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Review

Clinical Effectiveness of Pre-treatment with Chlorhexidine in Adhesive Dental Restorations. Systematic Review and Meta-analysis.

Eficacia Clínica del Pretratamiento con Clorhexidina en Restauraciones Dentales Adhesivas. Revisión Sistemática y Metanálisis.

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Abstract: Objective: To determine, by means of a systematic review and meta-analysis, the clinical effectiveness of pre-treatment with chlorhexidine (CHX) in adhesive dental restorations. **Material and Methods:** A literature search was conducted until February 2020, in the biomedical databases: Pubmed, Embase, Scielo, Science Direct, Scopus, SIGLE, LILACS, Google Scholar and the Cochrane Central Registry of Clinical Trials. The selection criteria of the studies were defined, which were: randomized and controlled clinical trials, without language and time restrictions, and reporting the clinical effects (retention, marginal discoloration, marginal adaptation, postoperative sensitivity and secondary caries) of pre-CHX treatment in adhesive dental restorations. Study risk of bias was analyzed using the Cochrane Handbook of Systematic Reviews of Interventions. **Results:** The search strategy resulted in six articles of which five entered a meta-analysis. The studies reported that there was no difference in retention, marginal discoloration, marginal adaptation, postoperative sensitivity, and secondary caries from pre-treatment with CHX in adhesive dental restorations. **Conclusion:** The reviewed literature suggests that pretreatment with CHX does not influence the clinical effectiveness in adhesive dental restorations.

Keywords: *chlorhexidine; dentin; dental restoration, permanent; systematic review; meta-analysis; treatment outcome.*

Resumen: Objetivo: Determinar, mediante revisión sistemática y metaanálisis, la efectividad clínica del pre-tratamiento con clorhexidina (CHX) en restauraciones dentales adhesivas. **Material y Métodos:** Se realizó una búsqueda bibliográfica hasta febrero de 2020, en las bases de datos biomédicas: Pubmed, Embase, Scielo, Science Direct, Scopus, SIGLE, LILACS, Google Scholar y el Registro Cochrane Central de Ensayos Clínicos. Se definieron los criterios de selección de los estudios, que fueron: ensayos clínicos aleatorizados y controlados, sin restricciones de idioma y de tiempo, y que reporten los efectos clínicos (retención, decoloración marginal, adaptación marginal, sensibilidad postoperatoria y caries secundaria) del tratamiento pre-CHX

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en restauraciones dentales adhesivas. El riesgo de sesgo del estudio se analizó mediante el Manual Cochrane de Revisiones Sistemáticas de Intervenciones. **Resultados:** La estrategia de búsqueda dio como resultado seis artículos de los cuales cinco ingresaron en un metanálisis. Los estudios informaron que no hubo diferencias en la retención, la decoloración marginal, la adaptación marginal, la sensibilidad postoperatoria y la caries secundaria del pretratamiento con CHX en las restauraciones dentales adhesivas. **Conclusión:** La literatura revisada sugiere que el pretratamiento con CHX no influye en la efectividad clínica en las restauraciones dentales adhesivas.

Palabra Clave: *clorhexidina; dentina; restauración dental permanente; revisión sistemática; metaanálisis; resultado del tratamiento.*

INTRODUCTION.

Composite resins are the most widely used restorative materials due to their biometization with teeth.[1] However, their longevity and integrity depend on multiple factors, such as: the contraction of the polymerization or degree of conversion of the polymers and the hydrolysis or degradation of the hybrid layer; These can lead to postoperative sensitivity, secondary caries formation, and future restoration failure.[1-4]

Recently, many researchers have focused their studies on the longevity of the bond between adhesive systems and dentin.[1] It is known that in composite restorations the hybrid layer gradually degenerates as a result of hydrolytic degradation of the collagen fibers, even when bacteria and their toxins are not present.[1-3] This degradation can occur due to a number of factors, including: incomplete penetration and infiltration of monomers into the dentin substrate afterwards, or concomitant with demineralization; heterogeneous distribution of monomers throughout the hybrid layer; inadequate or insufficient polymerization; degradation and hydrolysis of both the resin component and the exposed and unhybridized collagen; and the activation of endogenous matrix metalloproteinases (MMP), with enzymatic activity capable of degrading type I collagen fibrils in the hybrid layer.[3,4]

Chlorhexidine (CHX) is a cationic bisguamide, widely known as the main broad-spectrum antimicrobial agent (bacteriostatic at low concentrations and bactericide at high concentrations) that serves to control and prevent gingivitis.[1,5] Its mechanism of action is based on the decomposition of the cytoplasmic membrane of microorganisms by altering their osmotic balance and causing precipitation of cell content.[3]

CHX is an inhibitor of synthetic proteases and its ability to inhibit, in a dose-dependent manner, the collagenolytic activity of MMP-2 and -8 and cysteine cathepsins present in the human dentin-pulp complex or in diseases has been described. inflammatory, such as periodontitis; improving the longevity of the bond between adhesives and dentin.[1,3,4] In fact, Gendron *et al*.,[6] found that the minimum concentrations suitable for this inhibition are 0.001% for MMP-2, 0.02% for MMP-8 and 0.002% for MMP-9.

Sinha *et al*.,[7] demonstrated that the application of CHX significantly increased the immediate bonding strength between the resin and the dentin, where as in Gunaydin *et al*.,[8] concluded that CHX reduced the immediate binding force, but after 6 months (5000 cycles) in the CHX-treated groups, the binding force was higher. Furthermore, it was observed that the application of an aqueous solution of CHX after acid etching resulted in stable resin-dentin bonds after approximately 14 months. Some dentists apply 2% CHX, for 60 seconds, to acid etched dentin in an attempt to increase the durability of resin-dentin bonds by inhibiting endogenous MMPs in the dentin matrix. This method is easy to adopt and probably the first to gain wider acceptance.[5]

A recent systematic review[1] has reported that even though there is evidence that CHX is capable of inhibiting the collagenolytic action of MMPs, it is not clear whether this ability is of clinical importance in composite restorations. And due to the many factors influencing the bond strength of a material to the dentin substrate, further research would be necessary, particularly clinical trials to clarify the effect of CHX on the longevity of dentin bonds. Therefore, the

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objective of this article was to determine the clinical effectiveness of pre-treatment with CHX in adhesive dental restorations.

MATERIALS AND METHODS.

The development of this review was carried out according to a protocol defined a priori by all the authors following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards[10]

Search

A comprehensive search strategy was carried out in the biomedical databases Pubmed, Embase, Scielo, Science Direct, Scopus, SIGLE (System of Information on Gray Literature in Europe), LILACS, Google Scholar and in the Cochrane Central Registry of Clinical Trials up to February 2020; using a combination of thematic headings using the following keywords and Boolean connectors: ((digluconate chlorhexidine*) OR chlorhexidine) AND (((dentin* adhesive) OR adhesive system*) OR bond*) AND (clinical trial).

The electronic search in the databases was carried out by two authors (HA and AR) independently and the final decision for inclusion was according to the following selection criteria:

Inclusion criteria

- Articles that report the use of CHX.
- Articles reporting clinical effects of CHX pretreatment (retention, marginal discoloration, marginal adaptation, post-operative sensitivity, and secondary caries) in adhesive dental restorations and that have a control group without CHX.
- Articles without language restriction and up to 10 years old.
- Articles that are clinical trials with a follow-up time greater than or equal to 3 months.

Exclusion criteria

- Articles that are from non-indexed journals.

Data selection and extraction process:

The titles and abstracts of each of the studies obtained with the inclusion and exclusion criteria previously described were reviewed; and the full texts of the studies that met these parameters were obtained in order to determine their risk of bias.

In order to assess the studies, a checklist was made in duplicate, in order to extract the information of interest and switch the data. Two reviewers (AR and FC) independently carried out the evaluation of the articles regarding name, author, year of publication, type of study, number of patients (proportion between males and females), number of teeth examined, mean age and age range of the patients, follow-up time, country where the study was conducted, study groups, number of patients per study group, number of teeth per study group, type of restoration (according to Black), types of treated teeth, evaluation criteria used, etching method, adhesive and resin used, time of use of chlorhexidine, inclusion and exclusion criteria, retention, absence of marginal discoloration, adequate marginal adaptation, absence of post-operative sensitivity, absence of caries secondary and risk of bias of each study. In order to resolve any discrepancies between the reviewers, they met and discussed together with a third reviewer (EI) in order to reach an agreement.

Assessment of the risk of bias of the studies

For the assessment of risk of bias, each study was analyzed according to the Cochrane Manual of systematic reviews of interventions[11]

Analysis of results

The data from each study was placed and analyzed in the RevMan 5.3 program (Cochrane Group, UK).

RESULTS.

Selection of studies

The initial search in the biomedical databases determined a total of 1475 titles, available until February 2020, of which 87 were repeated titles, leaving only 1388. The titles were read and 1279 were excluded, leaving 109, their abstracts were later read, discarding those who did not meet the inclusion criteria. Six articles were selected for an exhaustive review of their content, their methodology and five were used for a meta-analysis (Figure 1).

Characteristic and results of the studies

In all included studies[12-17] the number of patients ranged from 14 to 42 with a follow-up time from 6 months to 3 years. Four studies[13-15,17] reported that the mean age of the patients was between 46.7 and 49.7 years. Two studies[14,16] reported that the total number of patients in relation to their gender (males and females) was 28 and 44 respectively. Five

Figure 1. Flow chart of article selection.

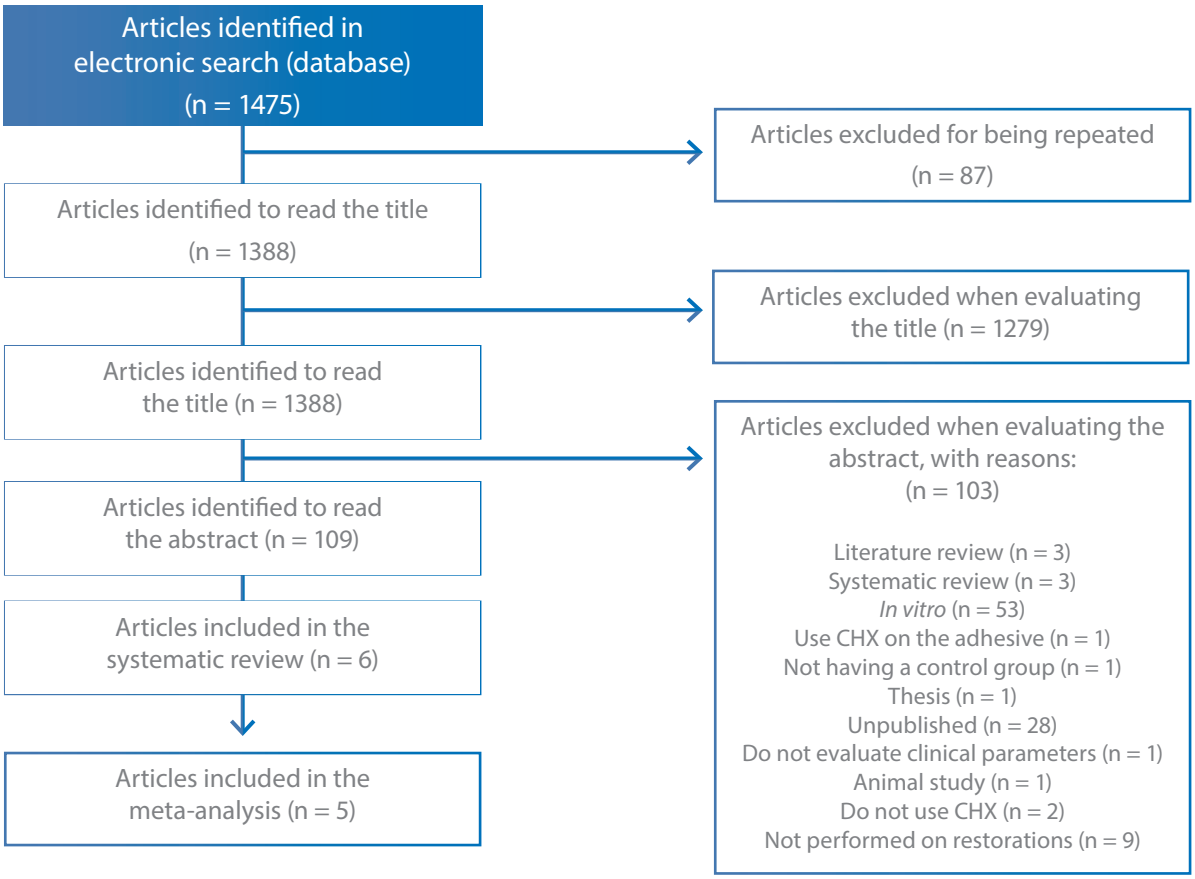
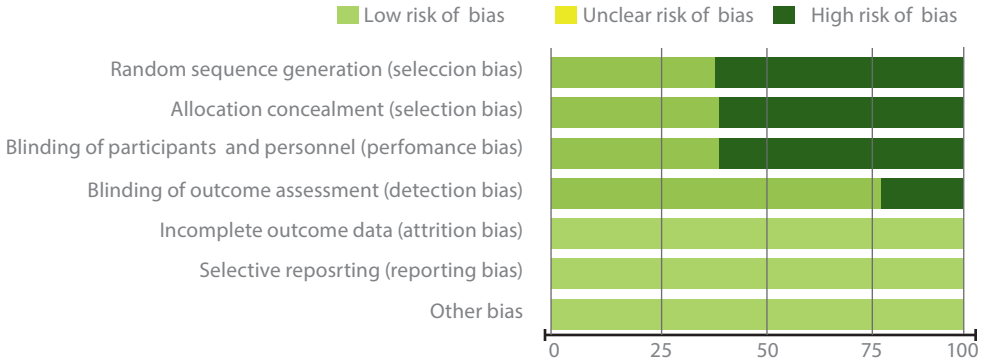


Figure 2. Risk of bias of included studies



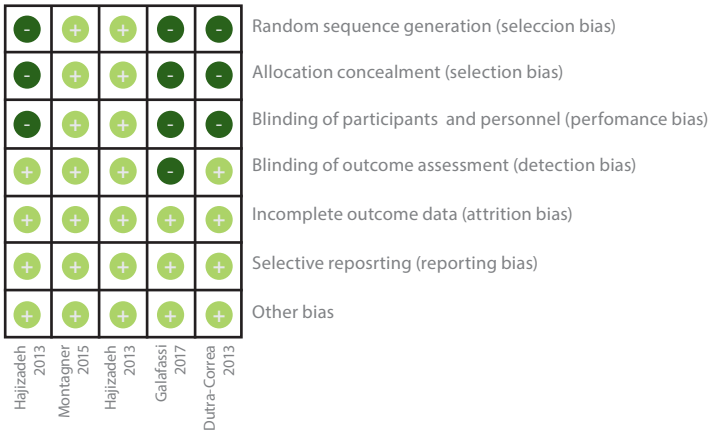


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Figure 3. **Forest plot and funnel plot of the event "Clinical effectiveness of CHX pre-treatment in adhesive dental restorations"**

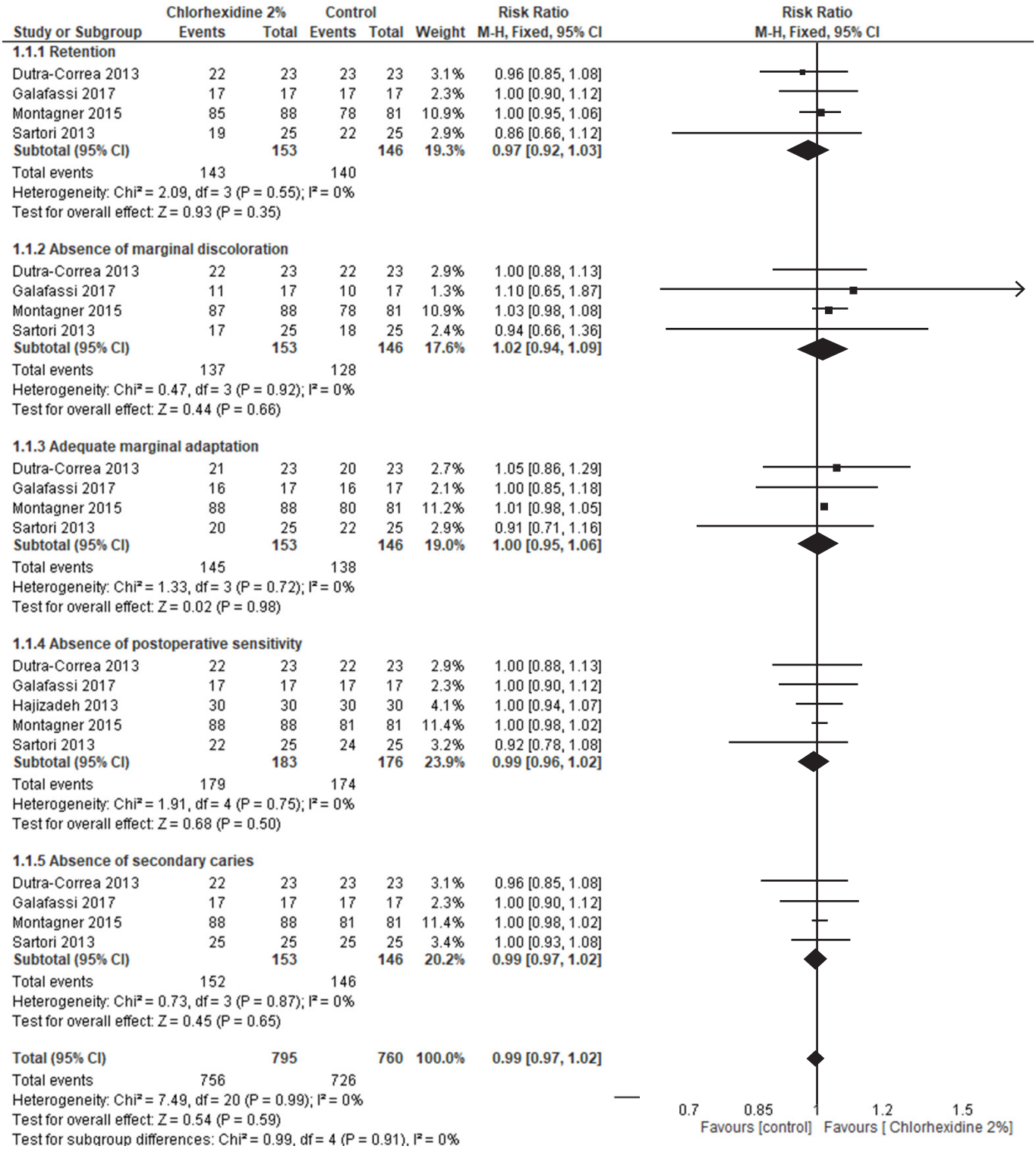

Table 1. Characteristics of included studies.

Author	Year	Type of study	Number of patients (male / female)	Number of teeth examined	Mean age (range)	Follow-up time	Country	Type of restoration	Type of teeth	Assessment	Etching	Time of use of CHX	Study groups	Number of patients per group	Number of teeth per group
Galafassi *et al.* [12]	2017	RCT crossover	17	68	(8 – 12)	1 year	Brazil	Class I	Permanent molars	Modified Criteria of the United States Public Health System	37% phosphoric acid for 30s (enamel) and 15s (dentin)	60 s	Er: YAG laser + CHX 2% Er: YAG laser + Deionized water High and low speed turbine + CHX 2% High and low speed turbine + Deionized water	17 17 17 17	17 17 17 17
Favetti *et al.* [13]	2017	RCT crossover of triple blind	29	105	49.7	3 years	Brazil	Class V	Incisors, canines and premolars	Criteria of the International Dental Federation	35% phosphoric acid for 20s (enamel) and 15s (dentin)	60 s	CHX 2% Control	29 29	49 56
Montagner *et al.* [14]	2015	RCT crossover of triple blind	42 (20 / 22)	169	49 (21 – 76)	6 months	Brazil	Class V	Incisors, canines and premolars	Criteria of the International Dental Federation	35% phosphoric acid for 15s (enamel) and 20s (dentin)	60 s	CHX 2% Control	42 42	88 81
Sartori *et al.* [15]	2013	RCT crossover	14	50	46.7 (33 – 64)	3 years	Brazil	Class V	Incisors, canines, premolars and molars	Clinical obser-vation criteria and verbal rating scale	32% phosphoric acid for 30s (enamel) and 15s (dentin)	30 s	CHX 2% Control	14 14	25 25
Hajizadeh *et al.* [16]	2013	RCT crossover of double blind	30 (8 / 22)	60	(20 – 35)	6 months	Iran	Class II	Premolars	Analog Visual Scale	35% phosphoric acid for 10s (enamel) and 5s (dentin)	60 s	CHX 2% Control	30 30	30 30
Dutra-Correa *et al.* [17]	2013	RCT	37	92	48.7 (27 – 79)	18 months	Brazil	Class V	Incisors, canines, premolars and molars	Modified Criteria of the United States Public Health System	36% phosphoric acid for 15s (enamel) and 15s (dentin)	20 s	XP Bond + CHX 2% XP Bond Xeno V + CHX 2% Xeno V	NR NR NR NR	23 23 23 23

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Table 2. Inclusion and exclusion criteria of included studies

Author	Year	Inclusion criteria	Exclusion criteria
Galafassi et al. 12	2017	Patients with the presence of four active carious lesions in the dentin that were located on the occlusal surfaces (class I) of the contralateral first permanent molars, with vital pulps and without sealants, amalgam, glass ionomer cement or composite resin restorations.	Not reported
Favetti et al. 13	2017	Patients with at least 2 non-carious cervical lesions in the incisors, canines or premolars and that are at least 1 mm deep on the buccal faces, and a small part may extend towards the interproximal region; with more than 20 teeth present in the mouth; over 18 years; able to understand free and informed consent; in good periodontal health.	Patients who smoked, with bruxism, with severe systemic diseases, undergoing orthodontic treatment, with non-carious cervical lesions but without antagonists, with teeth that show more than 50% wear on the incisal and / or occlusal faces, with the presence of decomposition or restoration in the area to be treated, with a plaque index and gingival bleeding index greater than 20%, with probing depth and clinical insertion loss greater than 4 mm, with probing bleeding, with lack of interest in exchange for follow-up or refusal to participate.
Montagner et al. 14	2015	Patients with at least two non-carious cervical lesions in the incisors, canines or premolars and that are at least 1 mm deep on the buccal faces, and a small part may extend towards the interproximal region; with more than 20 teeth present in the mouth; over 18 years; able to understand free and informed consent; in good periodontal health.	Patients with smoking, bruxism, severe systemic diseases, in active orthodontic treatment and malocclusion, non-carious cervical lesions without antagonist with wear greater than 50% of the incisal / occlusal surface, presence of caries or restorations in the area to be treated, plaque index or gingival bleeding index greater than 20%, depth on probing and clinical insertion loss greater than 4 mm with bleeding on probing, unwillingness to return to follow-ups or refusal to participate.
Sartori et al. 15	2013	Patients over 18 years of age, living in or near the university, with more than 20 natural teeth, with 2 or 4 non-carious cervical lesions in different hemiarcates (1 - 3 mm occluso-gingival height and depth 1 - 2 mm), non-retentive lesions with ≥ 50% of the enamel margins and ≥ 75% of the total dentin area, lesions with a healthy or restored adjacent tooth, cervical margins in dentin, with good to regular oral hygiene (plaque index <1 / 4 of the teeth).	Patients who cannot return to follow-ups, pregnant in lactation, who use pain relievers and/ or anti-inflammatories, with severe systemic or psychological diseases, under orthodontic treatment, who use fluorides or desensitizing agents, with bruxism, with periodontal disease, with caries, fractures, premature contacts, cracks or defective restorations, with scleral dentin (grade 4) accor ding to the classification of the University of North Carolina.
Hajizadeh et al. 16	2013	Patients older than 18 years, with 2 Class II injuries and requiring resin restoration.	Patients with amalgam restorations, who report dental and / or oral sensitivity, who consume medications that interfere with pain perception.
Dutra-Correa et al. 17	2013	Patients with 20 teeth, in good dental and periodontal health, with non-carious cervical lesions with a healthy adjacent tooth that presents an antagonist with a normal occlusion relationship.	Caries patients, with a history of episodes of tooth sensitivity, who have received treatment for tooth sensitivity either with toothpastes or any other product, bruxism, facets of wear on the posterior teeth, inability to return to follow-ups, dental fracture, who are consuming pain relievers, anti-inflammatories or any other type of psychotropic drug, pregnant and lactating, allergic to any component of the resins, with orthodontic treatment in the last 3 months, carved dental pieces or with fixed prostheses, with periodontics with pathological symptoms, with periodontal disease or with periodontal surgical treatment in the last 3 months.

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studies[12,14–17] reported that the ages of the patients ranged from 8 to 79 years. The countries where the studies were carried out were: Brazil,[12-15,17] and Iran.[16] (Table 1)

The total number of patients treated and teeth examined were 169 and 544 respectively. A control group that did not use CHX was used in all studies.[12-17] Among the types of restorations carried out, it was observed that four studies,[13,15,17] treated class V restorations, one study[12] treated class I restorations and 1 study[16] treated class II restorations (Table 1).

Within the evaluated clinical parameters, it was observed that four studies[12,14,15,17] reported retention, absence of marginal discoloration, adequate marginal adaptation and absence of secondary caries in the restorations; and in five studies[12,14-17] the absence of postoperative sensitivity was reported (Table 1).

Among the types of teeth treated, it was observed that two studies[13,14] treated incisors, canines and premolars; one study[12] treated molars; one study[16] treated premolars; and two studies[15,17] treated incisors, canines, premolars and molars. Three studies[13,14,16] reported that they used 35% phosphoric acid, one study[12] reported that they used 37% phosphoric acid, one study[15] reported that they used 32% phosphoric acid, and one study[17] reported that they used phosphoric acid at 36%.

Four studies[12-14,16] reported that chlorhexidine was used for 60 seconds, one study[15] used chlorhexidine for 30 seconds, and one study[17] used chlorhexidine for 20 seconds. The inclusion and exclusion criteria of each of the studies can be seen in Table 2.

Analysis of risk of bias of the studies

Two studies[16,18] showed a low risk of bias and four studies[12,13,15,17] showed a high risk of bias (Figure 2).

Synthesis of results (Meta-analysis)

Analysis of the clinical effectiveness of pre-treatment with CHX in adhesive dental restorations (Figures 3):

The clinical parameters evaluated to determine the effectiveness of pre-treatment with CHX in adhesive dental restorations, were determined in five studies[12,14–17] revealing that there was no significant difference, favoring the non-use of CHX.

Subgroup analysis

Retention, absence of marginal discoloration, adequate marginal adaptation and absence of secondary caries of adhesive dental restorations was determined in four studies[12,14,15,17] revealing that there was no significant difference. The absence of postoperative sensitivity was determined in five studies.[12,14-17] revealing that there was no significant difference.

DISCUSSION.

There are many factors that influence the bond strength of a restorative material to the dentinal substrate. Mechanical stresses from chewing forces, changes in temperature and pH, water absorption, resin contraction, and enzymatic action affect the integrity of the bonds in different extensions. Furthermore, the type and composition of the composite resin and the adhesive system, as well as the dentinal substrate are of great importance.[1]

Scientific studies have shown that the application of CHX for 60 seconds immediately after etching with three-step dental adhesives and two-step dental adhesives with etch and rinse preserves the strength of the bonding force between the composite and the dentinal substrate.[1] Its application before etching is not effective because the bond of chlorhexidine to mineralized dentin (and without etching) is almost 80% less than to demineralized dentin.[18] In addition, some studies have shown that the clinical application of 2% CHX for 60 seconds on etched dentin, after rinsing the acid and before applying the adhesive and resin, significantly minimizes the degradation of the bond strength of MMPs during at least up to 14 months.[1,5,20] For this reason, many dentists currently apply 2% CHX for 60 seconds to etched dentin in resin restorations in an attempt to increase the durability of resin-dentin bonds by inhibiting endogenous MMPs.[1]

However, the present systematic review and meta-analysis, which aimed to determine the clinical effectiveness of pre-treatment with CHX in adhesive dental restorations, based on randomized clinical trials (RCTs), demonstrated that pre-treatment with CHX does not caused an improvement in retention, marginal discoloration, marginal adaptation, postoperative sensitivity and secondary caries in adhesive dental restorations.

These results may possibly be due to the fact that

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the studies that support the use of CHX as a pre-treatment in adhesive dental restorations are in vitro studies and in clinical trials there are multiple factors that cannot be replicated in the laboratory.

However, multiple studies have not reported side effects for CHX (such as brown staining or unpleasant taste alteration) in short-term applications. Therefore, it would not have any negative effect when used in the adhesion process.[9]

Regarding the effect of CHX on dental adhesives, a comparison could not be made in the present review as all included studies used etch and rinse adhesive. Several studies have shown that etch and rinse adhesives achieve higher bond values than single stage self-etch adhesives.[21] The reason is that weak acids have the potential to activate MMPs, particularly when their pH is between 2.3 and 5, which is the case with many self-etching adhesives, making them very effective in activating gelatinous action.[5] Therefore, the adhesion depends on the adhesive system used, being the non-simplified adhesive systems (etching and rinsing) more stable and effective than the simplified adhesive systems (self-etching).[22]

In this study, a fixed effects model was used for the meta-analysis due to the homogeneity (I^2=0%) that existed between each of the studies. The strength of the present systematic review lies in the selection of the studies because an exhaustive search of the most important databases was used and strict selection criteria were used.

Unfortunately, the present study cannot be compared with other systematic reviews, because the systematic reviews that have been carried out have been based on in vitro studies, sometimes including very few studies in humans. However, the authors believe that these results cannot be generalized yet, because to the RCTs analyzed only two studies showed a low risk of bias. Furthermore, these studies are from South American and Asian countries and, therefore, these countries are not representative of the whole world, which can cause a dilemma since each continent and country has its own culture, ethnicity and type of food; and we believe these factors may influence future results.

As such, we recommend conducting well-designed RCTs avoiding heterogeneity between each of the studies and dealing with this issue in the other countries of the rest of the continents, in order to compare the results and reach a clearer and clearer conclusion general.

CONCLUSION.

In general and based on the results obtained, pre-treatment with CHX does not influence the clinical effectiveness of adhesive dental restorations.

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Authors' contributions: Arbildo H: Planned the protocol for the systematic review and meta-analysis, searched databases, supervised the progress made, is the corresponding author, performed the meta-analysis and revised the final manuscript; Rendón A: Searched databases, extracted data from the selected articles, collected data and revised the final manuscript; Cruzado F : Extracted data from the selected articles, collected data, assessed the methodological quality of the included studies, and revised the final manuscript; Infantes E: Extracted the data from the selected articles, collected data, assessed the methodological quality of the included studies, and revised the final manuscript; Agüero J: Collected the data; Resolved any discrepancy between the reviewers when evaluating the methodological quality of the included studies and revised the final manuscript; Vásquez H: Drafted the manuscript and revised the final manuscript.
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