhesive layer; c=resin composite; H= hybrid layer; R= resin tags. Black rectangles represent areas of separation of the hybrid layer Black rectangle indicates areas of hybrid layer separation.

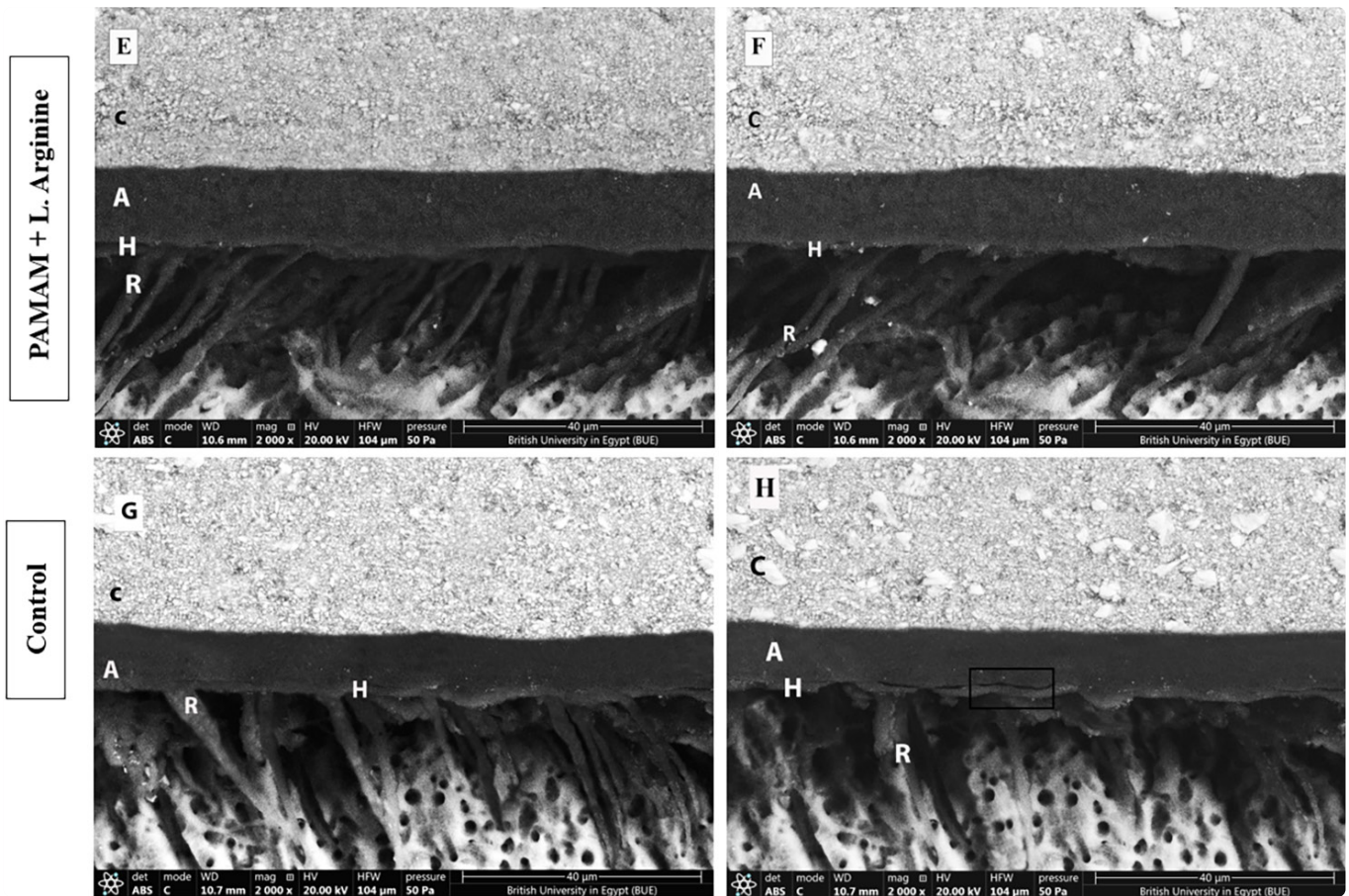


Figure 3: Representative SEM images at magnification 2000X of the resin-dentin interface of the different groups. The images (E and G) represent specimens before thermocycling while (F and H) images represent specimen after thermocycling aging. Abbreviations: A= adhesive layer; c=resin composite; H= hybrid layer; R= resin tags. Black rectangles represent areas of separation of the hybrid layer Black rectangle indicates areas of hybrid layer separation.

DISCUSSION

Based on the results of the present study, the null hypotheses tested was partially rejected, as demineralized dentin pretreatment using PAMAM-NH₂ and L.arg impacted the μ TBS immediately but without a significant difference while following thermo-cycling aging, PAMAM-NH₂ significantly enhanced the bond strength with preservation of the adhesive interface.

The longevity of the directly applied restorations is compromised by adhesion and hybrid layer deterioration, which are primarily triggered through the dissolution of the resin composite and degradation of the interacting collagen fibrils alongside the adhesive system. Disintegration of these collagen fibrils occurs via the stimulation of cysteine cathepsins and MMPs, along with microleakages in the restoration, which are mostly induced by mechanical and hydraulic fatigue^{2,20}. Nowadays, researchers are concentrating on implementing various surface treatments that either promote a reduction in hybrid layer degradation or an increase in adhesion²¹. One basic amino acid is arginine, which is stable in aqueous solutions and able to alkalinize the local pH via the process outlined by Gupta *et al.*²². Because arginine attracts negatively charged dentin, it helps in the precipitation of phosphate and calcium at the entry

of dentinal tubules that are found in saliva and toothpaste. On the other side, PAMAM-NH₂ dendrimer is classified as one kind of hyperbranched polymeric macromolecule exhibiting a substantial attraction for the denuded dentin collagen²³.

Therefore, it is hypothesized that PAMAM-NH₂ could firmly adsorb on exposed collagen fibrils, resulting in an adequately sustainable antimicrobial action as well as enhancing the production of needle-like crystals in the dentinal tubules and across the dentin surface when applied to acid-etched dentin as a cavity cleanser. The regenerated minerals possess excellent potential to withstand acid challenges²⁴. Further investigations are required to boost the durability of the composite-dentin bond, reinforce tooth structure using this technique, assess remineralization in clinically applicable situations, and inhibit caries in patients with saliva reduction²⁵. So, this investigation aimed to analyze the impact of demineralized dentin pretreatment using 8% (L.arg), (G3-PAMAM-NH₂), and their combination on microtensile bond strength (μ TBS) and resin-dentin micromorphology.

Regarding the μ TBS results of the present study, PAMAM-pretreated dentin specimens (group 2) exhibited the highest bond strength mean values compared to the other groups. These findings were consistent with a recent investigation in which

bond strength results indicated that dentin pretreatment with PAMAM did not reduce immediate tensile bond strength¹⁴. Furthermore, these findings were aligned with another study²⁶, which hypothesized that several anionic amide groups in PAMAM could bind to collagen fibrils via electrostatic interaction, contributing to its adsorption potential.

In the current investigation, resin-dentin μ TBS was improved upon pretreatment with an 8% L. arg solution. Previous studies^{27,28} concluded that the μ TBS of the two self-etching bonding systems to dentin was not affected following treatment with 8.0% arginine. Furthermore, when G-Bond was employed after applying the 8.0% arginine solution, there was a considerable improvement in microtensile bond strength, which correlated with the application duration of the desensitizing paste. Additionally, Aguiar *et al.*²⁹ reported that prolonged use of traditional or arginine-calcium carbonate toothpaste had no consequences on dentin bond strength after a two-step self-etch adhesive was employed while improving the stiffness and rigidity of the dentin. Another study found that desensitizing toothpaste with arginine did not interfere with dentin adhesion¹⁰.

This was in contradiction with another study¹⁶ that demonstrated that at acidic pH levels, arginine is an unstable and soluble molecule. Self-etching adhesives have a low pH and using them after pretreating the dentin surface with 8% arginine could cause the precipitate that forms when the arginine interacts with the dental substrate to dissolve. This would weaken the bond strength of these adhesive systems. Although bond strength wasn't affected when three-step (etch and rinse) adhesive was associated with arginine, these findings suggest that arginine may be used in conjunction with three-step (etch and rinse) adhesives.

In this study, the bond strength decreased in the combined (PAMAM+ L.arg) pretreated group. This could be explained by the penetration of PAMAM and then L .arg through the exposed tubules and their precipitation across the dentin surfaces, which might weaken the succeeding etching process of All Bond adhesives and hinder the establishment of an adequate hybrid layer and resin tags. This could be due to variations in the adhesive's etching ability, which has a mild acidity of 3.2. According to the bonding process, an adequate resin-dentin bond is dependent on the resin monomers' potential to produce micromechanical integration through the developed dentin porosities⁹. This could be related to the high specific surface area of PAMAM and L.arg, which are difficult to prime with adhesives. The outcomes of this study were assisted by the failure mode pattern distribution illustrated in (Figure 1). Generally, there is an association between low bond strength values and a high adhesive failure tendency. The majority of investigated specimens exhibited mixed failures (M) as their primary mode of failure, with a minor occurrence of cohesive failures (CC or CD).

The study's findings after thermocycling showed that all groups' microtensile bond strengths had completely declined. However, the PAMAM group's bond strength was considerably higher than that of all other groups, suggesting that PAMAM pretreatment extended the resin-dentin bonds. This finding was supported by previous study results, which demonstrated that PAMAM exhibits its anti-proteolytic activity and inhibits the enzymatic disintegration of exposed collagen fibrils inside the hybrid layers, thereby improving the stability of resin-dentin bonds¹⁴.

Considering the findings of the SEM images for resin dentin bond interface analysis (Figure 2), specimens pretreated with L.arg (group 1) revealed a uniform hybrid layer and numerous, well-defined resin tags. This finding was in accordance with another study¹⁶, which confirmed the preservation of the intertubular dentin following treatment with L.arg. possibly due to the reaction of the arginine with the collagen fibrils or dentin.

Comparatively, the SEM images of PAMAM pretreatment specimens (group 2) revealed a homogeneous, thick hybrid layer with abundant resin tags, as supported by a previous study¹³, which revealed that the resin tags displayed morphological consistency in both the PAMAM group and the control group. The permeability quantitative analysis also, revealed that using PAMAM-NH₂ as a cavity cleanser didn't reduce adhesive monomer penetration.

From the limitations of the study; the assessment of the mineral content using EDX analysis, evaluation of endogenous enzymatic activity level utilizing in situ zymography. Also, clinical trials are further needed for evaluation of these tested modalities in clinically applicable situations.

CONCLUSIONS

Under the current study's limitations, PAMAM-NH₂ pretreatment possessed a favorable impact on the adhesion process and the dentin- resin bonding durability. Arginine pretreatment had no adverse influence on the bonding of an immediately loaded resin composite.

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