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Effect of Galardin as Matrix Metaloproteinase Inhibitor on the Dentin Bonding Durability of Old and Current Generations of Adhesive Systems

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A B S T R A C T

Objectives: This study aimed to evaluate the effect of Galardin as a specific matrix metalloproteinase (MMP) inhibitor on dentin bonding durability of different generations of adhesive systems.

Materials and Methods: An in vitro study was performed on 32 extracted sound human molars. The occlusal enamel was removed prior to random assignment of the teeth into 8 groups by adhesive type and application/no application of Galardin. Each group was subdivided into 2 subgroups with/without aging. Adhesives were applied after the application of Galardin in the respective groups according to the manufacturer's instructions, and composite resin was incrementally built up to a height of 6mm. After performing the aging protocols for the respective subgroups, the teeth were sectioned into bar-shaped samples with a cross-sectional area of 1mm^2. The micro-tensile band strength (μTBS) test was then performed. Data were analyzed by three-way ANOVA, Bonferroni and Games-Howell post-hoc tests, and Chi-square test (alpha=0.05).

Results: The type of adhesive system, aging, and Galardin application had statistically significant effects on μTBS (P<0.001). Application of Galardin increased the μTBS (P<0.001) while aging decreased it (P<0.001). The interaction effect of aging and type of adhesive system on μTBS was also statistically significant (P<0.001). The other two-way and three-way interaction effects were not statistically significant (P>0.05).

Conclusion: Application of Galardin increased the μTBS values both immediately and after 6 months irrespective of the adhesive system type. Aging significantly decreased the μTBS. Type of adhesive also significantly affected the μTBS.

Keywords: Dental Bonding; Matrix Metalloproteinase Inhibitors; N-(2(R)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl)-L-tryptophan methylamide

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INTRODUCTION

Dentin bonding can be performed by using an etch-and-rinse (ER) or self-etch (SE) adhesive. Both methods have the same basic problem, which is the need to create a pathway for the adhesive resin to flow into the collagen-rich

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connective tissue. Neither ER nor SE adhesives can completely penetrate into the dentinal collagen fibrils, which means that collagen fibrils that are exposed to moisture are still present at the deepest level of the hybrid layer. In demineralized dentin, endogenous proteases, including matrix metalloproteinases (MMPs) are reactivated and can hydrolyze collagen fibers in the presence of water. The stability of adhesive bonding to dentin reduces following the degradation of collagen fibers by MMPs [1]. Thus, inhibition of MMPs might be the key to solve this problem.

MMPs are endogenously active zinc- and calcium-dependent proteolytic enzymes capable of degrading all components of the extracellular matrix. MMP-2, MMP-8 and MMP-9 are the primary MMPs responsible for the degradation of the dentin collagen matrix [2]. The endogenous dentin MMPs are inactive and can be activated by pH change in the process of caries development or bonding procedures [2,3]. There have been several natural and synthetic MMP inhibitors tested on dentin to increase the stability and longevity of the hybrid layer [4-6]. The collagenolytic/gelatinolytic activity of the human dentin matrix has already been found to be inhibited by non-specific protease inhibitors such as chlorhexidine digluconate (CHX) at 0.2% and 2% concentrations [7-9]. The inhibitory effect of CHX has been useful in preservation of the hybrid layer for long-term under in vivo and in vitro conditions [4, 6]. However, since CHX as an anti-proteolytic agent available as a mouthwash and oral antiseptic is very convenient for preventing the degradation of dentine matrix, it may be hypothesized that a MMP inhibitor acting at a much lower concentration will be equally effective or more effective than CHX [10]. Galardin, also known as GM6001 or Ilomastat is one such specific inhibitor that has been shown to be an inhibitor for MMP-2, MMP-3, MMP-8 and MMP-9 [11]. It has a collagen-like structure to interact at the active site of MMPs and contains a hydroxamate structure (R-CO-NH-OH) which chelates with the zinc ion present in the active site of MMPs [12]. Almahdy et al. [13] reported a significant increase in immediate bond strength to dentin after incorporation of Galardin in the chemical formulation of bonding agents. However, Breschi et al. [10] revealed that cleaning dentin with Galardin did not influence the immediate bond strength, and induced a 27% reduction in bond strength after one year of aging, which was remarkably lower than the reduction in the control group which was 45%. Search of the literature by the authors revealed no study investigating the influence of Galardin on durability of dentin bond in use of new generations of adhesive systems. Thus, this study was conducted to investigate the influence of Galardin on dentin bond durability in use of different generations of adhesive systems.

MATERIALS AND METHODS

This in vitro study evaluated 32 impacted third molars after obtaining ethical approval from the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.VCR.REC.1400.253). The teeth had been extracted for reasons not related to this study. After a visual examination, only teeth with no caries, fracture, and cracks were selected for the study. The teeth were immersed in 0.5% chloramine T solution. The occlusal enamel was cut under running water and dentin surfaces were ground by using 600-grit silicon carbide abrasive papers under copious water irrigation for 30 seconds. Then, the samples were randomly divided into 8 groups (n=4) based on the type of adhesive system and the application or no application of Galardin as follows:

-*Group 1:* Single Bond (SB; 3M ESPE, St. Paul, MN, USA)
-*Group 2:* Galardin+SB
-*Group 3:* Clearfil SE Bond (CSE; Kuraray Noritake Dental Inc., Tokyo, Japan)
-*Group 4:* Galardin+CSE
-*Group 5:* All-Bond Universal (ALB; Bisco Inc., Schaumburg, IL, USA) applied in ER mode (ALB-ER)
-*Group 6:* Galardin+ALB-ER
-*Group 7:* ALB applied in SE mode (ALB-SE)
-*Group 8:* Galardin+ALB-SE

A 5mol Galardin solution was prepared by mixing purchased powder (Sigma-Aldrich Company Ltd., Dorset, UK) of Galardin with

dimethyl sulfoxide (DMSO; Duksun, Seoul, Korea) as solvent. The Galardin solution was not added to the chemical components of the adhesives system, meaning it was not mixed with them. It was used as an additional irrigant after rinsing the etchant in the ER systems and before application of SE systems. Following the manufacturer's instruction for application (Table 1), composite resin build-ups were completed with Valux Plus (3M ESPE, St Paul, MN, USA) composite resin up to a height of 6 mm incrementally. Each layer was cured with Litex LED light curing device (Dentamerica Inc., City of Industry, CA, USA) under a light intensity of 1000mW/cm2 for 30 seconds. All the samples were stored in distilled water for 24 hours at 37°C and then thermocycled for 500 cycles (between 5 and 55°C). The samples in each group were then further randomly divided into two subgroups (n=2) depending on the aging strategy (water storage for 24 hours versus thermocycling). The second subgroup samples were additionally thermocycled for 5000 cycles (between 5 and 55°C). Once completed, samples were cut into bar-shaped pieces with a cross-section of 1mm^2 using a digitally controlled saw. Each tooth provided 8 samples. The μTBS was measured by a tensile tester (Bisco, Schaumburg, IL, USA) at a speed of 0.5mm/min. The fracture mode of the samples was determined under a stereomicroscope (SMZ800, Nikon, Tokyo, Japan) at x10 magnification.

-*Type I:* Cohesive failure in dentin
-*Type II*: Cohesive failure in composite block
-*Type III:* Adhesive failure
-*Type IV:* Mixed failure

Data analysis:

The normality of data distribution was confirmed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The potential differences among the study groups/subgroups were assessed using three-way ANOVA; post-hoc testing was performed using Bonferroni or Games-Howell test wherever significant

Table 1. Composition, manufacturer and utilization strategy of adhesive systems

Bond used		Method	Composition
Single Bond (3M ESPE, St. Paul, MN, USA)		37% phosphoric acid is applied on the dentin surface for 15 seconds. After washing with water, the dentin surface is dried so that it remains moist. Galardin solution (in the respective groups) is applied on the samples for 60 seconds. Next, 1-2 layers of the bonding agent are applied on the surface and rubbed for 5 to 10 seconds. Then, the surface is air sprayed at a distance of 5 cm for 5 seconds until no movement of the substance is observed. Finally, the surface should become shiny. Then, light curing is performed for 10 seconds.	BisGMA, HEMA dimethacrylates ethanol water photoinitiator a methacrylate copolymer of polyacrylic and polyitaconic acids
All-bond Universal (Bisco, USA)	Etch & Rinse	Etch :37% phosphoric acid is applied on the dentin surface for 15 seconds. After washing with water, the dentin surface is dried so that it remains moist. Adhesive: Galardin solution (in the respective groups) is applied on the samples for 60 seconds. Two layers of bonding agent are applied on the surface and rubbed for 10 to 15 seconds. Air spray is used for 10 seconds until the movement of the adhesive is not visible on the surface. The surface should have a glossy appearance. Finally, light curing is performed for 10 seconds.	Etchant Uni-Etch: 32% phosphoric acid, benzalkonium chloride Adhesive: MDP phosphate monomer Bis-GMA HEMA Ethanol Water Initiators
	Self-etch	Same as adhesive in Etch & Rinse system.No phosphoric-acid etching is performed.	Same adhesive composition as in the Etch-and-Rinse

Bis-GMA, bisphenol A-glycidyl methacrylate; HEMA, 2-hydroxyethyl methacrylate; 10-MDP, 10-methacryloyloxydecyl dihydrogen phosphate.

differences were found. The Chi-square test was used to determine if there was a significant association between the fracture mode of the samples and types of adhesive utilized. P<0.05 was considered statistically significant. Statistical tests were performed using SPSS version 24 (SPSS Inc., IL, USA).

RESULTS

μTBS:

Table 2 presents the mean μTBS values in the study groups. The results of three-way ANOVA showed that the type of adhesive system had a significant effect on μTBS (P<0.001). The μTBS was the highest in ABU-ER and the lowest in ABU-SE. Based on the Bonferroni post-hoc test, the difference in μTBS between the CSE and ABU-ER was not statistically significant (P=0.99), while the mean difference between other adhesive pairs was statistically significant (P<0.05; Fig. 1 and 2).

The effect of aging on μTBS was statistically significant (P<0.001). The effect of Galardin on μTBS was statistically significant as well (P<0.001). The interaction effect of adhesive type and aging was statistically significant as well (P<0.001). Pairwise comparisons by the Games-Howell post-hoc test showed that at 24 hours and also after thermocycling, there were statistically significant differences among the adhesive systems in μTBS. These differences are further reported in Table 3. In other cases, the interaction effect between the variables was not statistically significant (P>0.05).

Failure mode:

Figure 3 illustrates the failure modes. The Chi-square test showed that there was no statistically significant relationship between fracture mode and adhesive type (P=0.07). ABU-SE exhibited the highest frequency of adhesive failure, while ABU-ER dominantly demonstrated both mixed and cohesive failures. Following aging, an increase was observed in the frequency of adhesive failures and a corresponding decrease in other types of failure modes.

DISCUSSION

Some specific MMP inhibitors have been used for application prior to bonding the dentin in order to reduce degradation of collagen fibers or reduce the degree of degradation, and to increase the μTBS in the long term [10, 13].

Table 2. Mean μTBS values (MPa) in the study groups (n=16)

Adhesive	Galardin	Time	Microtensile bond strength (MPa)
Single Bond	Without Galardin	24h	60.19±10.75
		Aging	45.63±6.4
	With Galardin	24h	64.03±9.13
		Aging	48.75±8.37
Clearfil SE Bond	Without Galardin	24h	77.63±11.58
		Aging	46.03±9.92
	With Galardin	24h	84.25±11.81
		Aging	54.78±10.59
All-Bond Universal (Etch-and-Rinse)	Without Galardin	24h	68.72±8.72
		Aging	58.5±7.96
	With Galardin	24h	75.13±10.53
		Aging	66.41±7.26
All-Bond Universal (Self-etch)	Without Galardin	24h	49.66±7.32
		Aging	35.44±6.94
	With Galardin	24h	54.41±7.97
		Aging	39.19±5.81

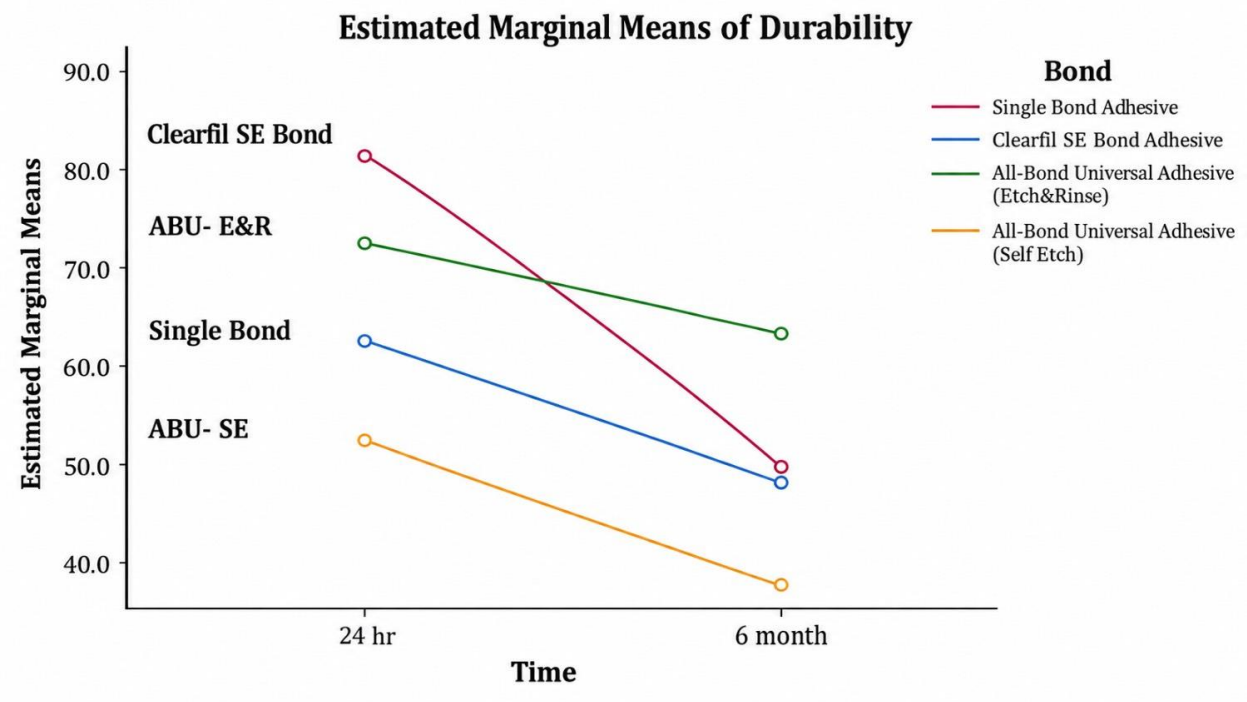


Fig 1. Trend of change in μTBS (MPa) based on the type of adhesive system over time.

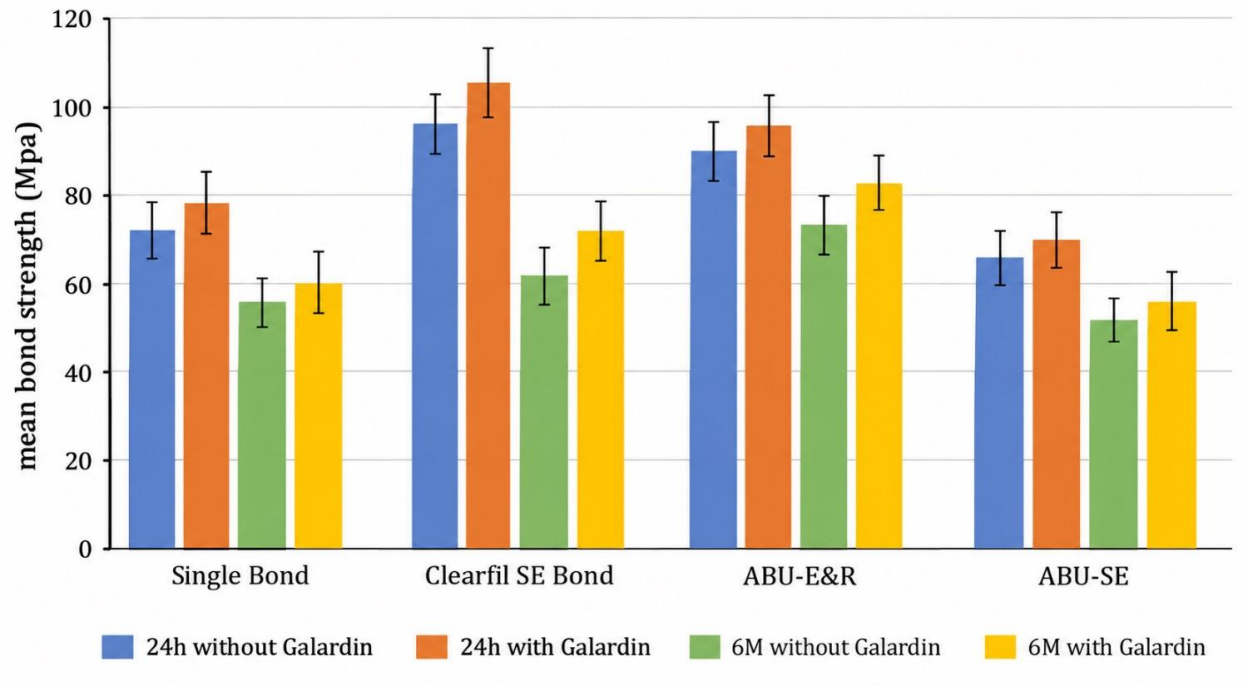


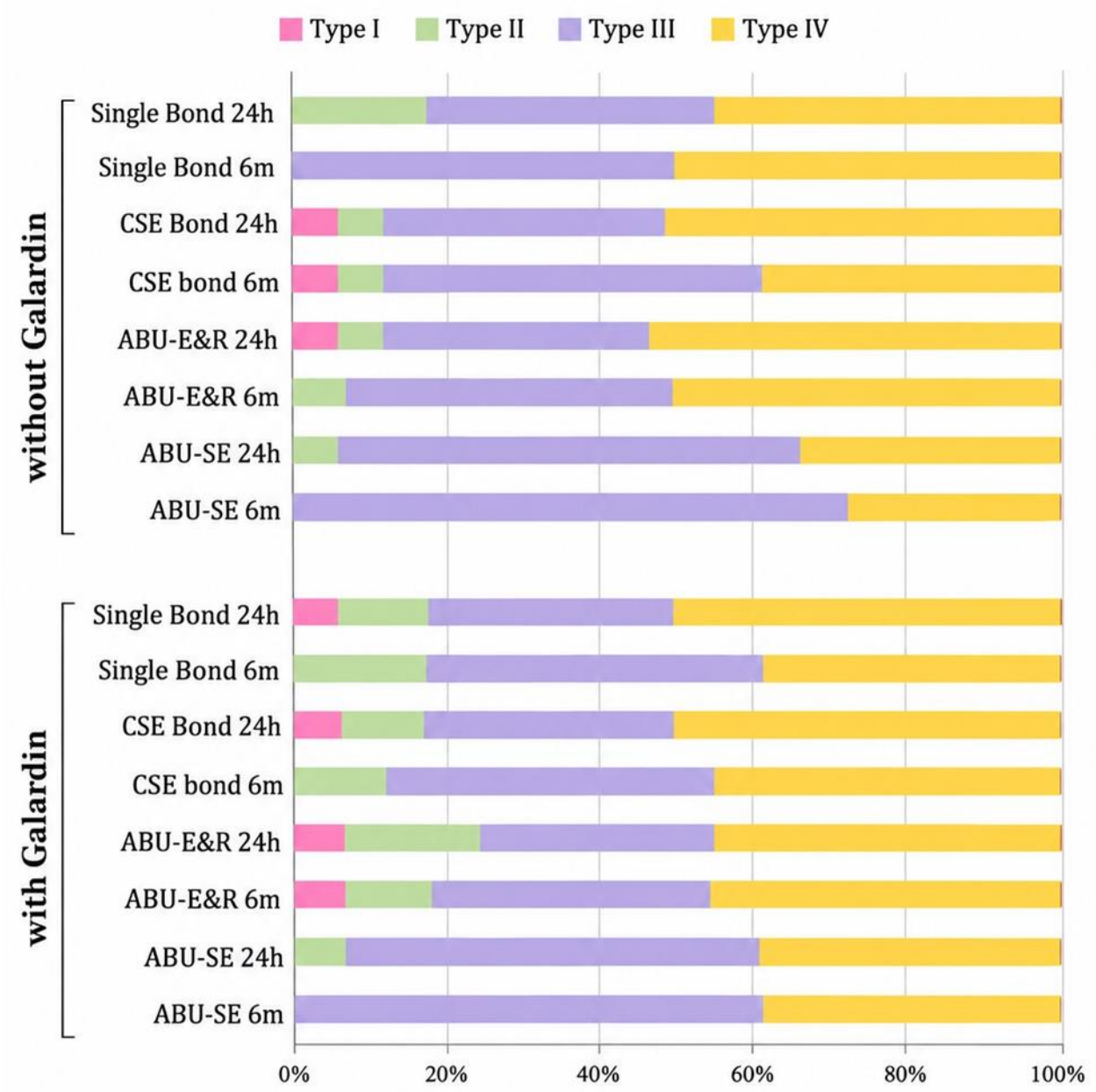
Fig 2. μTBS based on aging and Galardin application.

This study evaluated the effect of a synthetic MMP inhibitor (Galardin) on the durability of dentin bond of various generations of adhesive systems. The null hypothesis of the present study was that Galardin would have no significant effect on the immediate and long-term μTBS of various generations of adhesive systems to dentin, which was rejected. In fact, the results showed that application of Galardin as irrigant on dentin

Table 3. Pairwise comparisons of the bonding agents regarding μTBS (MPa) using the Games-Howell test

(I) Bonding agent	(J) Bonding agent	24 Hours		Aging	
		Mean Difference (I-J)	P-value	Mean Difference (I-J)	P-value
Single Bond	Clearfil SE Bond	-18.83	<0.001	-3.22	0.526
	All-Bond Universal (Etch-and-Rinse)	-9.81	0.001	-15.26	<0.001
	All-Bond Universal (Self-etch)	10.08	<0.001	9.87	<0.001
Clearfil SE Bond	All-Bond Universal (Etch-and-Rinse)	9.01	0.010	-12.05	<0.001
	All-Bond Universal (Self-etch)	28.91	<0.001	13.09	<0.001
All-Bond Universal (Etch-and-Rinse)	All-Bond Universal (self-etch)	19.89	<0.001	25.14	<0.001

increased the μTBS both in the short term (24 hours) and after aging. Thus, irrespective of adhesive type, application of Galardin was associated with fewer adhesive failures and a higher proportion of mixed/cohesive failures, consistent with the increase in μTBS observed with Galardin use. Breschi et al. [10] indicated that when ER adhesives were stored for one year, application of Galardin prevented bond degradation without any positive or negative influence on immediate bond strength. The difference in immediate TBS values in the two studies is likely due to the solvent used for the preparation of the Galardin solution. They prepared the Galardin solution using water while we used DMSO which is a specific solvent for Galardin. DMSO contains methyl and sulfur groups and is a good solvent for numerous chemicals. It has low vapor pressure and the capacity to accept hydrogen bonds. Moreover, oxygen in DMSO has a highly negative charge; thus, negatively charged DMSO ions can react with positively charged calcium ions and result in formation of high-energy ionic bonds [14]. Also, the surface free energy of DMSO is very high. Dillingham and Oakley [15] indicated that the wettability of DMSO was highly similar to the adhesive system, so the surface energy of DMSO might be one of the reasons why DMSO can have high surface wettability to form a strong bond to the tooth surface. In addition, Almahdy et al. [13] showed that incorporation of Galardin into the formulation of adhesives like Opti-Bond FL and G-Bond resulted in high values of immediate dentin bond strength, agreeing with our results. On the other hand, Ebrahimi et al. [16] showed that Galardin in low and high concentrations (0.2 and 5mol) dissolved in DMSO resulted in an increase in shear bond strength of resin cement to dentin and the value of shear bond strength had a direct correlation with Galardin concentration. Galardin contains an alcohol group in its structure, and alcohols are known to be able to decrease the diameter of collagen fibers, resulting in an increase in inter-fibrillar spaces in the hybrid layer and enhancing the infiltration of resin monomers. In the present study, the TBS was a function of the adhesive type, such that TBS was the highest in ABU-ER and the lowest in ABU-SE. In failure mode analysis, the frequency of adhesive failures was the highest in ABU-SE and the lowest in other adhesives. In contrast, ABU-ER showed the lowest frequency of adhesive failure and the highest frequency of cohesive/mixed failure. This finding was in agreement with the TBS values. Similarly, Muñoz et al. [17] found that the bond strength of ABU-SE was lower than that of ABU-ER; they also showed that all other SE-based adhesives had lower bond



	with Galardin								without Galardin							
	ABU-SE 24h	ABU-SE 6m	ABU-E&R 24h	ABU-E&R 6m	CSE bond 24h	CSE bond 6m	Single Bond 24h	Single Bond 6m	ABU-SE 24h	ABU-SE 6m	ABU-E&R 24h	ABU-E&R 6m	CSE bond 24h	CSE bond 6m	Single Bond 24h	Single Bond 6m
Type I	0	0	6.2	6.2	6.2	6.2	6.2	6.2	0	0	6.2	6.2	6.2	6.2	0	0
Type II	0	6.2	12.5	18.7	12.5	12.5	18.7	12.5	0	6.2	6.2	6.2	6.2	6.2	0	18.7
Type III	62.5	56.2	37.5	31.2	43.7	31.2	43.7	31.2	75	62.5	43.7	37.5	50	37.5	50	37.5
Type IV	37.5	37.5	43.7	43.7	43.7	50	37.5	50	25	31.2	50	55	37.5	50	50	43.7

Fig 3. Failure modes based on aging and Galardin application.

strength values than ABU-SE due to their mild pH. According to a meta-analysis performed by Rosa et al. [18] there was no difference in bond strength of ER versus SE systems when comparing mild universal adhesive systems. However, the bond strength in ER mode was greater than SE mode when using ultra-mild ABU adhesive system. Thus, ABU is the only universal adhesive to demonstrate lower bond strength in the SE than ER mode. It is believed that the smear layer actually provides a physical blockage that would impede penetration and complete and intimate merging of resin and hybrid layer formation in dentin. In the ER strategy, the smear layer is removed and the surface layer of dentin is demineralized which increases the penetration of adhesive into the demineralized surface layer, resulting in formation of a more properly impregnated hybrid layer [17]. Despite that, Wagner et al. [19] concluded that the ABU-SE does not result in significantly different TBS to dentin than ABU-ER, but in using the ER strategy, they did note longer resin tags and thicker hybrid layer. They proposed that variations in the reported results could be due to the active application technique of the adhesive. In addition, in the present study, CSE had a greater TBS than SB, which is consistent with the finding of Armstrong et al. [20] who found a lower bond strength to dentin for SB than for CSE. Another noteworthy finding of this study was that aging by 5000 thermal cycles increased the μTBS of the adhesives which was in accordance with earlier studies [21, 22]. Again, analysis of the failure modes showed that the frequency of adhesive failure increased in the aged group. The frequency of other failure modes decreased, which may indicate a reduction in μTBS of the adhesives. In this study, 5000 thermal cycles were applied which roughly correspond to 6 months of aging [23]. The aging effect resulting from thermocycling is attributed to the ability of hot water to promote the hydrolysis of unprotected collagen, to wash away incompletely polymerized resin monomers, and to apply cyclic tensile and compression stresses to the interface [24]. Besides, a void can be formed at the interface during the thermocycling process as a result of mismatch between the coefficient of thermal expansion of the adhesives and dentin; and consequently, water sorption and plasticization of the adhesive increase [25]. In the present study, the μTBS decreased in all the tested generations of adhesive systems due to thermocycling. The greatest decrease in μTBS was in CSE while the lowest decrease was observed in ABU-ER. Deng et al. [22] also found significant interaction effect of aging and adhesive type. Some others reported significantly lower values of bond strength for CSE compared to an ER system after 6 months of aging by thermocycling [21, 26]. Conversely, Sai et al. [27] demonstrated that the bond strength of universal adhesives such as ABU was lower than CSE but also showed higher stability of the bond after aging. The bond strength of 3-step ER and 2-step SE adhesive systems did not significantly decrease after one and six months in the present study; however, in the study by Armstrong et al. [20] the bond strength of both adhesive systems significantly decreased 15 months after bonding. It should be noted that due to the in vitro design of this study, there were some certain clinical factors that could not be simulated such as the effect of fluid flow through dentinal tubules, intrapulpal pressure, saliva, and influence of masticatory forces that could not be analyzed. Thus, further studies are recommended under conditions much closer to the clinical environment. Most importantly, it would be pertinent to analyze certain other factors such as biocompatibility and degree of conversion of bonding agents and their microleakage after the application of Galardin. Application of Galardin at varying concentrations with alternative viable solvents should be carried out along with an analysis of other MMP inhibitors.

CONCLUSION

Considering the above-mentioned limitations, it could be concluded that applying Galardin, regardless of the generation of adhesive, increased the immediate and 6-month μTBS to dentin. Furthermore, μTBS had a significant

correlation with the type of adhesive system, such that ABU-ER and CSE produced higher and ABU-SE produced the lowest μTBS. After aging, the μTBS decreased and CSE experienced the greatest reduction after aging.

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CONFLICT OF INTEREST STATEMENT

None declared.

GENERATIVE AI IN SCIENTIFIC WRITING

None declared.

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