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REVIEW ARTICLE

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The effect of chlorhexidine primer application on the clinical performance of composite restorations: a literature review

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Abstract

To discuss the effectiveness of chlorhexidine (CHX) used as therapeutic dentin primer in adhesively bonded composite restorations.

Overview: An electronic search in MEDLINE database, accessed through PubMed was conducted. No restrictions of languages and date of publication were made. The following key words were used: "chlorhexidine", "composite" and "composite resins." Clinical studies in which CHX was used during bonding procedures were included in this review. Six studies met the inclusion criteria. Of these, five studies were carried out on noncarious cervical lesions (NCCL). Only one study was carried out on class II preparation of permanent molars. In all studies, either etch-and-rinse and self-etch adhesive systems were used during bonding procedures. On the basis of the reviewed clinical trials, it can be concluded that CHX primer application does not seem to influence clinical outcome of composite restorations.

Clinical significance: Current scientific evidence cannot neither strongly recommend nor discourage the application of CHX as therapeutic primer in composite restorations. Studies with longer follow-up periods with adhesive restorations placed on dentin after caries removal, rather than only on NCCL, are desirable to further investigate the therapeutic effect of CHX during bonding procedures.

KEYWORDS

adhesive systems, chlorhexidine, composite restoration, hybrid layer, matrix metalloproteinases

1 | INTRODUCTION

Recent advances in dental materials made resin composites the materials of choice for the restoration of caries-affected teeth, exhibiting enhanced mechanical properties and improved esthetic behavior.[1] Resin composites rely on the application of adhesive systems to establish a reliable interaction with dentin, through the formation of the hybrid layer (HL) – a structure that is composed of demineralized collagen fibrils reinforced by resin matrix.[2] Different dentin adhesive systems have been proposed over time with the intent to simplify clinical procedures, limit operator mismanagement and improve bond durability of the restorations.[3] However, regardless of the adhesive strategy employed, HL remains the weakest portion within the adhesive-dentin interface, impacting the prognosis of the restoration. Secondary caries, in fact, is more likely to occur because of degradation of HL components, being responsible for failures of resin composite restorations, in particular in the posterior region of the mouth.

The key to successful and long term bonding lies in the stability and integrity of collagen fibrils within the HL.[4] The application of adhesives, however, result in incomplete hybridization of the dentin substrate, leaving behind unprotected collagen fibrils surrounded by water, that are prone to hydrolytic degradation.[5] In such a setting, endogenous dentinal enzymes degrade denuded collagen fibrils, contributing to the weakening of the adhesive joint between resin material and dentin and to the loss of bond strength over time.[4,5] The most prominent groups of endogenous enzymes are matrix metalloproteinases (MMPs) and cysteine cathepsins.[6]

MMPs are Zn^{2+} and Ca^{2+} dependent endogenous proteases that play an important role during dentin maturation, but they become trapped and inactive after the collagen matrix becomes mineralized.[7,8] Attention has been focused on investigating the mechanism underlying the MMP-2 and MMP-9-mediated degradation of the HL. Briefly, both MMPs are present in latent forms in mature, sound mineralized human teeth. When the matrix is demineralized, these MMPs are activated.[9] Furthermore, during restorative procedures, MMPs of the collagen matrix are exposed and can become active regardless of the adhesive strategy applied (etch-and-rinse or self-etch), gradually leading to the loss of HL integrity.[10] Hence, inhibition of collagenolytic enzymes has been proposed as a strategy to reduce HL degradation with consequent enhanced adhesive interface stability and increased composite restoration longevity.[6]

For these purposes, several solutions have been proposed, used as separate step (Figures 1) or directly blended to bonding systems constituents (etchant, primer or bonding).[6] Among them, the most studied MMPs inhibitor was chlorhexidine (CHX) which, apart from having antimicrobial effect, increased the longevity of HL in in vitro studies.[11-14] It has been observed recently that CHX could remain active within the HL even after 10 years of storage in artificial saliva, while preserving its MMPs inhibitory effects (Figures 2, 3, reprinted with permission from Breschi et al. Dent Mater. 2020 May;36 (5):672–680).[15]

In an attempt to increase the longevity of adhesive restorations and reduce the annual failure rates, the application of CHX as an additional therapeutic primer prior to bonding procedures has been investigated in clinical studies. Accordingly, this review aimed at giving an overview of clinical trials that evaluated the effects of CHX prior the application of adhesively-bonded restorations. The potential clinical benefits of using CHX as an additional therapeutic agent will be critically discussed.

2 | MATERIALS AND METHODS

2.1 | Search strategy

An electronic search with no language nor date restrictions was conducted in the MEDLINE database, accessed through PubMed (www.ncbi.nlm.nih.gov/pubmed). The following main keywords were used: "chlorhexidine", "composite" and "composite resins." Additionally, further manual search was performed: the list of references of the initially retrieved articles was screened and websites of the relevant journals were explored.

2.2 | Inclusion criteria

The present review focused only on clinical trials where CHX was used prior to placing adhesive restorations. Only articles in which adhesive systems and composite materials were used as restorative approach were included. No restrictions were placed on the type of adhesive system (etch-and-rinse, self-etch or universal systems) used for bonding procedures before composite materials layering.

2.3 | Exclusion criteria

In vitro studies, case reports, abstracts from conferences, clinical studies in which glass ionomer cements with atraumatic restorative treatment (ART) had been investigated and clinical studies where CHX had been used as a mouth rinse solution were not included in the present review.

The search strategy and the selection process were carried out by two investigators, independently from each other. The last search was conducted on 28 September 2020. After screening of the titles and the abstracts, full texts of all reviewed articles were obtained and carefully read.

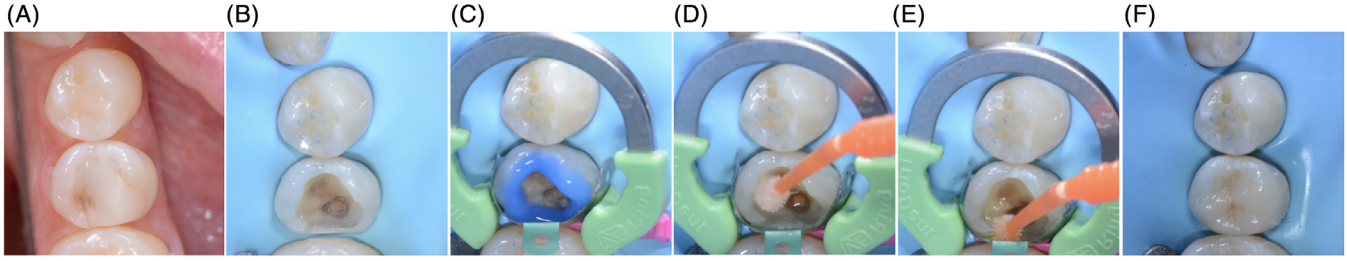

FIGURE 1 (A) Secondary caries and failing composite restoration on mandibular second premolar (B) Rubber dam isolation and prepared class II cavity (C) Selective enamel etching with phosphoric acid (D) Application of 2% aqueous CHX solution (E) Application of one-step self-etch adhesive system (F) Finalized class II composite restoration on second mandibular premolar

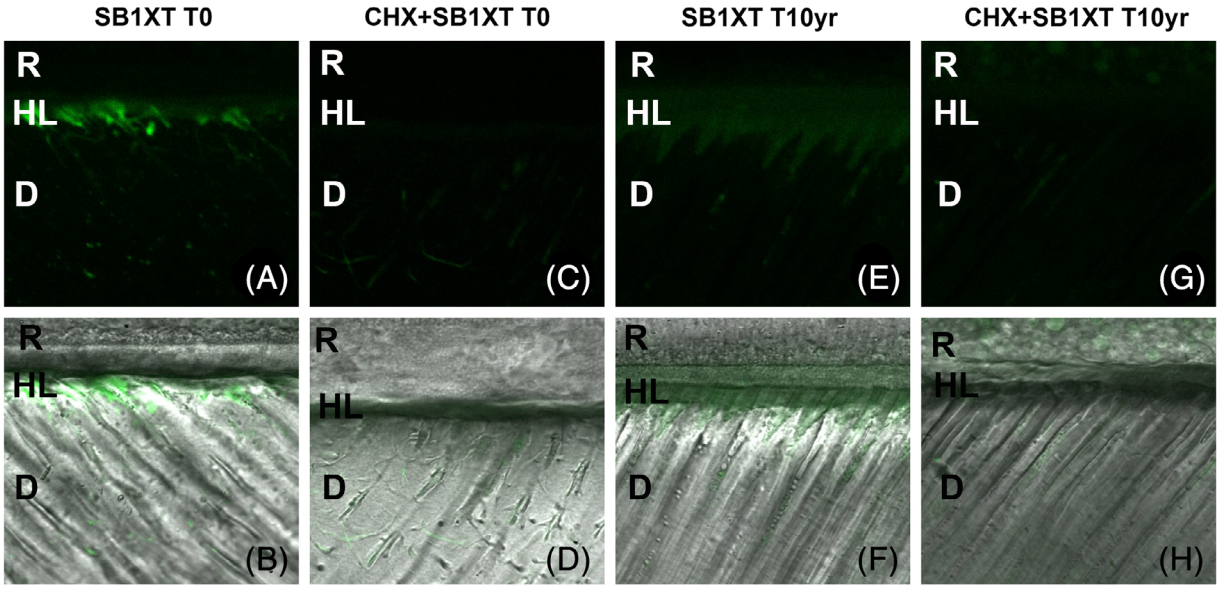

FIGURE 2 Resin-dentin interfaces incubated with quenched fluorescein-labeled gelatin. (A) Image acquired in the green channel, showing fluorescence (identifying intense endogenous enzymatic activity) in dentinal tubules and within the HL created with SB1XT without CHX pre-treatment at T0; (B) Image of SB1XT without CHX pretreatment, obtained by merging the differential interference contrast (DIC) image (showing optical density of the resin-dentin interface) and the image acquired in the green channel; (C) Image acquired in green channel of the HL created by the application of SB1XT to acid-etched dentin with CHX pre-treatment at T0, showing lower level of fluorescence; (D) Image of HL created with SB1XT without CHX pre-treatment obtained by merging the DIC image and image acquired in the green channel at T0; (E) Image acquired in green channel, showing fluorescence in the HL created with SB1XT without CHX pre-treatment at T10-yr; (F) Image of SB1XT with CHX pre-treatment at T10-yr, obtained by merging the DIC image and image acquired in green channel; (G) Image acquired in green channel of the HL created by the application of SB1XT to acid-etched dentin with CHX pre-treatment at T10-yr showing lower level of fluorescence compared to the control group; (H) Image of HL created with SB1XT with CHX pre-treatment obtained by merging the DIC image and image acquired in the green channel at T10-yr; SB1XT: Adper Scotchbond 1 XT; CHX: chlorhexidine D: dentin; HL: hybrid layer; R: resin composite

3 | RESULTS

On the basis of the previously stated inclusion and exclusion criteria, six articles were selected for the present literature review.[16-21]

Five out of six clinical studies (5/6) evaluated the effect of CHX on composite restorations placed in noncaries cervical lesions (NCCL).[16-18,20,21] The details of these studies are presented in Table 1. One study evaluated the effect of CHX on postoperative sensitivity in class II posterior composite restorations after removal of caries (data not shown in the table).[19]

The results of the studies included in this review are divided into the following sections: (a) primary outcome: retention and survival rates of the restorations; (b) secondary outcomes: marginal adaption, marginal staining, postoperative sensitivity and recurrence of caries.

3.1 | Retention and survival rates of the restorations

For the evaluation of clinical performances of adhesively placed composite restorations, either modified USPHS[16,17,21] or FDI criteria[18,20] were used in the studies. The follow-up periods varied from 6,[20] 18,[17] 24,[16] up to 36 months.[18,21]

Two-steps etch-and-rinse adhesives were the most used bonding systems among the screened articles, followed by self-etch systems (one-step and two-step, respectively). The studies in which two-step etch-and-rinse adhesive systems were used (5/6) reported that the application of CHX after dentin etching with phosphoric acid did not influence the retention rate of the restorations after the observed period of time (6, 18, 24 or 36 months of follow-up, respectively).[17,18,20,21] Similarly, CHX did not improve the retention rates of composite restorations placed with either two-step or one-step self-etch adhesive systems. The retention rates for 6- and 18-months follow up periods were high and varied from 96%–100%, depending on the group.[17] One study sought to incorporate CHX into the primer of two-step self-etch adhesives with the aim to increase the longevity of the restorations. However, after 2 years of clinical evaluation, it was concluded that the addition of CHX to these adhesives did not significantly improve their retention rates to NCCL. The selection of the adhesive system, rather than the incorporation of CHX into their formulations, was considered more crucial in determining the study results, where Clearfil SE Bond (CSE, Kuraray, Osaka, Japan) performed significantly better than AdheSE (ADS, Ivoclar Vivadent, Schaan, Liechtenstein) in the same experimental conditions. After 2 years, a significant reduction of the retention rates was observed for both ADS and ADS/CHX groups compared to the baseline.[16]

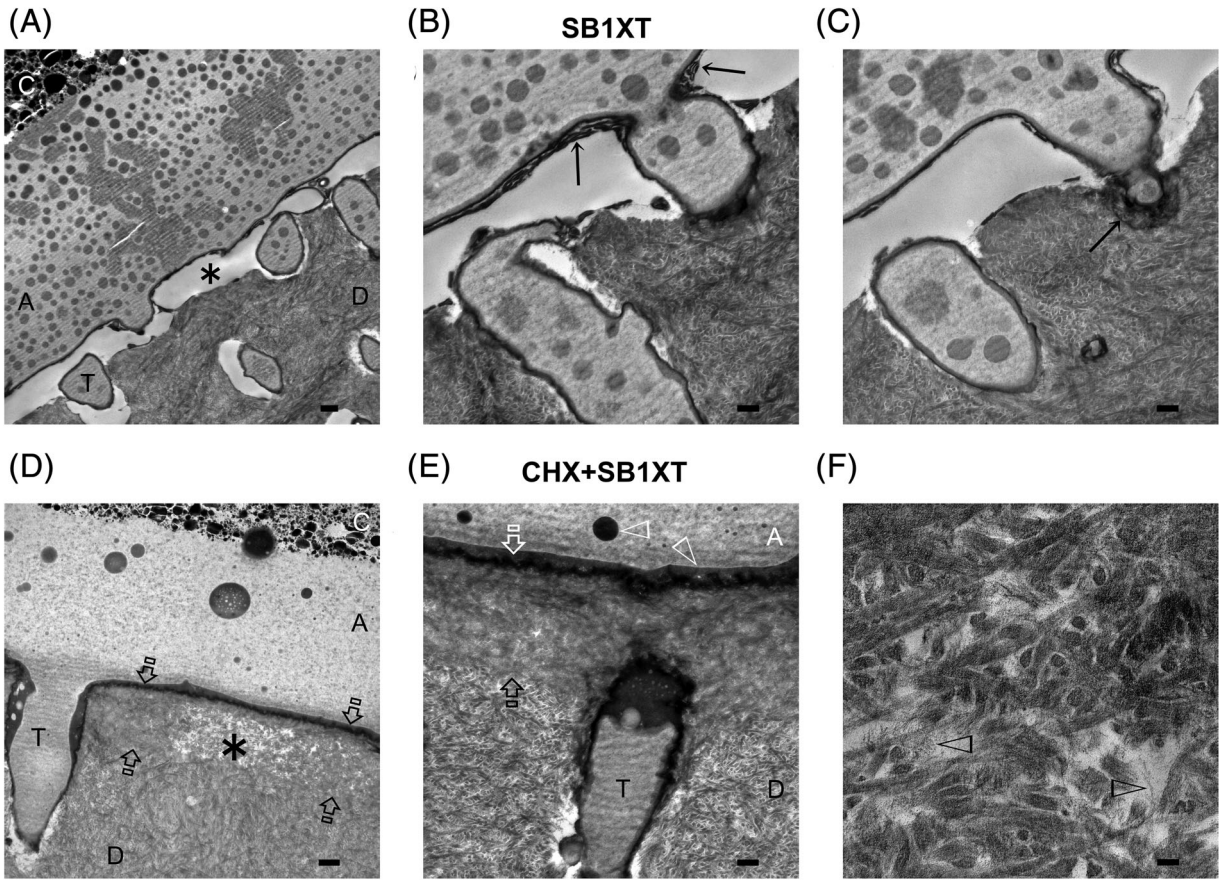

FIGURE 3 Transmission electron microscopy images of the resin-dentin interface. Specimens were completely demineralized and sections were stained intact after 10 years of water storage. Upper row: specimens bonded without a CHX-containing separate primer (SB1XT). Lower row: specimens bonded with the application of a CHX-containing separate primer (CHX + SB1XT). Bar widths (a) 1 μm; (b) 500 nm; (c) 500 nm; (d) 1 μm; (e) 500 nm (f) 100 nm. Abbreviations H: hybrid layer; A: adhesive; C: resin composite; D: intertubular dentin; T: dentinal tubule; Symbols - Asterisk: collagen fibrils within the hybrid layer that degraded completely (A) or partially (D); Black arrows: a thin layer of collagen that remained at the top (B) and bottom (C) of the partially-degraded hybrid layers; Open arrowheads: (E) polyalkenoic acid copolymer component of the adhesive, (F) the open arrowheads represent a high magnification of the asterisked region in Figure d where in the collagen fibrils have unraveled and degraded into microfibrils

One study indicated cavity configuration as a further factor in influencing the potential retention of the restorative materials: wedge-shaped cavities failed more than the saucer-shaped cavities, while deeper and wider cavities failed more than shallow and narrow ones.[20] Contrary to this finding, in another study it was observed that the cavity configuration did not necessarily influence the retention of restorations.[18] In this case, the margin location was relevant to the achievement of the results, with margin restorations located subgingivally failing more than those situated at the gingival or supragingival levels.[18]

3.2 | Marginal adaption, marginal staining, postoperative sensitivity and recurrence of caries

Modified USPHS and FDI criteria were also used for the evaluation of secondary clinical outcomes of the restorations. Similarly, to the previous evaluation procedures, the operators involved in this process were unaware of the treatment protocol thus allowing blinded evaluation of the clinical performance. When compared to the control groups, the application of CHX during bonding procedures seemed to have no impact on the observed parameters.[16-18,20,21] Marginal adaptation was seen to deteriorate over time, but no significant differences were observed between the tested groups.[17] Marginal staining increased for both Clearfil SE and Clearfil SE + CHX groups after 2 years of clinical service, when compared to the baseline.[16] Recurrence of caries was not detected in any of the included studies.[16-20]

Only one randomized clinical study reported on postoperative sensitivity as the main outcome.[19] In this study, the effects on postoperative sensitivity of CHX application in class II posterior composite restorations after caries removal with rotary instruments was evaluated. It was conducted as double-blind research, and consisted of two groups: (a) control group where no CHX was used and (b) CHX group in which 2% CHX solution was applied for 60 s on dentin surface after it had been previously etched by phosphoric acid and a two-step etch-and-rinse adhesive was applied. Lower postoperative sensitivity

TABLE 1 Overview of the clinical studies included in the review

Author, year, location	Study design	Groups and number of restorations placed	CHX application details	Adhesive system / composite resin	Outcome
Neimar Sartori, 2013, Brazil[21]	CT; split-mouth; single blind	2 groups: 1) CHX group; 2) control group. 70 restorations (n = 35 CHX group, n = 35 control group)	2% CHX solution scrubbed on dentin surface for 30 s	Two-step etch-and rinse adhesive system (Adper Single Bond 2, 3 M ESPE, St. Paul, MN, USA) + nanofilled composite (Filtek Supreme XT, 3 M ESPE)	No difference in the restoration retention and failure rates between the CHX and the control groups, up to 36 months of follow-up
Maristela Dutra-Correa, 2013, Brazil[17]	CT; split-mouth; single blind	4 groups: 1) XP Bond; 2) XP Bond + CHX; 3) Xeno V adhesive; 4) Xeno V adhesive + CHX; 120 restorations (n = 30 per each group)	2% CHX solution applied with microbrush for 20 s	Two-step etch-and-rinse adhesive XP Bond (XPB, Dentsply Caulk; Milford, DE, USA) + hybrid composite EsthetX (Dentsply Caulk); One-step self-etch adhesive Xeno V (XEN, Dentsply DeTrey; Konstanz, Germany) + hybrid composite Esthet-X (Dentsply Caulk)	The application of CHX prior to the dentin adhesive did not influence the 6- and 18-months clinical outcome of the two adhesives
M.S.R.G. Araujo, 2015, Brazil[16]	RCT, split-mouth (paired tooth), double blind	4 groups: 1) Clearfill SE group (CSE); 2) CSE + CHX group; 3) AdhSE group (ADS); 4) ADS + CHX group 126 restorations (n = 32 in CSE group, n = 33 in CSE + CHX group, n = 32 in ADS group, n = 29 in ADS+ CHX group)	50 mL of 20% CHX digluconate was incorporated into to 950 mL of the Clearfil SE primer or AdheSE primer to form a mixture with a CHX concentration of 1.0 wt%. Clearfil SE Primer was applied to the enamel and dentine surfaces for 20 s. AdheSE primer was rubbed into the enamel and dentine surfaces for 30 s	Two-step self-etch adhesives (Clearfil SE Bond, Kuraray, Osaka, Japan) and AdheSE (Ivoclar Vivadent, Schaan, Liechtenstein) + nanocomposite resin (Filtek Z-250, 3 M ESPE, St. Paul, MN, USA)	The incorporation of CHX into the primer of the tested two-step self-etch adhesives did not add any clinical advantage up to 2 years of follow-up
Anelise Fernandes Montagner, 2015, Brazil[20]	RCT, split-mouth, triple blind	2 groups: 1) CHX group; 2) control (placebo) group. 169 (n = 88 CHX group, n = 81 control group)	2% CHX solution applied on dentin surface for 60 s	Two-step etch-and rinse adhesive system (Adper Single Bond 2; 3 M ESPE, St. Paul, MN, USA) + nanoparticle composite resin (Filtek Z350; 3 M ESPE, Irvine, CA, USA)	No differences in the restoration retention and failure rates between the CHX and the control groups after 6 months of follow-up
Morgana Favetti, 2017, Brazil[18]	RCT, split-mouth, triple blind	2 groups: 1) CHX group; 2) control (placebo) group. 182 restorations (n = 91 CHX group, n = 91 control group)	2% CHX solution scrubbed on dentin surface for 60 s	Two-step etch-and-rinse adhesive system (Single Bond 2, 3 M ESPE, St. Paul, MN, USA) + nanocomposite resin (Filtek Z350, 3 M ESPE, Irvine, CA, USA)	No differences in the restoration retention and failure rates between the CHX and the control groups, up to 36 months of follow-up

Abbreviations: CT, clinical trial; RCT, randomized controlled clinical trial.

was referred by patients with CHX pretreatment 24 h after the placement of the restorations. However, this perception gradually decreased in all patients and no further sensitivity was reported in neither of the groups after 7 days following the restorative procedures.[19]

4 | DISCUSSION

The present study aimed to revise the available literature on the effectiveness of CHX pre-treatment on the clinical performances of adhesive restorations. Six clinical studies published from 2013–2017 with follow-up times 6–36 months were included in the present review. The majority (4 out of 6) were randomized clinical studies (RCT)[16,18-20] and involved class V NCCL restorations.[16-18,20,21] The studies reported no differences in retention and survival rates of the restorations or marginal adaption and staining, postoperative sensitivity and recurrence of caries between the control and experimental groups.

Another recent study, that was not included into the results of this review due to its study regimen (a combination of in vitro and in vivo evaluations), investigated the use of a CHX solution in combination with different etch-and-rinse and self-etch bonding systems.[22] For this purpose, class I composite restorations were placed in vivo on third molars, which had been designated for extraction. For each adhesive applied, one tooth was treated with 2% CHX solution, while the contralateral tooth was left untreated and served as the control group. The teeth were extracted either after 24 h or after 6 months of the placement of the restoration and processed for the microtensile bond-strength test. Interestingly, the authors concluded that CHX application before adhesive systems caused lower immediate bond-strength values when compared to the control group. However, CHX-treated groups yielded higher bond-strength values in aged specimens, thus highlighting the time-dependent task of CHX on protection and preservation of bonding over time.

Further, two systematic reviews with meta-analyses estimated the influence of CHX on adhesively placed composite restorations.[23,24] These papers focused on extracting and interpreting data from in vitro studies in which the inhibitory MMPs effect of CHX was evaluated based on values obtained from microtensile bond-strength tests. The meta-analyses revealed that CHX application on demineralized dentin did not have a significant influence on immediate bond-strength values. However, the beneficial effect of CHX on resin-based restorations became evident in the function of time, since significantly higher mean bond-strength values were observed in groups where CHX was used between phosphoric acid etching step and adhesive application. The reported differences in microtensile bond-strengths between CHX and control groups were 5.02 MPa, 6.2 MPa and 10.52 MPa for 6, 12 and 24 months, respectively.[23] These values were calculated by the authors of the meta-analyses, based on the data from the available in vitro studies, and it was speculated that the effect of CHX on bond-strength is time-dependent. In order to confirm the time-dependent attribute of the inhibitory effect of CHX, the authors ran further subgroup analyses, which demonstrated that the adhesive system did not influence microtensile bond-strength. However, it should be pointed out that this meta-analysis[23] only considered different brands of etch-and-rinse adhesives and no self-etch adhesive systems were included.

With the attempt to inhibit endogenous dentinal enzymatic activity and therefore improve bond durability of resin-based restorations, CHX can be used in different modes in clinical settings: (a) as a separate aqueous primer[17,18,20,21] as shown in Figure 1; (b) blended within the primer of two-step self-etch adhesive systems,[16] or (c) incorporated into adhesives.[25] It has long been known that CHX has a direct inhibitory effect against MMP-2,-8 and – 9, with MMP-2 being more sensitive than MMP-8 and -9.[26] Although CHX has been widely investigated in in vitro and clinical studies, the mechanism responsible for its MMPs inhibiting property has not yet been entirely elucidated. The proposed mechanism of action involves a chelating mechanism, since CHX is capable of removing zinc and calcium ions which are necessary for the activity of MMPs, but it can also react with catalytic sites within MMPs.[27] Although the mechanism of MMPs inhibition by CHX is thought to be purely electrostatic and therefore reversible, CHX has a high substantivity to dentin, both mineralized and demineralized.[28] In the clinical settings, after orthophosphoric acid etching (three-step or two-step etch-and-rinse strategy) or priming (two-step self-etch strategy), dentin remain partially demineralized, allowing the CHX to exhibit affinity toward the demineralized as well as the underlying mineralized dentinal tissue.

Etch-and-rinse systems are the oldest adhesives in the evolution of dentin bonding agents. When supplied in the three-step version, they involve acid-etching, priming and application of a separate adhesive. In the two-step version, after acid-etching, dentin is simultaneously primed and bonded since the hydrophilic primer and the hydrophobic resin are blended in one solution.[29] Regardless of the number of steps, when used with etch-and-rinse systems, CHX is usually applied as 2% aqueous solution after the dentin surface had been previously etched with 32%–37% phosphoric acid. The separate etching step removes the smear layer and minerals from the dentin surface, and after the phosphoric acid had been rinsed with water, exposed collagen fibrils are left behind.[30] In this case, dentin can be considered as partially demineralized, and applying CHX to this kind of substrate allows it to bind to both collagen matrixes, as well as to the underlying mineralized matrix.[28] Once CHX solution is brushed on dentin, no water rinsing is expected to be performed, since the bound CHX could be displaced by the presence of abundant water.[31] Rather, the CHX-impregnated dentin should be immediately covered by the adhesive system, which, if followed by an adequate polymerization,[32] should promote the incorporation of CHX within the HL over a prolonged period of time.

On the other hand, simplified self-etch adhesives do not require separate etching step with phosphoric acid. They either come as two- or one-step adhesives, depending whether the self-etching primer and the adhesive resin are provided separately or combined into one single solution.[33] Simplified adhesives are composed from acidic monomers that simultaneously condition and prime dentin, through a

partially dissolved smear layer. Since they do not include a separate etching step, the initial substrate for one-step self-etch adhesive systems is mineralized dentin. Compared to partially demineralized dentin, mineralized dentin contains inorganic phase in the form of negatively charged hydroxiapatite which are prone to bind positively charged molecules such those of CHX.[31] However, for the two-step self-etch adhesives, due to the fact that demineralization is achieved by application of primer that contains acidic monomers, the substrate in this specific case can be considered to be partially demineralized dentin, with CHX binding mechanisms similar to the ones previously described for the etch-and-rinse adhesives.

Even though the in vitro studies reported that CHX had the ability to preserve bond-strength of composite restorations even after 5 years of artificial aging,[23] and to preserve the integrity of the HL after 10 years of aging,[15] all the clinical trials included in this paper clearly demonstrated that CHX did not affect the retention and survival rates of composite restorations placed in NCCL. There are several possible explanations for these observations. Firstly, the longest observation period was 36 months,[18,21] and this can be considered as medium-term clinical trial. Failure of restorations due to HL degradation may take longer time to manifest, and some authors suggest that it can take between 5–10 years to observe significant difference between control and experimental groups.[34] Furthermore, there is a considerable difference between the substrates used in the reported in vitro and in vivo studies. The in vitro studies that observed a potential therapeutic effect of CHX were conducted on middle deep to deep healthy coronal dentin.[11,15,35-37] Contrary, the in vivo studies were mainly developed on NCCL.[16-18,20,21] Even though NCCL are considered appropriate to test clinical behavior of adhesively placed restorations since they provide minimal micro-retention,[38] the bond durability in NCCL is clearly compromised due to the specific dentin structure found in these lesions. NCCL are characterized by the presence of obliterated dentinal tubules with sclerotic casts followed by hypermineralized layer and bacterial contamination on the lesion's surface. Interestingly, tensile bond strengths to NCCL were found to be more than 25% lower than those bonded to cavities created in normal cervical root dentin.[39] It is important to emphasize that the structure of hypermineralized surface layer, partially mineralized bacterial layer and intratubular mineral casts may considerably vary depending on the region of the NCCL. For instance, thinner hypermineralized layer was observed in gingival and occlusal surfaces, while apical and deepest part of the wedge-shaped NCCL contained thicker hypermineralized layer. This means that, when applying an etch-and-rinse adhesive system to sclerotic dentin, phosphoric acid is able to partially or even completely dissolve the hypermineralized layer in gingival and occlusal areas of NCCLs. Consequently, the thickness of HL formed in these areas is similar to those formed in sound acid-etched dentin and corresponds to the thickness of approximately 5 μm. However, the morphology of HL in areas with massive hypermineralized layer can be unpredictable, and its reported thickness can be reduced up to 2 μm, with some zones barely demonstrating traces of HL formation, even after the acid etching step had been applied.[40] On the other hand, the etching pattern of mild self-etch primers is less effective compared to phosphoric acid, and it has to be expected that it cannot etch beyond the hypermineralized layer into the sclerotic dentin.[41] Even though thickness of HL is not always directly associated with the highest bond strengths,[42] and high bond strengths can be obtained with minimal infiltration of resin into root dentin,[43] the incorporation of CHX into HL can clearly be compromised by the diffusion barriers of the NCCL sclerotic dentin. Consequently, the beneficial effect of CHX on bond strength preservation observed in most in vitro studies may not be evident in clinically placed composite restorations in NCCL. It should also be mentioned that survival rates of composite restorations in cervical lesions depend on the choice of the adhesive system: restorations placed with three-step etch-and-rinse and two-step self-etch performed better than those placed with two-step etch-and-rinse and one-step self-etch systems.[44]

Furthermore, in a clinical setting, the borders of the cavity preparation (at least partially also in NCCL) are mainly located into enamel. Adhesive bonding to enamel is superior compared to bonding to dentin due to the differences in the morphology and composition of these two tooth tissues.[45] The enamel contains only 4% of water and organic matter and the only MMP found in the enamel is enamelysin (MMP-20).[46] Hence, the inhibitory effect of CHX would be expected to be more prominent in dentin, which is a water-rich tissue, prone to hydrolytic degradation. Therefore, in medium-term clinical studies, it would probably be impossible to account for the full effect of CHX. Further studies are warranted to evaluate the influence of CHX therapeutic primer when applied on dentin surfaces different from those found in NCCL to combine the results of in vitro and in vivo studies in a more realistic perspective.

5 | CONCLUSIONS

Based on the available literature, it can be concluded that, despite several in vitro findings, currently there is still no evidence that supports the use of CHX to improve the prognosis of adhesively-bonded composite restorations. Discrepancies in methodology and conclusions between laboratory and clinical studies were observed, thus direct correlations are challenging to interpret. Finally, additional randomized controlled clinical trials with longer follow-up periods and different dentin substrates, rather than only NCCL, are necessary to investigate the possible beneficial effect of CHX as therapeutic primer on clinical performance of composite restorations.

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REFERENCES

1. Ferracane JL. Resin composite–state of the art. *Dent Mater*. 2011;27 (1):29-38.

2. Nakabayashi N, Nakamura M, Yasuda N. Hybrid layer as a dentin-bonding mechanism. *J Esthet Dent*. 1991;3(4):133-138.
3. Masarwa N, Mohamed A, Abou-Rabii I, Abu Zaghlan R, Steier L. Longevity of self-etch dentin bonding adhesives compared to etch-and-rinse dentin bonding adhesives: a systematic review. *J Evid Based Dent Pract*. 2016;16(2):96-106.
4. Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, De Stefano Dorigo E. Dental adhesion review: aging and stability of the bonded interface. *Dental Materials: Official Publ Academy Dental Mater*. 2008;24(1):90-101.
5. Mazzoni A, Pashley DH, Nishitani Y, et al. Reactivation of inactivated endogenous proteolytic activities in phosphoric acid-etched dentine by etch-and-rinse adhesives. *Biomaterials*. 2006;27(25):4470-4476.
6. Breschi L, Maravic T, Cunha SR, et al. Dentin bonding systems: from dentin collagen structure to bond preservation and clinical applications. *Dent Mater*. 2018;34(1):78-96.
7. Hannas AR, Pereira JC, Granjeiro JM, Tjaderhane L. The role of matrix metalloproteinases in the oral environment. *Acta Odontol Scand*. 2007;65(1):1-13.
8. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*. 2003;92(8):827-839.
9. Mazzoni A, Mannello F, Tay FR, et al. Zymographic analysis and characterization of MMP-2 and -9 forms in human sound dentin. *J Dent Res*. 2007;86(5):436-440.
10. Mazzoni A, Scaffa P, Carrilho M, et al. Effects of etch-and-rinse and self-etch adhesives on dentin MMP-2 and MMP-9. *J Dent Res*. 2013;92(1):82-86.
11. Breschi L, Mazzoni A, Nato F, et al. Chlorhexidine stabilizes the adhesive interface: a 2-year in vitro study. *Dent Mater*. 2010;26(4):320-325.
12. Carrilho MR, Geraldeli S, Tay F, et al. In vivo preservation of the hybrid layer by chlorhexidine. *J Dent Res*. 2007;86(6):529-533.
13. Mobarak EH. Effect of chlorhexidine pretreatment on bond strength durability of caries-affected dentin over 2-year aging in artificial saliva and under simulated intrapulpal pressure. *Oper Dent*. 2011;36(6):649-660.
14. Zheng P, Zaruba M, Attin T, Wiegand A. Effect of different matrix metalloproteinase inhibitors on microtensile bond strength of an etch-and-rinse and a self-etching adhesive to dentin. *Oper Dent*. 2015;40(1):80-86.
15. Breschi L, Maravic T, Comba A, et al. Chlorhexidine preserves the hybrid layer in vitro after 10-years aging. *Dent Mater*. 2020;36(5):672-680.
16. Araujo MS, Souza LC, Apolonio FM, et al. Two-year clinical evaluation of chlorhexidine incorporation in two-step self-etch adhesive. *J Dent*. 2015;43(1):140-148.
17. Dutra-Correa M, Saraceni CH, Ciaramicoli MT, Kiyan VH, Queiroz CS. Effect of chlorhexidine on the 18-month clinical performance of two adhesives. *J Adhes Dent*. 2013;15(3):287-292.
18. Favetti M, Schroeder T, Montagner AF, Correa MB, Pereira-Cenci T, Cenci MS. Effectiveness of pre-treatment with chlorhexidine in restoration retention: a 36-month follow-up randomized clinical trial. *J Dent*. 2017;60:44-49.
19. Hajizadeh H, Ghavamnasiri M, Majidinia S. Randomized clinical evaluation of the effect of chlorhexidine on postoperative sensitivity of posterior composite resin restorations. *Quintessence Int*. 2013;44(10):793-798.
20. Montagner AF, Perroni AP, Correa MB, Masotti AS, Pereira-Cenci T, Cenci MS. Effect of pre-treatment with chlorhexidine on the retention of restorations: a randomized controlled trial. *Braz Dent J*. 2015;26(3):234-241.
21. Sartori N, Stolf SC, Silva SB, Lopes GC, Carrilho M. Influence of chlorhexidine digluconate on the clinical performance of adhesive restorations: a 3-year follow-up. *J Dent*. 2013;41(12):1188-1195.
22. Gunaydin Z, Yazici AR, Cehreli ZC. In vivo and in vitro effects of Chlorhexidine pretreatment on immediate and aged dentin bond strengths. *Oper Dent*. 2016;41(3):258-267.
23. Hamdan-Nassar T, Bellot-Arcis C, Paredes-Gallardo V, et al. Effect of 2% Chlorhexidine following acid etching on microtensile bond strength of resin restorations: a meta-analysis. *Medicina (Kaunas)*. 2019;55(12):769.
24. Zhang X, Wang L, Liu S, Bai H, Niu W. Evaluation of the bond strength of chlorhexidine incorporated into the adhesive system composition: a PRISMA guided meta-analysis. *J Dent Sci*. 2020;15(3):315-328.
25. Maravic T, Comba A, Cunha SR, et al. Long-term bond strength and endogenous enzymatic activity of a chlorhexidine-containing commercially available adhesive. *J Dent*. 2019;84:60-66.
26. Gendron R, Grenier D, Sorsa T, Mayrand D. Inhibition of the activities of matrix metalloproteinases 2, 8, and 9 by chlorhexidine. *Clin Diagn Lab Immunol*. 1999;6(3):437-439.
27. Uitto VJ, Turto H, Huttunen A, Lindy S, Uitto J. Activation of human leukocyte collagenase by compounds reacting with sulfhydryl groups. *Biochim Biophys Acta*. 1980;613(1):168-177.
28. Carrilho MR, Carvalho RM, Sousa EN, et al. Substantivity of chlorhexidine to human dentin. *Dent Mater*. 2010;26(8):779-785.
29. Pashley DH, Tay FR, Breschi L, et al. State of the art etch-and-rinse adhesives. *Dent Mater*. 2011;27(1):1-16.
30. Carvalho RM, Yoshiyama M, Pashley EL, Pashley DH. In vitro study on the dimensional changes of human dentine after demineralization. *Arch Oral Biol*. 1996;41(4):369-377.
31. Kim J, Uchiyama T, Carrilho M, et al. Chlorhexidine binding to mineralized versus demineralized dentin powder. *Dent Mater*. 2010;26(8):771-778.
32. Cadenaro M, Maravic T, Comba A, et al. The role of polymerization in adhesive dentistry. *Dent Mater*. 2019;35(1):e1-e22.
33. Van Meerbeek B, Yoshihara K, Yoshida Y, Mine A, De Munck J, Van Landuyt KL. State of the art of self-etch adhesives. *Dent Mater*. 2011;27(1):17-28.
34. Pannuti CM, Sendyk DI, GraCas YTD, et al. Clinically relevant outcomes in dental clinical trials: challenges and proposals. *Braz Oral Res*. 2020;34(Suppl 2):e073.
35. Breschi L, Cammelli F, Visintini E, et al. Influence of chlorhexidine concentration on the durability of etch-and-rinse dentin bonds: a 12-month in vitro study. *J Adhes Dent*. 2009;11(3):191-198.
36. Stanislawczuk R, Pereira F, Munoz MA, et al. Effects of chlorhexidine-containing adhesives on the durability of resin-dentine interfaces. *J Dent*. 2014;42(1):39-47.
37. Zhou J, Tan J, Chen L, Li D, Tan Y. The incorporation of chlorhexidine in a two-step self-etching adhesive preserves dentin bond in vitro. *J Dent*. 2009;37(10):807-812.
38. Osborne-Smith KL, Burke FJ, Wilson NH. The aetiology of the non-carious cervical lesion. *Int Dent J*. 1999;49(3):139-143.
39. Kwong SM, Cheung GS, Kei LH, et al. Micro-tensile bond strengths to sclerotic dentin using a self-etching and a total-etching technique. *Dent Mater*. 2002;18(5):359-369.
40. Kwong SM, Tay FR, Yip HK, Kei LH, Pashley DH. An ultrastructural study of the application of dentine adhesives to acid-conditioned sclerotic dentine. *J Dent*. 2000;28(7):515-528.
41. Tay FR, Pashley DH. Resin bonding to cervical sclerotic dentin: a review. *J Dent*. 2004;32(3):173-196.
42. Yoshiyama M, Matsuo T, Ebisu S, Pashley D. Regional bond strengths of self-etching/self-priming adhesive systems. *J Dent*. 1998;26(7):609-616.
43. Yoshiyama M, Carvalho RM, Sano H, Horner JA, Brewer PD, Pashley DH. Regional bond strengths of resins to human root dentine. *J Dent*. 1996;24(6):435-442.

44. Schwendicke F, Gostemeyer G, Blunck U, Paris S, Hsu LY, Tu YK. Directly placed restorative materials: review and network meta-analysis. *J Dent Res*. 2016;95(6):613-622.
45. Goldberg M, Kulkarni AB, Young M, Boskey A. Dentin: structure, composition and mineralization. *Front Biosci (Elite Ed)*. 2011;3: 711-735.
46. Sulkala M, Larmas M, Sorsa T, Salo T, Tjaderhane L. The localization of matrix metalloproteinase-20 (MMP-20, enamelysin) in mature human teeth. *J Dent Res*. 2002;81(9):603-607.

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