SVOA Dentistry

e-ISSN 2753-9172

ScienceVolks Open Access

Research Article

Evaluating the Effect of Matrix Metalloproteinase (MMP) Inhibitors on the Bond Strength of Dentin Bonding Agent – In Vitro Study

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https://doi.org/10.58624/SVOADE.2026.07.036

Received: July 09, 2026

Published: September 15, 2026

Citation: Adalsaniya R, Panda A, Jadeja T, Doshi Y. Evaluating the Effect of Matrix Metalloproteinase (MMP) Inhibitors on the Bond Strength of Dentin Bonding Agent – In Vitro Study. *SVOA Dentistry* 2026, 7:5, 286-295. doi: 10.58624/SVOADE.2026.07.036

Abstract

Background: Degradation of the resin–dentin hybrid layer remains a major challenge affecting the longevity of adhesive restorations, particularly in primary teeth. Activation of endogenous matrix metalloproteinases (MMPs) during acid etching leads to collagen breakdown and reduced bond durability. The use of MMP inhibitors as dentin biomodifiers has been proposed to improve adhesive performance.

Aim: To evaluate and compare the effect of different MMP inhibitors on the shear bond strength (SBS) of dentin bonding agents in primary teeth.

Materials and Methods: Eighty extracted sound human primary posterior teeth were randomly divided into four groups (n=20): Group I – 2% chlorhexidine, Group II – 17% EDTA, Group III – 2% minocycline, and Group IV – control (0.01 M phosphate-buffered saline). After standardized dentin preparation and acid etching with 37% phosphoric acid, the respective MMP inhibitors were applied for 60 seconds. Adhesive application and composite build-up were performed using a standardized protocol. Specimens were stored in artificial saliva at 37°C for 48 hours and subjected to shear bond strength testing using a universal testing machine. Data were analyzed using one-way ANOVA and Tukey post hoc test.

Results: Statistically significant differences were observed among all groups ($p < 0.001$). The highest mean SBS was recorded in the chlorhexidine group (11.56 ± 0.37 MPa), followed by minocycline (10.25 ± 0.32 MPa), EDTA (9.31 ± 0.54 MPa), and control (4.49 ± 0.28 MPa). All MMP inhibitor groups demonstrated significantly higher SBS than the control group.

Conclusion: Application of MMP inhibitors significantly enhances the shear bond strength of dentin bonding agents in primary dentin. Among the tested agents, 2% chlorhexidine showed the most effective improvement, suggesting its potential clinical use for improving the durability of adhesive restorations in primary teeth.

Keywords: *Matrix metalloproteinases; MMP inhibitors; Chlorhexidine; Minocycline; EDTA; Shear bond strength; Dentin bonding agent; Primary teeth; Adhesive restorations; Dentin biomodification.*

Introduction

Contemporary restorative dentistry focuses on minimally invasive treatment approaches, supported by significant advancements in adhesive technologies and tooth-coloured restorative materials. There has been a paradigm shift toward the preservation and repair of existing restorations rather than complete replacement, which has increased the clinical reliance on adhesive procedures in routine dental practice.[1]

The foundation of modern adhesive dentistry was established in 1955 when Buonocore demonstrated that acid etching of enamel enhances bonding by creating a roughened surface for micromechanical retention.[2] Currently, phosphoric acid etchants (30–40%) are routinely used to achieve predictable adhesion and effective marginal sealing in resin-based restorative procedures.[3]

In contrast to enamel, bonding to dentin is considerably more complex due to its heterogeneous composition, higher organic content, and intrinsic moisture. Dentin consists of approximately 30% organic matrix, primarily collagen, and about 20% water by volume, which complicates resin infiltration and polymerization. [1,4] Adhesion to dentin is based on the formation of a hybrid layer, which is created by infiltration of resin monomers into the demineralized collagen network, followed by in situ polymerization. [4,5]

The hybrid layer serves as the fundamental basis of resin–dentin bonding and plays a crucial role in determining bond strength and durability. Ideally, it should exhibit uniform resin penetration, optimal thickness, and the formation of resin tags extending into dentinal tubules to enhance micromechanical retention. However, discrepancies between the depth of demineralization and resin infiltration may result in exposed collagen fibrils that are not adequately protected by resin. These unsupported fibrils are susceptible to hydrolytic and enzymatic degradation over time, compromising the integrity of the bond. [6,7]

Furthermore, the hybrid layer behaves as a semi-permeable membrane due to the presence of residual water and hydrophilic resin components, making it prone to water sorption and nanoleakage. This leads to fluid movement across the interface, accelerating degradation and reducing the longevity of restorations. [6,8]

A major factor contributing to hybrid layer degradation is the activation of endogenous proteolytic enzymes, particularly matrix metalloproteinases (MMPs), during acid etching. These zinc- and calcium-dependent endopeptidases, including MMP-2, MMP-3, MMP-8, and MMP-9, are present in dentin and become activated when the collagen matrix is exposed. If resin infiltration is incomplete, these enzymes progressively degrade collagen fibrils, weakening the resin–dentin interface and leading to bond failure. [7,8]

To address this limitation, dentin biomodifiers have been introduced to enhance the stability of the hybrid layer. These include both synthetic agents, such as chlorhexidine, EDTA, tetracyclines, and carbodiimide, and natural compounds such as proanthocyanidins and flavonoids. These agents function by inhibiting MMP activity, stabilizing collagen, and improving resin infiltration, thereby enhancing the durability of the resin–dentin bond. [9]

Among these, MMP inhibitors have gained considerable attention due to their ability to preserve hybrid layer integrity. Chlorhexidine is widely studied for its strong MMP inhibitory activity and substantivity, which helps maintain bond strength over time. [6,10] EDTA acts as a chelating agent that removes the smear layer and inhibits MMP activity by binding essential metal ions. [7,11] Minocycline, a semisynthetic tetracycline derivative, inhibits MMP activity through both chelation and non-antimicrobial mechanisms, and also provides antiinflammatory and antioxidant benefits that contribute to stabilization of the dentin matrix. [11,12]

Although these biomodifiers have shown promising outcomes in permanent dentin, limited data are available regarding their effectiveness in primary dentin. Primary teeth differ structurally, exhibiting lower mineral content, higher organic composition, increased permeability, and wider dentinal tubules. These characteristics may negatively influence bonding performance and reduce restoration longevity. [13,14]

Furthermore, most existing studies have focused on individual MMP inhibitors or short-term outcomes, with limited comparative evaluation of multiple agents in primary dentin. Therefore, further research is necessary to assess and compare the effectiveness of different MMP inhibitors as dentin bonding modifiers in primary teeth.

Methodology

The present in vitro experimental study was conducted to evaluate and compare the effect of different matrix metalloproteinase (MMP) inhibitors on the shear bond strength of dentin bonding agents in primary teeth. Ethical approval for the study was obtained from the Institutional Ethics Committee prior to the commencement of the investigation. A total of eighty extracted human primary posterior teeth were collected from the Department of Pediatric and Preventive Dentistry. The teeth were extracted for reasons unrelated to the present study, such as orthodontic or physiological exfoliation. Only sound, caries-free teeth with intact crown structure and normal morphology were included in the study, while teeth with caries, cracks, fractures, restorations, or developmental defects were excluded to ensure standardization.

Immediately after extraction, the teeth were thoroughly cleaned to remove adherent soft tissue and debris using an ultrasonic scaler. The cleaned specimens were then stored in 0.1% thymol solution prepared by dissolving 0.1 g of thymol crystals in 100 mL of distilled water. The storage was carried out at a temperature of 4°C to inhibit microbial growth, and the duration of storage did not exceed three months prior to specimen preparation.

For specimen preparation, each tooth was sectioned approximately 1 mm below the cementoenamel junction using a low-speed diamond disc under continuous water irrigation to prevent overheating and dehydration. The coronal portion of each tooth was then embedded in self-cure acrylic resin blocks of standardized dimensions, ensuring that the exposed dentin surface was oriented parallel to the long axis of the block. The exposed dentin surfaces were examined under a stereomicroscope to confirm the absence of any residual enamel.

To achieve surface standardization and create a uniform smear layer, the dentin surfaces were wet-ground using 600-grit silicon carbide abrasive paper for a duration of 60 seconds. The specimens were then rinsed thoroughly with distilled water to remove debris and gently airdried.

The prepared specimens were randomly divided into four experimental groups, each consisting of twenty samples.

GROUP	MMP INHIBITORS	CONCENTRATION
	Chlorhexidine solution	2%
GROUP – 2	EDTA solution	17%
GROUP – 3	Minocycline solution	2%
GROUP - 4 (CONTROL GROUP)	Phosphate-buffered saline	0.01M

All specimens were subjected to a standardized bonding protocol. The exposed dentin surfaces were etched with 37% phosphoric acid gel for 15 seconds to remove the smear layer and demineralize the superficial dentin. Following etching, the surfaces were thoroughly rinsed with distilled water for 15 seconds to eliminate residual acid and debris. The specimens were then blot-dried using sterile absorbent paper to achieve a visibly moist dentin surface, which is essential for maintaining the integrity of the collagen network. (Figure 1)

Subsequently, the respective MMP inhibitor solutions were applied to the dentin surface of each group using a disposable microbrush. Approximately 1 mL of the solution was actively applied with gentle agitation for 60 seconds at room temperature to ensure adequate penetration into the demineralized dentin matrix. After application, the surfaces were rinsed with distilled water for 20 seconds to remove excess solution and then gently air-dried for 5 seconds using an oil-free air syringe. (Figure 2)

Following pretreatment, adhesive was applied in accordance with the manufacturer's instructions. Two consecutive coats of the adhesive were applied using a disposable microbrush with gentle agitation for 15 seconds to enhance penetration into the collagen network. Excess solvent was evaporated using a gentle stream of oil-free air for 5 seconds, and the adhesive layer was then light-cured using an LED curing unit at an intensity of 800 mW/cm² for 10 seconds, maintaining a fixed distance of approximately 1 mm from the dentin surface. (Figure 3)

For composite build-up, a cylindrical Teflon mold measuring 3 mm in diameter and 2 mm in height was positioned centrally over the bonded dentin surface. A nanohybrid composite resin material was placed incrementally within the mold, and each increment was light-cured for 20 seconds to ensure complete polymerization. After curing, the mold was carefully removed, and each specimen was examined for any defects or voids. (Figure 4)

All prepared specimens were then stored in artificial saliva at 37°C for 48 hours to simulate oral conditions prior to mechanical testing. Shear bond strength testing was performed using a universal testing machine. Each specimen was securely mounted in a custom-made jig to ensure stability, and a shear force was applied at the composite–dentin interface using a chiselshaped loading head. The load was applied at a constant crosshead speed of 1 mm/min until failure occurred. (Figure 5 & 6)

The maximum load at failure was recorded in Newtons for each specimen. The shear bond strength was calculated in megapascals using the formula SBS = F/A, where F represents the maximum force at failure and A represents the bonded surface area. The bonded area was determined based on the dimensions of the composite cylinder and calculated as 7.07 mm^2.

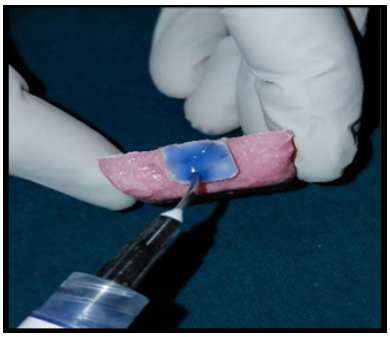

Figure 1. Etchant application

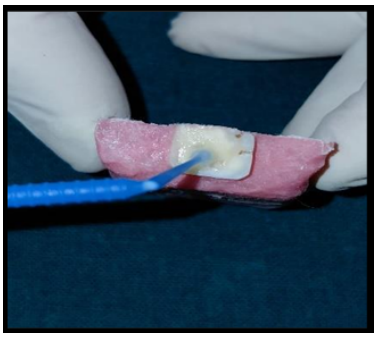

Figure 2. Application of MMP inhibitors

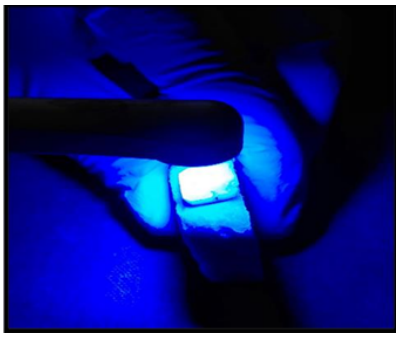

Figure 3. Application of Dentin Bonding

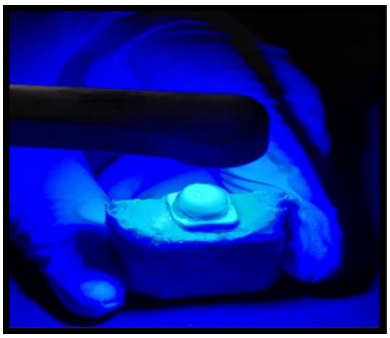

Figure 4. Dentin resin build up

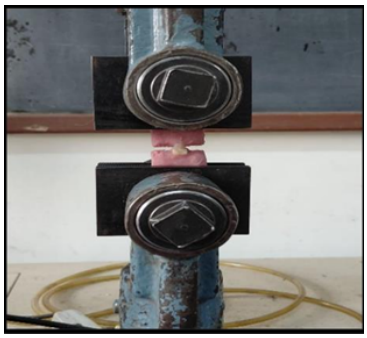

Figure 5. Specimen mounted on Universal Testing Machine

Figure 6. Measurement of shear bond strength

Results

The present in vitro study evaluated the effect of different matrix metalloproteinase (MMP) inhibitors on the shear bond strength (SBS) of dentin bonding agents in primary teeth. A total of 80 specimens were analyzed and divided into four groups: 2% chlorhexidine, 17% EDTA, 2% minocycline, and control. The data obtained were subjected to descriptive and inferential statistical analysis, including one-way ANOVA, post hoc Tukey test, and effect size estimation.

Table 2. Descriptive Statistics of Shear Bond Strength (MPa) Among the Study Groups.

			Descriptive							
			Shear Bond Strength							
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Between-Component Variance
						Lower Bound	Upper Bound			
2% Chlorhexidine		20	11.5605	.37045	.08284	11.3871	11.7339	10.65	12.11	
17% EDTA		20	9.3085	.53780	.12025	9.0568	9.5602	8.29	10.26	
2% Minocycline		20	10.2520	.32012	.07158	10.1022	10.4018	9.71	10.77	
Control		20	4.4960	.28023	.06266	4.3648	4.6272	3.96	4.92	
Total		80	8.9043	2.71168	.30318	8.3008	9.5077	3.96	12.11	
Model	Fixed Effects			.38970	.04357	8.8175	8.9910			
	Random Effects				1.54024	4.0025	13.8060			9.48180

Table 2 presents the descriptive statistics of shear bond strength among the study groups. The highest mean SBS was observed in the 2% chlorhexidine group (11.56 ± 0.37 MPa), followed by the 2% minocycline group (10.25 ± 0.32 MPa) and the 17% EDTA group (9.31 ± 0.54 MPa), while the control group showed the lowest mean value (4.49 ± 0.28 MPa). The 95% confidence intervals for all groups were narrow, indicating good precision of the estimated means. The EDTA group exhibited slightly higher variability compared to the other groups, whereas the control group showed the least variability.

Table 3. One-way ANOVA for Intergroup Comparison of Shear Bond Strength.

ANOVA					
Shear Bond Strength					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	569.364	3	189.788	1249.692	<.001
Within Groups	11.542	76	.152		
Total	580.906	79			

Table 3 shows the results of one-way ANOVA used for intergroup comparison of shear bond strength. The analysis revealed a highly statistically significant difference among the groups ($F = 1249.692$, $p < 0.001$). The between-group variation was considerably higher than the withingroup variation, indicating that the differences in shear bond strength were primarily due to the effect of the different MMP inhibitors rather than random variation.

Table 4. One-way ANOVA for Intergroup Comparison of Shear Bond Strength

ANOVA Effect Sizes[a]				
		Point Estimate	95% Confidence Interval	
			Lower	Upper
Shear Bond Strength	Eta-squared	.980	.970	.984
	Epsilon-squared	.979	.969	.984
	Omega-squared Fixed effect	.979	.969	.984
	Omega-squared Random effect	.940	.912	.952
a. Eta-squared and Epsilon-squared are estimated based on the fixed-effect model.				

Table 4 illustrates the effect size analysis using eta-squared (η^2), epsilon-squared (ε^2), and omegasquared (ω^2). All effect size values were extremely high ($\eta^2 = 0.980$, $\varepsilon^2 = 0.979$, $\omega^2 \approx 0.979$), indicating that nearly 98% of the variation in shear bond strength can be attributed to the type of MMP inhibitor used. The narrow confidence intervals further confirm the reliability and precision of these estimates, demonstrating a very strong practical significance of the treatment effect.

Table 5. Post Hoc Pairwise Comparison of Shear Bond Strength Using Tukey HSD Test

	Multiple Comparisons					
	Dependent Variable: Shear Bond Strength					
	Tukey HSD					
(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
2% Chlorhexidine	17% EDTA	2.25200*	.12323	<.001	1.9283	2.5757
	2% Minocycline	1.30850*	.12323	<.001	.9848	1.6322
	Control	7.06450*	.12323	<.001	6.7408	7.3882
17% EDTA	2% Chlorhexidine	2.25200*	.12323	<.001	-2.5757	-1.9283
	2% Minocycline	-.94350*	.12323	<.001	-1.2672	-.6198
	Control	4.81250*	.12323	<.001	4.4888	5.1362
2% Minocycline	2% Chlorhexidine	-1.30850*	.12323	<.001	-1.6322	-.9848
	17% EDTA	.94350*	.12323	<.001	.6198	1.2672
	Control	5.75600*	.12323	<.001	5.4323	6.0797
Control	2% Chlorhexidine	-7.06450*	.12323	<.001	-7.3882	-6.7408
	17% EDTA	-4.81250*	.12323	<.001	-5.1362	-4.4888
	2% Minocycline	-5.75600*	.12323	<.001	-6.0797	-5.4323

Table 5 presents the results of the Tukey post hoc test for pairwise comparison among the groups. All intergroup comparisons were found to be statistically highly significant ($p < 0.001$). The 2% chlorhexidine group showed significantly higher shear bond strength compared to all other groups. The 2% minocycline group demonstrated significantly higher values than the EDTA and control groups, while the 17% EDTA group also showed significantly higher bond strength than the control group. The control group consistently exhibited the lowest values. The confidence intervals for all comparisons did not cross zero, confirming the statistical significance of the observed differences.

Overall, the results indicate that the application of MMP inhibitors significantly improves shear bond strength in primary dentin, with chlorhexidine showing the most pronounced effect, followed by minocycline and EDTA.

Discussion

Adhesion to dentin remains a complex process due to its hydrated and heterogeneous structure, consisting of a collagen matrix reinforced by hydroxyapatite and traversed by dentinal tubules. This complexity is further pronounced in primary dentin, which exhibits lower mineral content, higher organic composition, increased permeability, and wider dentinal tubules compared to permanent dentin. These structural differences adversely affect bonding performance and increase susceptibility to degradation. Previous studies have reported that primary dentin is more prone to bond deterioration and reduced durability of adhesive restorations. [4,3,15]

The success of adhesive restorations depends on the formation and stability of the hybrid layer, which is created by infiltration and polymerization of resin monomers within the demineralized collagen matrix. An ideal hybrid layer provides effective micromechanical interlocking and resistance to microleakage. However, incomplete resin infiltration may leave exposed collagen fibrils vulnerable to degradation, especially in primary dentin. [1,5]

One of the major factors responsible for hybrid layer degradation is the activation of endogenous matrix metalloproteinases (MMPs), including MMP-2, MMP-3, MMP-8, and MMP-9. These enzymes are activated during acid etching and degrade exposed collagen fibrils, leading to reduced bond strength and long-term failure of the adhesive interface. [7,8,17]

To overcome this limitation, dentin biomodifiers, particularly MMP inhibitors, have been introduced to enhance hybrid layer stability. These agents inhibit enzymatic activity and improve collagen resistance to degradation. In the present study, all MMP inhibitor groups demonstrated significantly higher shear bond strength compared to the control group, indicating their beneficial effect on bond integrity. [9]

Among the tested agents, chlorhexidine exhibited the highest shear bond strength. This can be attributed to its strong MMP inhibitory action and substantivity, allowing prolonged interaction with dentin. It inhibits MMPs by chelating calcium and zinc ions and binding to enzyme active sites. Previous studies have also reported its effectiveness in preserving hybrid layer integrity and improving bond durability. [6,10]

Minocycline also demonstrated significantly improved bond strength compared to EDTA and control groups. Its mechanism involves chelation of metal ions and direct inhibition of MMP activity. Additionally, its antioxidant and anti-inflammatory properties contribute to stabilization of the dentin matrix. These findings are consistent with previous reports on tetracycline derivatives as effective MMP inhibitors. [12,16]

The EDTA group showed moderate improvement in bond strength. Although EDTA inhibits MMP activity by chelating metal ions, it also causes demineralization of dentin, which may result in incomplete resin infiltration and formation of a weaker hybrid layer. This explains its comparatively lower performance. [7,11]

The control group exhibited the lowest bond strength, highlighting the negative effect of uninhibited MMP activity. In the absence of biomodifiers, exposed collagen fibrils undergo enzymatic degradation, leading to compromised hybrid layer formation and reduced adhesion. [6,17]

Statistical analysis revealed a highly significant difference among all groups, confirming that the type of MMP inhibitor has a strong influence on shear bond strength. The large effect size further supports that the observed differences are clinically significant and not due to chance. Similar findings have been reported in systematic reviews evaluating the effectiveness of MMP inhibitors in dentin bonding. [18,19]

Clinically, the application of MMP inhibitors is a simple and effective strategy that can be incorporated into adhesive protocols without increasing complexity. Their use enhances collagen stability, reduces enzymatic degradation, and improves long-term bond durability, particularly in primary teeth. [7,10]

Limitation of the Study

This study was conducted under in vitro conditions, which do not fully replicate the complex oral environment, including factors such as saliva, temperature variations, and masticatory forces. The evaluation was limited to short-term storage without aging procedures like thermocycling, which may affect long-term bond durability.

Only shear bond strength was assessed, which may not completely represent clinical stress conditions. Additionally, the study was limited to a single adhesive system, specific concentrations of MMP inhibitors, and a relatively small sample size of primary teeth, which may influence the generalizability of the results.

Conclusion

Within the limitations of this in vitro study, it can be concluded that the application of matrix metalloproteinase (MMP) inhibitors significantly enhances the shear bond strength of dentin bonding agents to primary dentin. All tested MMP inhibitors demonstrated superior bond strength compared to the control group, indicating their positive role in improving the stability of the resin–dentin interface.

Among the evaluated agents, 2% chlorhexidine exhibited the highest shear bond strength, followed by 2% minocycline and 17% EDTA. The superior performance of chlorhexidine can be attributed to its strong MMP inhibitory activity and substantivity, which contribute to preservation of the hybrid layer and prevention of collagen degradation.

The findings of this study suggest that incorporation of MMP inhibitors as a pretreatment step after acid etching is an effective strategy to enhance bond strength and potentially improve the longevity of adhesive restorations in primary teeth.

However, as this was an in vitro study, further long-term clinical investigations are recommended to validate these results and assess their applicability in clinical practice.

Conflicts of Interest

The authors declares no conflict of interest.

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