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قسم العلاج التحفظي

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Introduction

Dental adhesives and resins have gone through a great deal of advancements since the discovery of enamel etching to improve adhesion by Buonocore¹. These advances allowed resin composites to become the principal material for cavity restoration with high immediate bonding performance. Furthermore, the developments in the recent concepts of self-etching primers and adhesive systems have proven to be effective, both scientifically and clinically^{2 3 4} (**Tay et al., 2002, Van Meerbeek et al., 2011, Kurokawa et al., 2015**).

However, the bonding stability of resinous adhesives to dentin remained problematic, and gap formation at the tooth-restoration interface is inevitable⁵ (**Chigira et al., 1994**).

Secondary caries was accused of being the main reason for failure and for replacement of posterior resin composite restorations^{6 7} (**Deligeorgi et al., 2001, Demarco et al., 2012**). Furthermore, recurrent caries at the gingival margins was reported as being the primary reason for early failure of Class II composite resin restorations⁸ (**Wang et al., 2006**).

Adhesive dentistry allowed for a paradigm shift towards minimally invasive caries treatment, however, some active bacteria remain after removal of the infected dentin due to leaving the affected dentin¹⁰ (**Yildirim et al., 2008**).

Therefore, it was postulated that the longevity of resin composite restoration may be improved by applying strategies that reduce the threat of secondary caries⁹ (**Takahashi et al., 2006**). An effective antibacterial action from adhesive systems could be an alternative to halt residual contamination after caries removal and to increase the restorations durability^{9, 11} (**Takahashi et al. 2006, Imazato et al., 2003**).

The restorative dentist must always keep in mind the fact that dental caries is a disease that could be prevented¹² (***Bargramian et al., 2009***). Antibacterial adhesives could prevent the colonization of microorganisms in gaps formed by resin shrinkage and interface degradation, even in cases of adhesives with decent bond strength, thus decreasing the chances of recurrent caries¹³ (***Imazato et al., 2007***).

In the past, it was suggested that some dental products components possess cavity disinfecting properties. Such components included benzalkonium chloride (BAC), antibacterial monomers (Methacryloyloxydodecylpyridinium Bromide), chlorhexidine gluconate and fluoride-based oral disinfectants (***Fereshteh et al., 2012***). More recently, antibacterial agents have been incorporated to dental adhesive systems in an attempt to enhance their longevity and durability¹⁴⁻¹⁹ (***Araujo et al., 2015***).

With regards to topical antibacterial agents, the incorporation of fluoride-ions into adhesive systems proved to reduce antibacterial activity at the hybrid layer through nanoleakage, thus providing for additional benefit to the fluoride-induced acid-base resistant zone^{20 21} (***Itthagarun et al., 2001, Kirihaara et al., 2013***). The formation of a caries inhibition zone adjacent to the hybrid layer was observed when using a fluoride-releasing adhesive²² (***Shinohara et al., 2006***).

Chlorhexidine digluconate has been used as a disinfectant after cavity preparation in restorative treatment, and more recently, as a matrix metalloproteinase (MMPs) inhibitor with great success^{23 24 2} (***Tay et al., 2002, Carrilho et al., 2010, Ricci et al., 2010***). It was reported to reduce the microorganisms in plaque and saliva, decreasing the level of *S. mutans* in both concentration of chlorhexidine solutions, 0.2 and 2%^{15, 23}. Therefore, it was postulated that the incorporation of chlorhexidine as an antimicrobial agent into the adhesive layer might allow for bactericidal properties, decreasing the chances of secondary caries and subsequently increasing the durability of resin composite restorations²⁵.

Recent evidence, strongly suggests, that the chances of recurrent caries under resin composite restorations could be immensely reduced through incorporating antibacterial agents into the adhesive systems used, thus increasing the longevity and durability of the restorations.

In order for this adhesive system new formulation to become applicable, it should not jeopardize the bonding ability of the adhesive system to dental substrate.

Therefore, it was thought to be beneficial to evaluate the effects of incorporating antibacterial agents into self-etch adhesive systems on the micro-tensile bond strength (μ TBS) of resin composites to dentin.

Review of Literature

I. Search Strategy

A review of studies investigated effects on bond strength of the interventions; including in-vitro as well clinical studies, was performed. **PubMed** and **GoogleScholar** between 2005 and 2014 were searched (*searches done between 9.Dec.2014 and 12.Dec.2014*) by use of relevant MeSH terms related to the effects of incorporation of namely two antibacterial agents into self-etch adhesive systems, chlorhexidine and fluoride, on the micro-tensile, micro-shear bond strength, and stability of bond interface. For each of the MeSH terms, non-MeSH terms and brand names were searched such as "*chlorhexidine-containing*", "*Sodium Fluoride*", "*Peak Universal Bond*" and other relevant terms. All terms used are listed below.

Inclusion criteria: studies were included in the review if chlorhexidine-containing or fluorides-containing self-etch adhesive systems were the primary intervention and studied any of the above mentioned outcomes, also, if antibacterial agent was applied separately prior to application of adhesive system.

Exclusion criteria: studies investigated only antibacterial effects or cariological effects of the mentioned interventions were excluded in the review, Also excluded, studies investigated other material's bonding strength to dentin "ex. glass fiber post" or used silorane-based resin composite, studies investigated bonding to defective dentin "ex. fluorotic, carious etc."

Index and Used MeSH terms:

("chlorhexidine [MeSH] OR chlorhexidine gluconate [MeSH] OR chlorhexidine acetate [MeSH] OR chlorhexidine-containing OR Peak Universal Bond" OR "fluorides [MeSH] OR sodium fluorides [MeSH] OR acidulated phosphate fluoride [MeSH] OR Adhese One F OR fluoride-containing") AND ("self-etch" OR "adhesive system" OR "antibacterial adhesive") AND ("bond strength" OR "micro-tensile" OR "micro-shear" OR "bond stability" OR "mechanical properties")

II. Effect of Chlorhexidine on bond strength of adhesive system

In order to identify the optimal concentration, *Stanislawczuk et al. 2009* evaluated the effect of addition of diacetate chlorhexidine in different concentrations into two simplified etch-and-rinse adhesive systems on mechanical properties, including micro-tensile bond strength (μ TBS)¹⁹. They formulated ten experimental adhesive systems by addition of different concentrations of chlorhexidine (0 [control], 0.01, 0.05, 0.1 and 0.2%) in the two etch-and-rinse systems. Specimens were constructed and aged in water. They concluded that the addition of chlorhexidine diacetate in concentrations until 0.2% in the adhesive systems was found to increase the longevity and stability of resin-dentin interface, without adversely affecting the adhesives' mechanical properties.

Zhou et al., 2009, conducted a study to evaluate whether the incorporation of chlorhexidine in a two-step self-etching adhesive can preserve dentin bond strengths²⁶. This study compared different concentrations of chlorhexidine: 0.05%, 0.1%, 0.5% and 1.0%, added directly to a commercial primer (Clearfil SE Bond). Each specimen was divided into two halves, one was bonded with parental bond without chlorhexidine, and the other half was bonded with the novel bond containing different concentrations of chlorhexidine, and then specimen was stored and aged. Results showed significant reduction in bond strength of all control groups after twelve-month of storage. They concluded that when incorporated in the primer of commercial bond, chlorhexidine can preserve dentin bond as long as the concentration of chlorhexidine in the primer is higher than or equal to 0.1%.

Dalli et al., 2010, studied the effect of chlorhexidine gel on bonding strength to dentin when added before or after etching. The purpose of this in vitro study was to evaluate the effect of 1% chlorhexidine gel on dentin bond strengths of posterior composite resin. The results of this study showed the use of 1% chlorhexidine gel before aid etching had significantly increased shear bond strength than after etching.

Hiraishi et al., 2010, investigated the effect of incorporating chlorhexidine in an experimental self-etching primer on the bond strength of adhesive resin cement to dentin¹⁶. They prepared the novel self-etching primer by adding chlorhexidine diacetate to a commercial primer (ED primer 2.0, Kurary) to obtain chlorhexidine concentrations of 1.0 wt% and 2.0 wt% then apply it on human occlusal dentin surface before building the composite blocks. They found that the addition of chlorhexidine to the primer had significant effects on antibacterial activity whilst having no adverse effects on μ TBS when adding 1.0 wt% chlorhexidine to the primer.

Yiu et al., in 2012, evaluated the effect of chlorhexidine incorporation into experimental dentin adhesives with different hydrophilicities on the microtensile bond strength (μ TBS) to dentin²⁷. Chlorhexidine-containing adhesives were prepared by adding 2.0 wt %chlorhexidine diacetate to ethanol-solvated adhesives. Three ethanol-solvated experimental adhesives with varying degrees of hydrophilicity were prepared as the control groups. The specimens were prepared and testing was performed 24 hours after preparations and 12 months after storage in artificial saliva. The results showed that the incorporation of chlorhexidine had no effect on the immediate bond strength of the experimental adhesives, however, significant reduction in bond strength with storage in artificial saliva was observed in all adhesive groups, except for chlorhexidine-adhesives .

Nishitani et al., 2013, compared bond strength (μ TBS) of an all-in-one self-etching adhesive containing concentrations of 0.5, 1, 2, or 5% chlorhexidine²⁸. They concluded that μ TBS of experimental adhesives containing up to 1% chlorhexidine were not significant when compared with chlorhexidine-free control adhesives. However, addition of 2 or specially 5% chlorhexidine experimental adhesives produced significant reductions in both μ TBS and the percent of conversions.

Sabatini et al., 2013, investigated a novel adhesive system containing 0.2% chlorhexidine diglucanate for its ability to improve stability of the adhesive interface

compared with the use of 2% chlorhexidine as a therapeutic primer¹⁸. Fabricated specimens were stored for either 24 hours or six months. They concluded that although chlorhexidine demonstrated inhibition of dentin proteolytic activity, however, chlorhexidine incorporation whether as into a commercially available adhesive or when used as a therapeutic primer did not show any difference in bond strength at baseline or after six months of storage when compared with the control group without chlorhexidine.

Pomacondor-Hernandez *et al.*, 2013, evaluated the effect of replacing a component of a self-etch adhesive system (Adper Scotchbond SE, Liquid A+ Liquid B) by 2% chlorhexidine on bond strength to dentin after 24 hours, 3 months or 6 months of water storage¹⁷. Teeth were sectioned to expose dentin surface and were assigned into 2 groups. In the experimental group, the liquid A was replaced by 2% CHX, and then resin composite blocks were incrementally built on the bonded surfaces. The teeth were sectioned and prepared for microtensile bond strength testing. It was observed that both groups behaved similarly at baseline and after 6-month water storage, and was concluded that replacing a component of an adhesive system with 2% CHX did not influence significantly the bonding performance and longevity of the evaluated adhesive.

Toman *et al.*, 2014, conducted a study assessing the influence of chlorhexidine diglucanate application on bond strength of glass fibre reinforced composite posts to root dentin using adhesive luting systems²⁹. Two luting systems were applied, with or without the incorporation of CHX. The resulting bond strength values after 6-month of water storage were affected by the type of luting agent and CHX incorporation. It was concluded that application of CHX with etch-and-rinse luting agent improved long-term bond strength between glass fibre reinforced composite posts and root dentine.

Andre *et al.*, 2015, evaluated the dentine bond strength and the antibacterial activity of different adhesives against strict and anaerobic and facultative bacteria. The

study compared three adhesives containing antibacterial components, i.e. glutaraldehyde, MDBP and Chlorhexidine (Peak Universal Bond), and the same versions without antibacterial agents were tested. The antibacterial activity of all adhesives was evaluated by direct contact method against four strict anaerobic and four facultative bacteria. For bond strength, the adhesives were applied according to manufacturers' instructions and specimens restored with resin composite. Teeth were prepared for micro-tensile testing by sectioning in production of beams specimens that were stored in artificial saliva for one week and one year. The study results showed that chlorhexidine containing adhesive system killed only strict anaerobic bacteria after 24 h. Also, saliva storage for one year had no significant reducing effect on the bond strength for most of the adhesives tested, including peak universal bond. The study concluded that chlorhexidine containing self-etch adhesive systems may be a good alternative in restorative procedures performed on dentin, considering its adequate bond strength and better antibacterial activity.

III. Chlorhexidine as an Matrix metalloproteinase Inhibitor

Currently, improvements in bond durability were reported after application of aqueous solution of 2% chlorhexidine (*Consepsis*, Ivoclar Vivadent) as an added step prior to bonding agent application with etch-and-rinse adhesives³⁰ (***Pappas et al., 2005***). The ability to inhibit the effects of the host-derived MMPs can reduce the degradation of collagen matrix in resin-dentin bonds, thus improving the durability of the bond^{31 27} (***Siqueira et al., 2007, Yiu et al., 2012***).

It was found that the application of chlorhexidine in concentrations higher than 0.1% after acid etching in etch and rinse system can preserve dentin bond²⁶ (***Zhou et al., 2009***). The complete effects of incorporating chlorhexidine into adhesive systems remain unclear. The literature mainly reported on the mechanical and adhesion properties of restorative materials²⁵.

In 2015, ***Mazzoni et al.*** published a review concerned with the role of dentin MMPs in caries progression and bond stability³². They described dentin as being a

biological composite with collagen matrix embedded with nanosized hydroxyapatite mineral crystallites. Matrix metalloproteinases (MMPs) and cysteine cathepsins are families of enzymes present in dentin and capable of degrading virtually all extracellular matrix components playing a crucial role in dentin caries pathogenesis and loss of collagen in the adhesive hybrid layer under composite restorations. Changes in collagen and noncollagenous protein structure may participate in observed decreases in mechanical properties of caries-affected dentin. These enzymes also remain entrapped within the hybrid layer during the hybridization process, and the acidic bonding agents can reactivate these proteases. It is worth mentioning that there are multiple in vitro and in vivo reports showing that the durability of the adhesive bond is increased when nonspecific enzyme-inhibiting strategies are used. Different chemicals, i.e. chlorhexidine being the most famous enzyme-inhibiting agent, have been successfully employed as therapeutic primers in the bonding procedures. In addition, the incorporation of enzyme inhibitors into the adhesives and resin blends has been recently promoted.

On the other hand, ***Araujo et al., 2015***, conducted a 24-month double-blind randomized clinical study to evaluate the clinical performance of two self-etch adhesives containing or not chlorhexidine diglucanate in non-carious cervical lesions¹⁴. They added chlorhexidine into two self-etch adhesive systems and used the formulated adhesives to restore non-carious cervical lesions using micro-hybrid resin composite. The restorations were evaluated at baseline and 2-years using modified USPHS criteria. The results showed no significant difference between baseline and 2-year for any criteria when adhesives with and without the addition of CHX were compared. The trial concluded that the inclusion of CHX into the primer of both self-etch systems did not add clinical advantages over the 2-year period.

IV. Effect of Fluoride on bond strength of adhesive system

Nishimura et al., 2006, evaluated the bond durability of a fluoride-releasing all-in-one adhesive system in cervical cavities³³. The period of this study was one year,

and teeth were restored with a fluoride-releasing adhesive system. The restored teeth were extracted after 1 day, 1 month and 1 year then subjected to μ TBS testing and fracture modes were observed using scanning electron microscope (SEM). The results showed no significant difference in the μ TBS between 1 day and 1 month, however, a significant decrease in bond strength was noted over 1 year. Within the limitations of this study, it concluded the tensile bond strengths of the all-in-one adhesive decreased over one year period.

However, ***Peris et al., 2006***, conducted a study with the objective of evaluating the microtensile bond strength (μ TBS) and caries formation on adhesive-dentin interface before and after dynamic chemical formation of secondary caries³⁴. Restorations were prepared on dentin surfaces of bovine incisors using four adhesive systems, of which two fluoride adhesive systems were applied and two conventional parental adhesives as control. Teeth were sectioned into multiple slaps, of which half the slaps were subjected to secondary caries formation using pH cycling model. Caries formation was assessed by polarized light microscopy at deferent depths from the adhesive-dentin bonded interface. They concluded that the presence of fluoride in adhesive systems is not capable of inhibiting secondary caries or maintain bond strength values following caries formation .

Shinohara et al., 2006, evaluated the effect of incorporating fluoride into adhesive systems on microtensile bond strength (μ TBS) to dentin³⁵, as well as analyzed the dentin-adhesive interface after acid-base challenge using SEM. They concluded that the incorporation of fluoride in adhesive systems contributed significantly to preventing secondary caries, while in the same time did not interfere with the adhesive bond strength.

In a different study, ***Shinohara et al., 2009***, conducted another study to evaluate the influence of fluoride-containing adhesive on microtensile bond strength (μ TBS) and in vitro secondary caries inhibition at the resin-dentin interface after 24 hours and

3 months water-storage²². Specimens were prepared for μ TBS testing and stored in distilled water at 37 °C for 24h and 3 months. The specimens were then sectioned, polished and observed with polarized light microscopy (PLM) to evaluate acid inhibition zones. After 24h and 1 month water-storage, the fluoride-containing adhesive demonstrated significant increase of μ TBS values. And again, PLM interface analysis demonstrated an inhibition zone adjacent to the hybrid layer only when the fluoride-containing adhesive was used.

El-Deeb et al., 2013, evaluated the dentin bond strength durability of adhesives containing modified-monomer with or without fluoride after storage in artificial saliva and under intra-pulpal pressure. The study investigated four different self-etch adhesive systems, two of which self-etch adhesives with the same modified monomer (bis-acrylamide) one with fluoride (AdheSE One F) and the other without (AdheSE One). Specimens were aged in artificial saliva either for 24 hours or six months prior to testing. Bonded specimens were sectioned into sticks and subjected to microtensile bond strength testing. Based on the results of this study, fluoride addition did not affect dentin bond durability. Although single-step adhesive system in this study showed stability, these systems remained lower than those of multistep adhesive systems³⁶.

Peschke et al., 2009, conducted a 12-month clinical trial to compare the performance of a one-step (AdheSE One) and a two-step (AdheSE) self-etching adhesive system in Class V cavities. 40 restorations were placed in non-carious cervical lesions using Tetric EvoCream, 20 using one-step and 20 using two-step adhesive system. The restorations were evaluated 1 week, 6 months and 12 months after placement using modified USPHS criteria for the following characteristics: surface texture, marginal irregularities, discolorations and openings, tooth/restoration fractures, secondary caries and hypersensitivities. The results were that all restorations showed excellent clinical characteristics at baseline appointment (after 1 week). After 6 months mild marginal impairments were noted in both groups. While at 12 months

recall, insignificant degradation of margin quality was recorded, but one loss of retention was recorded in the two-step group (AdheSE). The study concluded that there was no significant differences in clinical performance were found between the one-step and the two-step self-etching adhesive during an observation period of 12 months. Both systems showed good clinical function in this short-term period. These data favors the use of this particular single-bottle self-etch adhesive over its parental two-step self-etch system, due to its ease of application.

Itthagarun et al., 2001, examined the in vitro caries inhibiting potential of fluoridated and non-fluoridated rewetting agents when applied to before the use of water-free adhesive system bonded to acid-etched enamel and dentin²⁰. The study applied two similar brands of rewetting agents, one containing fluoride and one without. After specimen collection and exposing enamel and root dentin of twelve caries-free premolars, artificial chemical carious lesions were induced in these specimens. Representative sections were processed to evaluate remnant apatite crystals using transmission electron microscopy (TEM) analysis and scanning transmission electron microscopy/energy dispersive X-ray (STEM/EDX). They concluded that use of fluoridated rewetting agent is useful in preventing secondary caries under the restoration when micro-leakage occurs, by providing the additional benefit of fluoride-induced demineralization inhibition.

On the other hand, ***Carvalho et al., 2009***, presented a study to evaluate the inhibition zone formation and mineral distribution along the interface of adhesive systems either containing fluoride and antibacterial MDPB primer or not³⁷, after induction of artificial caries using two methods, chemical and biological. Two adhesive systems were tested, one which contains fluoride and MDPB, and a conventional parental adhesive system as control. Specimens were subjected to secondary caries development by either chemical (acidic gel) or biological (*S. mutans* culture) methods for 5 days. Inhibition zone and outer lesion formation were observed by confocal laser scanning microscopy (CLSM) and the distribution of minerals along