

Efficacy of Antimicrobial Agents in Orthodontic Adhesive Systems and Brackets: A Narrative Review

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Objectives Development of white spot lesions (WSLs) in the course of orthodontic treatment would compromise the satisfaction of patients and clinicians. One suggested preventive strategy is to incorporate antimicrobial agents into orthodontic adhesive systems or to coat brackets with them. Several clinical and experimental studies have evaluated the effect of antimicrobial agents, but no consensus has been reached on the best preventive approach. Thus, the aim of this narrative review was to assess the clinical and experimental studies on the effect of incorporation of antimicrobial agents in orthodontic adhesives and brackets.

Methods PubMed (Medline), Scopus, and Google Scholar were searched for related articles published from 1990 to 2020. Both clinical and experimental studies were included in this review.

Results Different antimicrobial agents can be added to adhesive systems to prevent the formation of WSLs, and also preserve the bond strength of adhesives. Same as adhesive systems, coating of brackets with antibacterial agents can be performed to prevent bacterial proliferation and demineralization of enamel.

Conclusion Antimicrobial agents incorporated in bonding systems or used for coating of brackets can confer antimicrobial properties with no significant negative effect on bonding properties. However, clinical and long-term studies are required to confirm their effectiveness and absence of side effects.

Keywords Orthodontic Brackets; Dental Cements; Anti-Infective Agents; Tooth Demineralization

Introduction

White spot lesions (WSLs) around orthodontic brackets are among the common complications of fixed orthodontic treatment.¹ These lesions develop due to an increase in colonization of *Streptococcus mutans* (*S. mutans*) and other cariogenic bacteria, and subsequent demineralization of the enamel.² Several preventive efforts have been taken into account such as application of fluoride compounds, oral hygiene instruction, and dietary control.³ However, all these approaches depend on patient compliance. Therefore, preventive approaches that do not rely on patient compliance may be more effective. Thus, it is logical to add antimicrobial agents to orthodontic materials to prevent WSLs more forcibly.

Previous studies have shown that resin modified glass ionomer cements (RMGICs) are as effective as composite resins, exhibiting clinically acceptable bond strength besides releasing fluoride.⁴⁻⁶ However, some other studies have concluded that duration of fluoride release is short. Fluoride release from RMGICs begins with an initial burst at the time of bonding, followed by a prompt reduction.⁷⁻⁹ Some substances such as silver nanoparticles^{9, 10},

methacryloyloxydodecylpyridinium bromide (MDPB)⁸, quaternary ammonium polyethylenimine nanoparticles¹¹, quaternary ammonium resin, amorphous calcium phosphate nanoparticles¹², and curcumin nanoparticles¹³ have been added to orthodontic bonding systems as antimicrobial agent and have shown optimal antimicrobial effects. Also, some other studies have assessed coating of brackets with antimicrobial agents such as, titanium dioxide¹⁴, ZnO and CuO nanoparticles.¹⁵

Antimicrobial agents incorporated into orthodontic bonding systems should provide adequately high antimicrobial effect, while preserving optimal bonding properties. Despite numerous clinical and experimental studies, there is still no consensus on this topic. Thus, the aim of this narrative review was to evaluate the efficacy of addition of antimicrobial agents to orthodontic bonding systems and brackets and their effect on bonding properties.

Materials and Methods

The research protocol and null hypothesis were developed according to PICO, as demonstrated in Table 1.

Table 1- Null hypothesis and PICO format

PICO format	
Population	White spot lesions during orthodontic treatment
Intervention	Orthodontic brackets and bonding systems with additional antimicrobial agents
Comparison	Conventional orthodontic brackets and bonding systems
Outcome	<i>Primary:</i> antimicrobial activity of the added agents <i>Secondary:</i> changes in the brackets and bonding properties
Null hypothesis	
	Incorporation of antimicrobial agents into orthodontic bonding systems or coating of brackets with them would not yield significant antibacterial activity.

The PubMed (Medline), Scopus and Google Scholar databases were searched by 3 of the authors for articles published from 1990 to 2020. Manual search was also performed to identify non-indexed studies. Eventually, after omitting the duplicates, the remaining studies were selected

according to the eligibility criteria listed in Table 2. Studies that met the inclusion criteria underwent full-text analysis for data extraction. Both clinical and experimental studies were included in this review.

Table 2- Eligibility criteria	
Inclusion criteria	Exclusion criteria
Studies that evaluated antimicrobial agents in adhesive systems and other orthodontic materials such as brackets, and also, their effect on bonding properties in humans or animals (in vivo) or on extracted teeth (in vitro).	Reviews, case reports, case series; Studies that only examined bond strength of adhesive systems; Studies that used antimicrobial agents for restorative purposes; In vitro studies evaluating only antimicrobial properties without bonding brackets to teeth.

Results

Antimicrobial agents incorporated into adhesive systems:
Several antimicrobial agents and their effects on properties of adhesive systems such as their bond strength, enamel features, and bacterial proliferation have been evaluated by

numerous studies, which are mentioned in Table 3. The effects of these agents on bond strength were assessed by several studies.^{9, 12, 13, 16-20} Most of the studies had added these agents to Transbond XT (3M Unitek, Monrovia, CA) adhesive system.

Table 3- Studies on antimicrobial agents incorporated into orthodontic adhesive systems				
Study	Material type	Adhesive systems (control group)	Evaluated variables	Duration of antimicrobial evaluation
Altman et al. ¹⁶	1,3,5-triacryloylhexahydro-1,3,5-triazine at a concentration of 10%, 15% and 20%	Transbond XT	bacterial growth, degree of conversion, Knoop hardness and bond strength	48 h
Uysal et al. ⁸	Clearfil Protect	Transbond XT	Enamel microhardness and depth of demineralization	30 days
AZ et al. ¹⁷	Clearfil Protect	Transbond XT	volume and depth of white spot lesions	28 days
Degrazia et al. ²⁵	Triazine and niobium phosphate bioglass	Transbond XT	Demineralization and bacterial growth	7 and 14 days
Sharon et al. ¹¹	quaternary ammonium polyethylenimine nanoparticles	Neobond	biofilm formation and bacterial growth	48 h
Wang et al. ⁹	Silver nanoparticles	Fuji, Transbond XT	biofilm formation, bacterial growth and bond strength	2 days
Eslamian et al. ²¹	Silver nanoparticles	Transbond XT	Bacterial growth and bond strength	24 h
Yassaei et al. ²²	Hydroxyapatite, titanium oxides, zinc oxide, copper oxide and silver oxide nanoparticles	Transbond XT	Bacterial growth	3, 15 and 30 days
Sodagar et al. ¹³	Curcumin nanoparticles	Transbond XT	biofilm formation, bacterial growth and bond strength	3 days
Yaseen et al. ²³	Cinnamon nano powder	Heliosit Orthodontic Resin	Bacterial growth, shear bond strength and adhesive remnant index	24 h
Swapna et al. ¹⁸	Transbond Plus, Discover LC	Transbond XT	Depth of demineralization and bond strength	--
Yu F. et al. ¹⁹	2-methacryloxyethyl hexadecyl methyl ammonium bromide	Transbond XT	bacterial growth (aging), laser scanning, electron microscope observation, Agar diffusion assay and bond strength	1 day and 6 months
Yansong Ma et al. ²⁰	2-methacryloyloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate and nanoparticles of amorphous calcium phosphate	Transbond XT	dental plaque microcosm biofilm model, Polarized-light microscopy, Cross-sectional hardness and bond strength	24 h
Yan Liu et al. ¹²	2-methacryloxyethyl dodecyl methyl ammonium bromide and amorphous calcium phosphate nanoparticles	Transbond XT	bacterial growth (aging), ion release, microhardness, Surface roughness and bond strength	6, 12, 24, 48, and 72 h
Andriani et al. ²⁴	Titanium dioxide nanoparticles	Transbond XT	enamel microhardness and bacterial growth	30 days

Fluoride is commonly incorporated into adhesives. Some adhesive systems, such as Transbond Plus TM and Discover LC orthodontic adhesive TM are fluoride

releasing composites, which have shown lower degree of demineralization in experimental conditions and lower shear bond strength, but within the clinically acceptable

range.¹⁸

An experimental orthodontic adhesive developed by addition of 1,3,5-triacryloylhexahydro-1,3,5-triazine (TAT)(16) in 3 concentrations (10%, 15%, and 20%) decreased bacterial proliferation, increased degree of conversion in 15% and 20% concentrations, and resulted in greater shear bond strength and lower hardness. Thus, use of TAT in 15% and 20% concentrations was suggested to obtain antimicrobial effects besides proper shear bond strength.

Also, 2-methacryloxyethyl hexadecyl methyl ammonium bromide¹⁹ has shown strong and long-lasting bacteriostatic properties (up to 180 days), without adverse effects on shear bond strength at 1%, 3% and 5% concentrations.

Yansong et al.²⁰ developed an adhesive system by incorporating 2-methacryloyloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate, and amorphous calcium phosphate nanoparticles into RMGIC and observed lower enamel demineralization around brackets and better enamel hardness without affecting the bond strength. Also, another study¹² evaluated the addition of 2-methacryloxyethyl dodecyl methyl ammonium bromide and NACP to adhesive system and they observed that adhesives containing 5% 2-methacryloxyethyl dodecyl methyl ammonium bromide and 40% NACP can yield antibacterial and remineralizing features with no significant effect on their bond strength.

Wang et al.⁹ developed an antibacterial RMGIC containing silver nanoparticles. Experimentally, it significantly decreased microbial activity, not only on the surface but also away from the surface in the culture medium. This modified adhesive showed almost the same bond strength as RMGIC control group, but lower than Transbond XT. Thus, they suggested the use of silver nanoparticles in dental adhesives and sealants. On the other hand, Eslamian et al.²¹ incorporated silver nanoparticles into Transbond XT and evaluated its antibacterial effect and shear bond strength in extracted premolars bonded to metal brackets and the modified adhesive. They observed significant antibacterial activity, which lasted for more than 30 days, but it showed lower bond strength in comparison with the control group; however, it was within the acceptable range (5.9-7.8 MPa).

Another experimental study²² compared the antibacterial effects of incorporation of hydroxyapatite, titanium oxide, zinc oxide, copper oxide and silver oxide nanoparticles at 0.5% and 1% concentrations into Transbond XT. They assessed the proliferation of *S. mutans* at 3, 15 and 30 days. They observed greater antibacterial effect after addition of 1% copper oxide and 1% silver oxide; however, this effect was not long-term and they claimed that it is not justifiable to clinically use these agents.

Curcumin nanoparticles¹³ is another antimicrobial agent, which has shown significant antibacterial activity in 1% concentration, without affecting the bond strength. However, its main disadvantage is its insolubility.

Nano-cinnamon powder at 3% concentration added to

orthodontic adhesive system (Heliosit orthodontic resin) has shown proper inhibition of *S. mutans* in vitro with no significant effect on shear bond strength or adhesive remnant index.²³

Another experimental study¹¹ incorporated quaternary ammonium polyethylenimine nanoparticles into Neobond. They observed significantly greater antimicrobial effect against *S. mutans* and *Lactobacillus casei*. However, they did not evaluate its effect on adhesive properties.

Andriani et al.²⁴ evaluated the effect of addition of TiO₂ nanoparticles to an adhesive system on enamel demineralization by assessing enamel microhardness. They observed that 2% TiO₂ nanocomposites had higher efficacy to prevent enamel demineralization and preserve hardness; although their effect on shear bond strength remained unclear.

Also, an in-situ study²⁵ added 20 % triazine and niobium phosphate bioglass to an experimental orthodontic adhesive composed of 75% BisGMA and 25% TEGDMA, compared with Transbond XT. They assessed demineralization of enamel and proliferation of streptococci, *S. mutans*, and lactobacilli by inserting bovine enamel blocks with brackets bonded by the aforementioned adhesives in an intraoral device for up to 14 days. They observed anti-demineralization effect and inhibition of bacterial growth on enamels bonded with adhesives containing 20% triazine and niobium phosphate bioglass.

In addition to in vitro studies, a clinical study⁸ compared Clearfil Protect Bond (Kuraray Medical, Okayama, Japan) with Transbond XT. This adhesive contains MDPB, and releases fluoride. This study exhibited better antimicrobial effects and lower enamel demineralization after using this adhesive. However, another study found no significant difference in formation of WSLs after using the above-mentioned adhesive system.¹⁷

Thus, it may be concluded that different antimicrobial agents can be added to adhesive systems to control bacterial growth and subsequently formation of WSLs, and also preserve shear bond strength of adhesives. However, most of the afore-mentioned materials, except for Clearfil Protect Bond, have not been evaluated and approved by clinical studies. On the other hand, their effect on the adjacent soft tissue, biocompatibility of modified adhesives, and also their potential for causing allergic reactions in patients should be evaluated in the oral environment.

Antimicrobial agents for coating of orthodontic brackets:

Another method proposed by studies is coating of orthodontic brackets with antibacterial agents to prevent the formation of WSLs around brackets. Related studies have been mentioned in Table 4.

In this manner, a study on rats¹⁰ evaluated coating of brackets with silver nanoparticles by bonding the brackets on rats' incisors and assessed the inhibition of *S. mutans* for up to 75 days. They observed inhibition of *S. mutans* on day 30 and less formation of carious lesions. However, there was higher amounts of nanosilver in the saliva and

serum on day 7, the effect of which on human oral tissue has not yet been identified. Also, another study²⁶ showed favorable antimicrobial effect of metal and ceramic brackets coated with silver nanoparticles on

Staphylococcus aureus and Escherichia coli by the Kirby-Bauer disc diffusion method after 48 h of incubation. They suggested that not only metal brackets, but also esthetic brackets can be coated by these agents.

Table 4- Studies on antimicrobial agents for coating of orthodontic brackets

Study	Material type	Bracket type	Evaluated variables	Duration of antimicrobial evaluation
Gursoy et al. ¹⁰	Silver nanoparticles	Metal brackets	bacterial growth, clinical tooth caries	75 days
Ruiz et al. ²⁶	Silver nanoparticles	Metal and ceramic brackets	Bacterial growth	48 h
Ramezanzadeh et al. ¹⁵	Zinc oxide and copper oxide nanoparticles	Metal brackets	Bacterial growth	6-24 h
Salehi et al. ¹⁴	Nitrogen-doped titanium dioxide	Metal brackets	colony-forming units	30, 60 and 90 days

Another in vitro study¹⁵ applied nano-copper oxide (CuO) and nano-zinc oxide (ZnO) on the brackets and evaluated colony growth of *S. mutans* after 0, 2, 4, 6 and 24 h. They concluded that brackets coated by CuO and ZnO-CuO nanoparticles had greater antibacterial effect than ZnO-coated brackets.

Aside from the studies that evaluated the antimicrobial effects of different agents in the short-term, an experimental study, by Salehi et al.¹⁴ evaluated antibacterial efficiency of stainless steel orthodontic brackets coated with nitrogen-doped titanium dioxide by counting the colony forming units up to 90 days. These modified brackets caused significant reduction of colony count, which was not affected by time.

Eventually, similar to modified adhesive systems, coated brackets can also be used to control enamel demineralization. Different agents have shown desirable results so far, although no clinical evaluations have approved these results.

Discussion

Even the best orthodontic treatment ended with multiple WSLs will not be satisfactory neither for the patient nor for the orthodontist. The prevalence of WSLs varies from 2% to 96%.²⁷ These lesions cannot be reversed spontaneously over time and should be reversed by remineralization or should be restored (28-30). However, there is still no reliable evidence to determine a proper strategy for management of post-orthodontic WSLs.²⁷ Thus, it seems reasonable to search for a strategy to prevent these lesions rather than restoring them.

Several methods have been suggested for optimal oral hygiene in compliant patients such as the use of fluoride releasing agents and antiseptics.³¹ Beside fluoridated toothpastes and mouthwashes, which again demand patient's compliance, another approach is to use fluoride-releasing bonding systems.³² Although compomers and glass ionomer cements have resulted in better reduction of demineralization compared with fluoride-releasing adhesives³³⁻³⁵, they lead to lower bonding strength and higher bracket failure.²⁸ Fluoride-releasing elastomers might be helpful but they exhibit lower physical properties

in the oral environment.³⁶

Another proposed method is incorporation of antimicrobial agents in bonding agents or coating of orthodontic brackets with antimicrobial agents, which were discussed in this review. It sounds rational to add antimicrobial agents to orthodontic brackets or adhesives to prevent colonization of *S. mutans* and other bacteria³⁷, and to eliminate the need for patient cooperation. For this purpose, we found and reviewed multiple studies assessing this strategy.

In order to confer antibacterial properties to adhesive systems, studies have evaluated addition of agents such as, 1,3,5-triacryloylhexahydro-1,3,5-triazine¹⁶, 2-methacryloxyethyl hexadecyl methyl ammonium bromide¹⁹, 2-methacryloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate, NACP (20), 2-methacryloxyethyl dodecyl methyl ammonium bromide¹², silver nanoparticles⁹, curcumin nanoparticles¹³, TiO₂²⁴ and MDPB.⁸ Addition of silver nanoparticles both on the brackets and also to the composition of adhesives has shown successful antimicrobial results. All these agents have shown proper antimicrobial effects without decreasing the shear bond strength of adhesives, although addition of 1% copper oxide and 1% silver oxide did not cause long-term antibacterial effect.²² On the other hand, there are still intangible questions about these agents such as duration of release of these agents and their activity inside the oral environment, their effects on enamel beneath the adhesive, their side effects on the adjacent gingiva and oral mucosa, and their systemic release in the human body, all of which must be answered by well-designed clinical studies.

A recent systematic review in 2018³⁸ evaluated 32 in vitro studies incorporating antibacterial agents in orthodontic bonding systems and obtained evidence for optimal efficacy of these agents beside proper bond strength. Same as this review, they emphasized on the need for confirmation of results by clinical studies. Although, in this review our focus was mainly on studies evaluating the effects of these agents on bonded brackets and not only on adhesives.

Also, brackets coated by silver nanoparticles¹⁰, nano copper oxide (CuO), nano zinc oxide (ZnO)¹⁵, and nitrogen-doped titanium dioxide¹⁴ all exhibited satisfying antibacterial properties against *S. mutans*. Same as adhesive systems,

these results should be evaluated by clinical studies to more precisely assess their properties.

Conclusion

Antimicrobial agents incorporated in bonding systems or used for coating of brackets increased the antimicrobial properties with no significant negative effect on bonding

properties.

Although many studies have shown favorable results, well-designed clinical and long-term studies are still required to confirm their effectiveness and assess their side effects.

Conflict of Interest

None Declared ■

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