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 nanoparticles9, 10, methacryloyloxydodecylpyridinium bromide (MDPB)8, quaternary ammonium polyethyleneimine 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>
<thead>
<tr>
<th>Table 1- Null hypothesis and PICO format</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PICO format</strong></td>
</tr>
<tr>
<td>Population: White spot lesions during orthodontic treatment</td>
</tr>
<tr>
<td>Intervention: Orthodontic brackets and bonding systems with additional antimicrobial agents</td>
</tr>
<tr>
<td>Comparison: Conventional orthodontic brackets and bonding systems</td>
</tr>
<tr>
<td>Outcome: Primary: antimicrobial activity of the added agents</td>
</tr>
<tr>
<td>Secondary: changes in the brackets and bonding properties</td>
</tr>
</tbody>
</table>

 Null hypothesis: Incorporation of antimicrobial agents into orthodontic bonding systems or coating of brackets with them would not yield significant antibacterial activity.

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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.

### 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. Most of the studies had added these agents to Transbond XT (3M Unitek, Monrovia, CA) adhesive system.

#### Table 2- Eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>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.</td>
</tr>
</tbody>
</table>

#### 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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Material type</th>
<th>Adhesive systems (control group)</th>
<th>Evaluated variables</th>
<th>Duration of antimicrobial evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altman et al.</td>
<td>1,3,5-triacycloxyhexahydro-1,3,5-triazine at a concentration of 10%, 15% and 20%</td>
<td>Transbond XT</td>
<td>bacterial growth, degree of conversion, Knoop hardness and bond strength</td>
<td>48 h</td>
</tr>
<tr>
<td>Uysal et al.</td>
<td>Clearfil Protect</td>
<td>Transbond XT</td>
<td>Enamel microhardness and depth of demineralization volume and depth of white spot lesions</td>
<td>30 days</td>
</tr>
<tr>
<td>AZ et al.</td>
<td>Clearfil Protect</td>
<td>Transbond XT</td>
<td>Demineralization and bacterial growth</td>
<td>28 days</td>
</tr>
<tr>
<td>Degrizia et al.</td>
<td>Triazine and niobium phosphate bioglass</td>
<td>Transbond XT</td>
<td>Biofilm formation and bacterial growth</td>
<td>7 and 14 days</td>
</tr>
<tr>
<td>Sharon et al.</td>
<td>Quaternary ammonium polyethyleneimine nanoparticles</td>
<td>Neobond</td>
<td>Biofilm formation, bacterial growth and bond strength</td>
<td>48 h</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Silver nanoparticles</td>
<td>Fuji, Transbond XT</td>
<td>Bacterial growth and bond strength</td>
<td>2 days</td>
</tr>
<tr>
<td>Eslamian et al.</td>
<td>Silver nanoparticles</td>
<td>Transbond XT</td>
<td>Bacterial growth</td>
<td>24 h</td>
</tr>
<tr>
<td>Yassaei et al.</td>
<td>Hydroxyapatite, titanium oxides, zinc oxide, copper oxide and silver oxide nanoparticles</td>
<td>Transbond XT</td>
<td>Biofilm formation, bacterial growth and bond strength</td>
<td>3, 15 and 30 days</td>
</tr>
<tr>
<td>Sodagar et al.</td>
<td>Curcumin nanoparticles</td>
<td>Transbond XT</td>
<td>Bacterial growth, shear bond strength and adhesive remnant index</td>
<td>3 days</td>
</tr>
<tr>
<td>Yaseen et al.</td>
<td>Cinnamon nano powder</td>
<td>Heliosit Orthodontic Resin</td>
<td>Depth of demineralization and bond strength</td>
<td>24 h</td>
</tr>
<tr>
<td>Swapna et al.</td>
<td>Transbond Plus, Discover LC</td>
<td>Transbond XT</td>
<td>Bacterial growth (aging), laser scanning, electron microscope observation, Agar diffusion assay and bond strength</td>
<td>--</td>
</tr>
<tr>
<td>Yu F. et al.</td>
<td>2-methacryloxyethyl hexadecyl methyl ammonium bromide</td>
<td>Transbond XT</td>
<td>Dental plaque microcosm biofilm model, Polarized-light microscopy, Cross-sectional hardness and bond strength, Surface roughness and bond strength</td>
<td>1 day and 6 months</td>
</tr>
<tr>
<td>Yan Liu et al.</td>
<td>2-methacryloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate and nanoparticles of amorphous calcium phosphate</td>
<td>Transbond XT</td>
<td>Bacterial growth (aging), ion release, microhardness, enamel microhardness and bacterial growth</td>
<td>24 h</td>
</tr>
<tr>
<td>Andriani et al.</td>
<td>Titanium dioxide nanoparticles</td>
<td>Transbond XT</td>
<td>--</td>
<td>30 days</td>
</tr>
</tbody>
</table>

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...
An experimental orthodontic adhesive developed by addition of 1,3,5-triacyloylhexahydro-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 study21 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.3 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.22 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 (Heliofilm 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 polyethyleneimine 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 antimicrobial 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 study3 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 study 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>
<thead>
<tr>
<th>Study</th>
<th>Material type</th>
<th>Bracket type</th>
<th>Evaluated variables</th>
<th>Duration of antimicrobial evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gursoy et al.</td>
<td>Silver nanoparticles</td>
<td>Metal brackets</td>
<td>bacterial growth, clinical tooth caries</td>
<td>75 days</td>
</tr>
<tr>
<td>Ruiz et al.</td>
<td>Silver nanoparticles</td>
<td>Metal and ceramic brackets</td>
<td>Bacterial growth</td>
<td>48 h</td>
</tr>
<tr>
<td>Ramezanizadeh et al.</td>
<td>Zinc oxide and copper oxide nanoparticles</td>
<td>Metal brackets</td>
<td>Bacterial growth</td>
<td>6-24 h</td>
</tr>
<tr>
<td>Salehi et al.</td>
<td>Nitrogen-doped titanium dioxide</td>
<td>Metal brackets</td>
<td>colony-forming units</td>
<td>30, 60 and 90 days</td>
</tr>
</tbody>
</table>

Another in vitro study 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. 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%. 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. 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. Beside fluoridated toothpastes and mouthwashes, which again demand patient’s compliance, another approach is to use fluoride-releasing bonding systems. Although composites and glass ionomer cements have resulted in better reduction of demineralization compared with fluoride-releasing adhesives, they lead to lower bonding strength and higher bracket failure. Fluoride-releasing elastomers might be helpful but they exhibit lower physical properties in the oral environment.

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 bacteria, 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-triacyloylhexahydro-1,3,5-triazine, 2-methacryloyloxyethyl hexadecyl methyl ammonium bromide, 2-methacryloyloxyethyl phosphorylcholine, dimethylaminohexadecyl methacrylate, NACP (20), 2-methacryloyloxyethyl dodecyl methyl ammonium bromide, silver nanoparticles, curcumin nanoparticles, TiO2 and MDPB. 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. 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 2018 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 nanoparticles, nano copper oxide (CuO), nano zinc oxide (ZnO), and nitrogen-doped titanium dioxide 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

**References**

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Mohammad Behnaz, et al.

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