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Does Addition of 10-MDP Monomer in Self-etch Adhesive Systems Improve the Clinical Performance of Noncarious Cervical Lesion Restorations? A Systematic Review and Meta-analysis

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Clinical Relevance

The presence of 10-MDP monomer in self-etch adhesive systems did not influence the clinical performance of noncarious cervical lesion (NCCL) restorations.

SUMMARY

Background: Functional acidic monomers are able to chemically interact with hydroxyapatite, and this bond appears to be very stable. Therefore, this aspect of the 10-MDP molecule made it attractive and added to self-etch adhesives. Objectives: The objective of this Systematic Review (SR) and Meta-analysis (MA) was to determine whether systems with the 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) functional monomer in their formula showed better clinical performance in restorations placed in noncarious cervical lesions (NCCL) when compared to systems without it.

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Data and sources: An e-search was conducted through MEDLINE via PubMed, Cochrane Library, Scopus, Web of Science, OpenGrey, Clinical Trials, Current Controlled Trials, and EU Clinical Trials Register, and a search through the references of included studies was also performed. Randomized Controlled Clinical Trials, in which the effectiveness of self-etch adhesive systems, with or without the 10-MDP functional monomer for NCCL, was discussed, were included. Risk of bias was performed according to the Cochrane Collaboration tool, and the certainty of evidence was evaluated through GRADE.

Study selection: The data were grouped, heterogeneity (I^2) was tested, and after duplicate removal, 4208 manuscripts were retrieved. From these, 11 studies were included in the qualitative analysis (risk of bias), with nine classified as low risk and two unclear. GRADE analysis detected moderate-to-high certainty of evidence, so the quantitative synthesis [Meta-analysis (MA)] was performed including the 11 studies.

Results and Conclusion: There were no statistical differences in the clinical performance of restorations conducted using "with or without 10-MDP" adhesive types, for all evaluated criteria (p=0.05), with heterogeneity ranging from 0% to 53%. Thus, the presence of 10-MDP functional monomer did not influence the clinical performance of restorations placed in NCCL.

INTRODUCTION

Due to its organic–inorganic nature, dentin still remains a challenging substrate when a stable and long-lasting bond is desired. Self-etch systems bond composite resin materials to dental substrates; however, some drawbacks still need to overcome,[1-4] so, to improve their effectiveness, different functional monomers have been included in adhesive system formulae, and their effectiveness has been studied over the past decades.[5,6]

In a recent systematic review (SR) and meta-analysis (MA),[7] 2-hydroxyethyl methacrylate (HEMA)-free adhesive was compared to HEMA-containing systems, and similar clinical behaviour was found. HEMA is a monomer present in a great number of systems and plays an important role, due to its hydrophilicity, wettability, and miscibility.[8,9] However, some other monomers that have different functions are also found in adhesive systems, especially in self-etch systems.

Functional acidic monomers, for instance, present in self-etch mode, are able to chemically interact with hydroxyapatite (HAp) and are composed by specific carboxylic, phosphonic, or phosphate groups, such as: Phenyl-P, 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) and 4-methacryloyloxyethyl trimellitic acid (4-MET).[10]

Depending upon the acid dissociation constants (pKa values), etching aggressiveness in self-etch adhesive systems can be classified into "strong" (pH$<$1), "intermediately strong" (pH$\approx$1.5), "mild" (pH$\approx$2), and "ultramild" (pH$\geq$2.5).[11] The more aggressive the system, the deeper demineralization of the tooth substrate occurs, resembling that of phosphoric acid-etching treatment.[12]

Mild self-etch adhesives bond to tooth tissue through a twofold micromechanical and chemical bonding mechanism. They only partially demineralize dentin, with some HAp remaining around the collagen within a submicron, hybrid layer.[13,14] Thus, functional acidic monomers, such as 10-MDP, that are able to react with calcium, would certainly bond electrostatically to HAp, forming calcium salt around the partially demineralized collagen fibers. This possibility has been proved by X-ray photoelectron spectroscopy (XPS).[5]

After patent expiration of the 10-MDP molecule from Kuraray, this monomer quickly became present in the compositions of several brands of so-called multimode or universal adhesives. Several aspects of the 10-MDP molecule made it attractive: firstly, it readily adhered to HAp, and this bond appeared to be very stable, as confirmed by the low dissolution rate of its calcium salt in water.[15] Secondly, 10-MDP bonding versatility has allowed its use beyond dental substrates, to several others, such as zirconia, lithium-disilicate, and metals, which has been very interesting from a clinical viewpoint.[16,17] Therefore, 10-MDP was introduced very quickly into multimode adhesive system compositions (the so-called universal adhesives) globally.

It is important to mention that 10-MDP is not the only constituent in adhesive system compositions, but is present amongst a blend of monomers, solvents, initiators and, nowadays, nanoparticles, which combine to complete the adhesive process.[10] However, due to the great interest in the addition of 10-MDP to adhesive systems, and the good results

presented in laboratory studies,[18-23] the aim of this paper was to present a review of the clinical performance of noncarious cervical lesion (NCCL) resin restorations made with adhesives that either did, or did not, contain the 10-MDP monomer, through SR and MA.

METHODS

Protocol and Registration

This study protocol was registered at the Prospective Register of Systematic Reviews (PROSPERO - CRD42016050538), and it followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement on the reporting of SR.[24]

Information Sources, Eligibility criteria and Search Strategy

The Medical Subject Heading (MeSH) terms, synonyms, and free terms (keywords) in the search strategy were defined using the PICOS[25] guidelines:

1. Population (P): Adult patients with NCCLs
2. Intervention (I): Composite resin restorations placed in NCCLs in a self-etch mode, with 10-MDP-containing adhesive systems
3. Comparison (C): Composite resin restorations placed in NCCLs in a self-etch mode without 10-MDP in the adhesive system formulae
4. Outcome (O): Clinical performance of restorations (note that no outcome was used in the search strategy to maximize its results)
5. Study design (S): Randomised controlled clinical trials (RCTs) and controlled clinical trials (CCTs).

In this sense, only RCTs comparing the clinical effectiveness of self-etch adhesive systems with and without the functional monomer 10-MDP for NCCL direct resin composite restorations in the permanent dentition of adult patients (male and female) of any age group were included. Editorial letters, historical reviews, pilot studies, *in vitro* studies, and cohort, observational, and descriptive studies, such as case reports and case series, were excluded.

To identify articles for inclusion in this review, an electronic search of the literature was conducted up to 21 March 2019, plus an alert for recently published articles was requested from the following databases: MEDLINE via PubMed, Web of Science, Scopus, Cochrane Library, OpenGrey, Clinical Trials, Current Controlled Trials, and EU Clinical Controlled Trials. No restrictions were applied on either publication date or language, except that the study must have included a follow-up of at least 1 year.

The search strategies were defined appropriately for each database (Table 1), and searches were performed by two independent reviewers (RPO and JCPB) to identify eligible studies. Full-text versions of all articles that appeared to meet the inclusion criteria were obtained for subsequent evaluation and data extraction. Next, a hand search was performed in the reference lists of included articles to identify any additional relevant studies that had not been found during database searches.

Study Selection and Data Collection Process

According to the described search strategy, article selection was first performed by title and abstract. If articles appeared in more than one database, they were included only once; and, in cases with different follow-up periods for the same study, only the last version was accepted. Full-text articles were obtained when there was not sufficient information in the title and abstract, and for cases lacking data within the full text, the authors were contacted weekly, for up to five weeks, to clarify the data. Subsequently, the two reviewers classified the articles that met the inclusion criteria. Each eligible study received an ID combining the first author and year of publication.

Relevant details about the study design, participants, interventions, and outcome were extracted, using customized extraction forms. If there were reports of the same study with different follow-ups, data extraction was performed using data from the largest follow-up period.

Risk of Bias in Individual Studies

The Cochrane Collaboration's tool for assessing risk of bias in RCTs was used by two independent reviewers (RPO and JCPB) to perform quality assessments of the trials. The assessment criteria contained six items: sequence generation, allocation concealment, blinding of the outcome assessor, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Any disagreement between the reviewers during data selection and quality assessment had to be discussed until an agreement was reached. If necessary, a third reviewer was involved as referee (TSPS).

The risk of bias for each domain of each quality assessment was scored following recommendations described in the Cochrane Handbook for Systematic

Table 1: *Search Strategies for Databases*

Pubmed #1 AND #2 AND #3 (21/03/2019)
#1 (tooth erosion[MeSH Terms]) OR "tooth erosion"[Title/Abstract]) OR "tooth erosions"[Title/Abstract]) OR "teeth erosion"[Title/Abstract]) OR "teeth erosions"[Title/Abstract]) OR tooth abrasion[MeSH Terms]) OR "tooth abrasion"[Title/Abstract]) OR "tooth abrasions"[Title/Abstract]) OR "teeth abrasion"[Title/Abstract]) OR "teeth abrasions"[Title/Abstract]) OR "dental abrasion"[Title/Abstract]) OR tooth wear[MeSH Terms]) OR "tooth wear"[Title/Abstract]) OR "teeth wear"[Title/Abstract]) OR "dental wear"[Title/Abstract]) OR "tooth abfraction"[Title/Abstract]) OR "teeth abfraction"[Title/Abstract]) OR permanent dental restorations[MeSH Terms]) OR "permanent dental restorations"[Title/Abstract]) OR "permanent dental restoration"[Title/Abstract]) OR "permanent dental fillings"[Title/Abstract]) OR "permanent dental filling"[Title/Abstract]) OR dental restoration, permanent[MeSH Terms]) OR "NCCL"[Title/Abstract]) OR NCCLs[Title/Abstract]) OR "noncarious cervical lesion"[Title/Abstract]) OR "noncarious cervical lesion"[Title/Abstract]) OR "noncarious cervical lesion"[Title/Abstract]) OR "cervical lesion"[Title/Abstract]) OR "cervical lesions"[Title/Abstract]) OR "class V lesion"[Title/Abstract]) OR "cervical restorations"[Title/Abstract]) OR "cervical restoration"[Title/Abstract]) OR "class v restoration"[Title/Abstract]) OR "class v"[Title/Abstract]) OR "class 5"[Title/Abstract]
#2 (monomer*[Title/Abstract]) OR "functional monomer"[Title/Abstract]) OR "10 MDP"[Title/Abstract]) OR 10-MDP[Title/Abstract]) OR MDP[Title/Abstract]) OR "phosphatic monomer"[Title/Abstract]) OR "methacryloyloxi-decyl-dihydrogen-phosphate"[Title/Abstract]) OR 10-methacryloyloxydecyldihydrogenphosphate[Title/Abstract]) OR "10-methacryloyloxydecyl dihydrogen phosphate"[Title/Abstract]) OR adhesives[MeSH Terms]) OR adhesives[Title/Abstract]) OR adhesive[Title/Abstract]) OR "adhesive material"[Title/Abstract]) OR dentin-bonding agents[MeSH Terms]) OR "dentin-bonding agents"[Title/Abstract]) OR dental-bonding agents[MeSH Terms]) OR "dental-bonding agents"[Title/Abstract]) OR dental bonding[MeSH Terms]) OR "dental bonding"[Title/Abstract]) OR bonding[Title/Abstract]) OR "dentin bonding"[Title/Abstract]) OR "dental adhesive"[Title/Abstract]) OR "dental adhesion"[Title/Abstract]) OR "agents, dentin bonding"[Title/Abstract]) OR "bonding agents, dentin"[Title/Abstract]) OR "dentin-bonding agents"[Title/Abstract]) OR "dentin bonding agents"[Title/Abstract]) OR "bonding, dental"[Title/Abstract]) OR "etch-and-rinse adhesive"[Title/Abstract]) OR "total-etch adhesive"[Title/Abstract]) OR "self-etch adhesive"[Title/Abstract]) OR "self-etching adhesive"[Title/Abstract]) OR "all-in-one adhesive"[Title/Abstract]) OR "one-bottle adhesive"[Title/Abstract]) OR "etching adhesive"[Title/Abstract]
#3 (clinical trial[MeSH Terms]) OR clinical trial*[Title/Abstract]) OR clinical*[Title/Abstract]) OR trial*[Title/Abstract]) OR clinical study[MeSH Terms]) OR clinical stud*[Title/Abstract]) OR prospective studies[MeSH Terms]) OR prospective stud*[Title/Abstract]) OR prospective evaluation*[Title/Abstract]) OR longitudinal studies[MeSH Terms]) OR longitudinal stud*[Title/Abstract]) OR longitudinal survey*[Title/Abstract]) OR controlled clinical trial[MeSH Terms]) OR controlled clinical trial*[Title/Abstract]) OR randomized controlled trial[MeSH Terms]) OR randomized controlled trial*[Title/Abstract]) OR random allocation[MeSH Terms]) OR "random allocation"[Title/Abstract]) OR observational study[MeSH Terms]) OR double-blind method[MeSH Terms]) OR "double-blind method"[Title/Abstract]) OR "double blind method"[Title/Abstract]) OR "double-blind study"[Title/Abstract]) OR "double blind study"[Title/Abstract]) OR single-blind method[MeSH Terms]) OR "single-blind method"[Title/Abstract]) OR "single blind method"[Title/Abstract]) OR "single-blind study"[Title/Abstract]) OR "single blind study"[Title/Abstract]) OR "comparative study"[Title/Abstract]) OR follow-up studies[MeSH Terms]) OR "follow-up studies"[Title/Abstract]) OR "follow-up study"[Title/Abstract]) OR "follow up study"[Title/Abstract]) OR "follow-up study"[Title/Abstract]) OR randomization*[Title/Abstract]) OR "double-masked method"[Title/Abstract]) OR "double masked method"[Title/Abstract]) OR "double-masked study"[Title/Abstract]) OR "double masked study"[Title/Abstract]) OR controlled clinical stud*[Title/Abstract]
Web of Science #1 AND #2 (21/03/2019)
#1 "tooth erosion" *OR* "teeth erosion" *OR* "tooth abrasion" *OR* "teeth abrasion" *OR* "dental abrasion" *OR* "tooth wear" *OR* "teeth wear" *OR* "dental wear" *OR* "tooth abfraction" *OR* "teeth abfraction" *OR* permanent dental restoration* *OR* "permanent dental filling" *OR* NCCL *OR* cervical lesion* *OR* non carious cervical lesion* *OR* non* carious cervical lesion* *OR* class V lesion* *OR* cervical restoration* *OR* class V restoration*
#2 monomer* *OR* "functional monomer" *OR* "10 MDP" *OR* 10-MDP *OR* MDP *OR* "phosphatic monomer" *OR* "methacryloyloxi-decyl-dihydrogen-phosphate" *OR* 10-methacryloyloxydecyldihydrogenphosphate *OR* "10-methacryloyloxydecyl dihydrogen phosphate" *OR* adhesive* *OR* "adhesive material" *OR* dentin-bonding agent* *OR* dentin bonding agent* *OR* dental-bonding agent* *OR* dental bonding agent* *OR* "dental bonding" *OR* "dentin bonding" *OR* bonding *OR* "dental adhesive" *OR* "dental adhesion"
Scopus #1 AND #2 AND #3 (21/03/2019)
#1 (TITLE-ABS-KEY ("tooth erosion") OR TITLE-ABS-KEY ("tooth erosions") OR TITLE-ABS-KEY ("teeth erosion") OR TITLE-ABS-KEY ("teeth erosions") OR TITLE-ABS-KEY ("tooth abrasion") OR TITLE-ABS-KEY ("tooth abrasions") OR TITLE-ABS-KEY ("teeth abrasion") OR TITLE-ABS-KEY ("teeth abrasions") OR TITLE-ABS-KEY ("dental abrasion") OR TITLE-ABS-KEY ("tooth wear") OR TITLE-ABS-KEY ("teeth wear") OR TITLE-ABS-KEY ("dental wear") OR TITLE-ABS-KEY ("tooth abfraction") OR TITLE-ABS-KEY ("teeth abfraction") OR TITLE-ABS-KEY ("permanent dental restoration") OR TITLE-ABS-KEY ("permanent dental fillings") OR TITLE-ABS-KEY ("permanent dental filling") OR TITLE-ABS-KEY ("dental restoration, permanent") OR TITLE-ABS-KEY ("NCCL") OR TITLE-ABS-KEY ("NCCLs") OR TITLE-ABS-KEY ("noncarious cervical lesion") OR TITLE-ABS-KEY ("noncarious cervical lesion") OR TITLE-ABS-KEY ("non carious cervical lesion") OR TITLE-ABS-KEY ("cervical lesion") OR TITLE-ABS-KEY ("cervical lesions") OR TITLE-ABS-KEY ("class V lesion") OR TITLE-ABS-KEY ("cervical restoration") OR TITLE-ABS-KEY ("cervical restorations") OR TITLE-ABS-KEY ("class V restoration") OR ("class V") OR TITLE-ABS-KEY ("class 5"))
#2 (TITLE-ABS-KEY (monomer*) OR TITLE-ABS-KEY ("functional monomer") OR TITLE-ABS-KEY ("10 MDP") OR TITLE-ABS-KEY (10-mdp) OR TITLE-ABS-KEY (mdp) OR TITLE-ABS-KEY ("phosphatic monomer") OR TITLE-ABS-KEY ("methacryloyloxi-decyl-dihydrogen-phosphate") OR TITLE-ABS-KEY ("10-methacryloyloxidecyl dihydrogen phosphate") OR TITLE-ABS-KEY (adhesives) OR TITLE-ABS-KEY (adhesive) OR TITLE-ABS-KEY ("adhesive material") OR TITLE-ABS-KEY ("dentin-bonding agents") OR TITLE-ABS-KEY ("dental-bonding agents") OR TITLE-ABS-KEY

Table 2: *Dichotomy of Results According to the Studies Evaluation Criteria*

Parameters	Modified USPHS Criteria I [26, 27, 31, 32, 36]		Modified USPHS Criteria II [29]		Slightly Modified USPHS Criteria [35]		Modified FDI Criteria [28]		Modified Ryge Criteria [33, 34]		Vanherle and others 1986 Criteria [30]
Unacceptable	Acceptable	Unacceptable	Acceptable	Unacceptable	Acceptable	Unacceptable	Acceptable	Unacceptable	Acceptable	Unacceptable	Acceptable
Marginal 3, 4 Adaptation	Alpha Bravo	Charlie	Alpha Bravo	Charlie	0, 1, 2	3, 4	5, 4, 3	2, 1	Alpha Bravo	Charlie	1, 2
Marginal 3, 4 Discoloration	Alpha Bravo	Charlie	Alpha Bravo	Charlie	0, 1, 2	3	5, 4, 3	2, 1	Alpha Bravo	Charlie	1, 2
Loss (necessary 3, 4 repair or replacement)	Alpha	Bravo Charlie	Alpha Bravo	Charlie	0	1	5, 4, 3	2, 1	Alpha Bravo	Charlie	1, 2
Secondary 2 Caries	Alpha	Bravo Charlie	Alpha	Charlie	0	1	5, 4, 3	2, 1	Alpha	Bravo	1
Postoperative 2 Hypersensitivity	Alpha	Bravo Charlie	Alpha	Charlie	0	1	5, 4, 3	2, 1	Alpha	Bravo	1

Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). For each entry, the judgement involved recording "Yes" indicating minimal risk of bias, "No" indicating elevated risk of bias, and "Unclear" indicating either lack of information or uncertainty over the potential for bias.

The following domains were considered as key for the bias risk assessment: sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other bias. To be considered to embody a low bias risk, studies had to present low bias risk in all the key domains. If the study was considered unclear in any key domains, authors were contacted to obtain information sufficient to allow a definitive judgement. When one or more of these criteria were classified as either unclear or as high bias risk, the whole study was considered either unclear or high bias risk, respectively.

Summary Measures and Results Synthesis

The extracted data were analysed using RevMan software (Review Manager v. 5.3, The Cochrane Collaboration, Copenhagen, Denmark). Five meta-analyses were performed according to the main parameters analysed: retention (RE), marginal adaptation (MA), marginal discoloration (MD), caries (CA), and postoperative sensitivity (POS). Each parameter and the overall effect (clinical performance) were analysed.

The outcomes were divided into acceptable or unacceptable (Table 2), according to the classification criteria used by each study. The prevalence of unacceptable (failures/events), and the total number of restorations for each group, were used to calculate the risk difference with a 95% confidence interval (CI). Random effects models were employed, and heterogeneity was tested using the I^2 index.

If some of the information needed for the MA was missing from any of the selected studies, the authors were contacted to see if the missing data could be provided. Where contact was necessary, up to five attempts at contact were made; and, if after these contact attempts no response was received from the authors, or the authors did not provide the data, the study was not included in the MA.

Assessing the Certainty of Evidence

The certainty of evidence was determined for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Randomized clinical studies started as high evidence, and the quality of evidence could decrease to moderate, low, or very low if serious or very serious issues related to risk of bias, inconsistency, indirectness, imprecision, or publication bias were present. In addition, the quality of the evidence designation could be upgraded if the magnitude of effect was large or very large, or if the effect of all plausible confounding factors was to reduce the effect or suggest spurious effects. In this way, the quality of the evidence varied from very low to high.

RESULTS

Study Selection

The selection methodology has been summarised in Figure 1. A total of 7927 citations was obtained from the database searches. Following the exclusion of duplicates, 4208 articles were identified, and then, after title screening, 215 studies re-

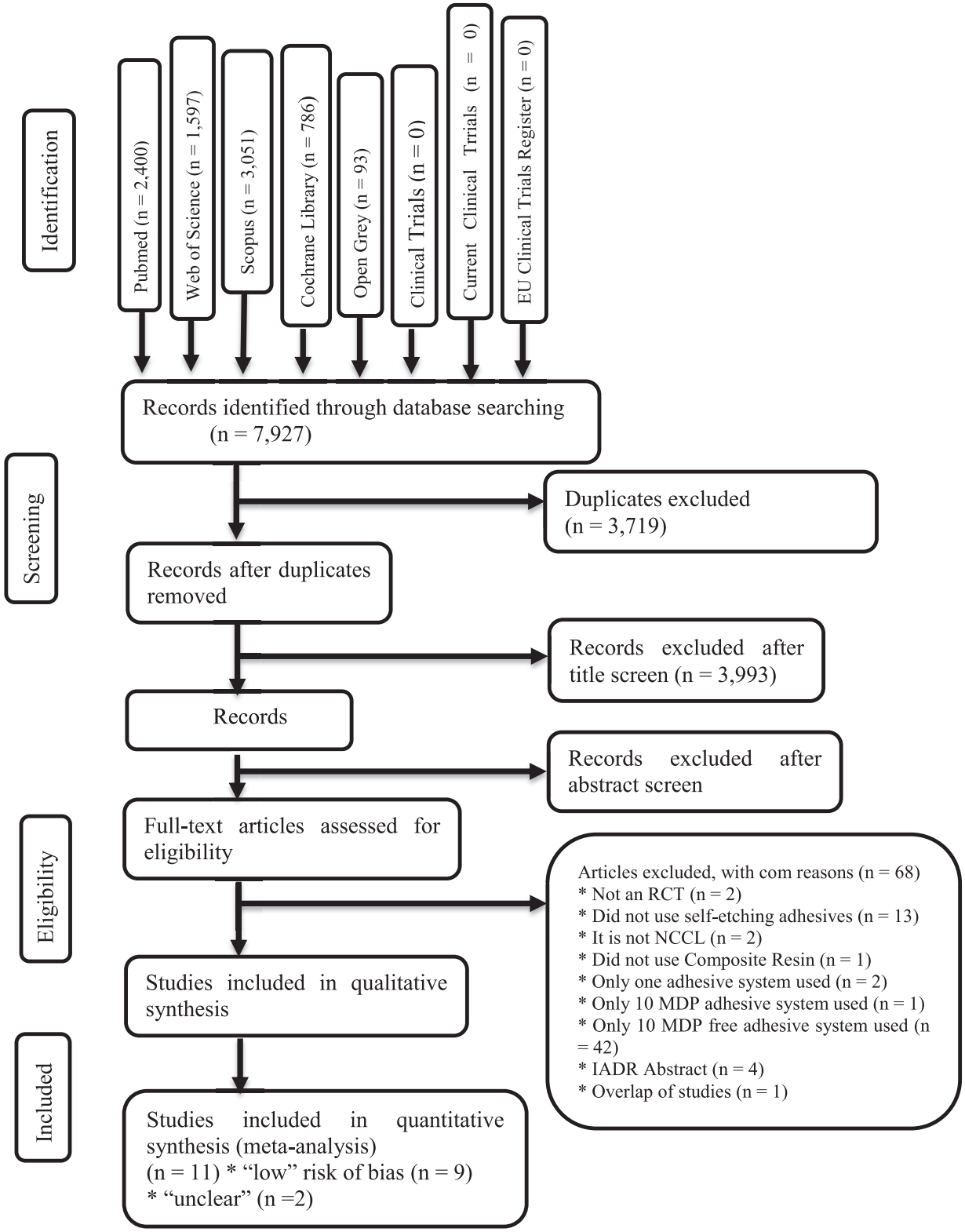

Figure 1. *Flow chart.*

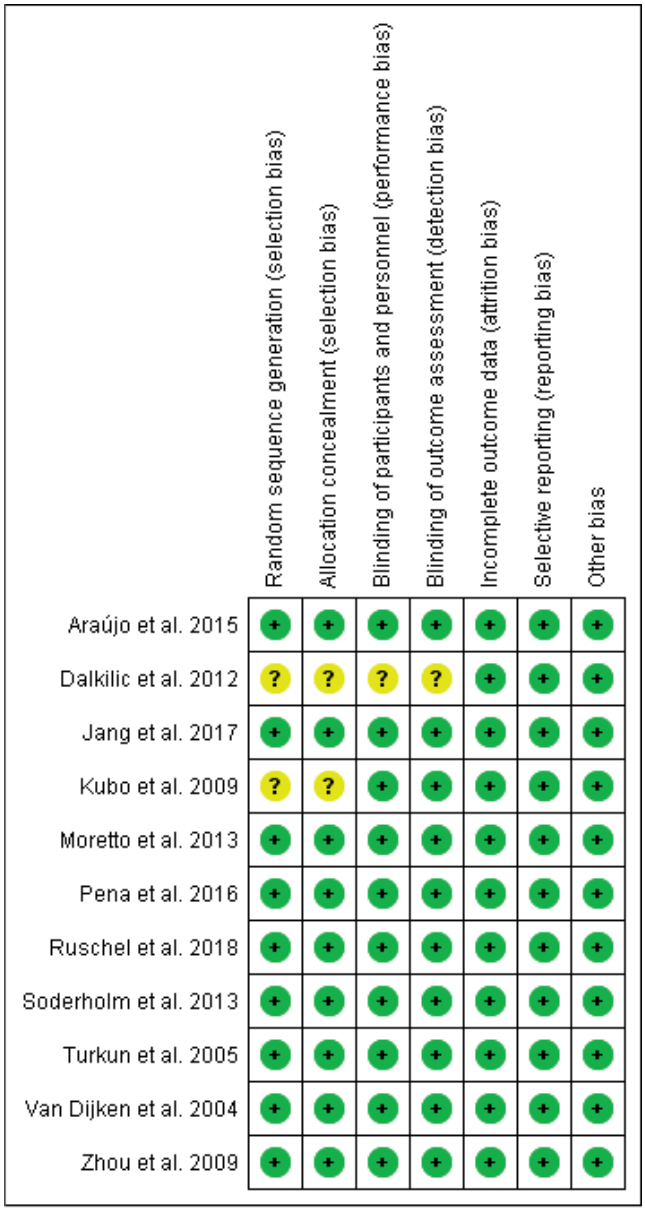

Figure 2. *Risk of bias.*

mained, with this number then further reduced to 79, through careful review of the abstracts. The full texts of the remaining 79 articles were examined for eligibility, leading to an additional 68 exclusions, with the remaining 11[26-36] admitted into our SR and MA.

Characteristics of the Included Articles

The characteristics of the 11 included studies, which varied in length from 1 to 4 years, have been listed in Table 3. The numbers of patients involved in these randomized clinical trials varied from 21 to 124, and their ages spanned 20–84 years. During the restoration procedure, there was generally just one operator involved, although the number of operators did range up to two. The incremental technique was the most commonly used filling method, and the most common isolation technique involved use of cotton rolls and saliva aspirators. In two studies,[32,35] exposed dentin was superficially prepared by bur roughening, and the enamel was bevelled in one study,[31] while both the procedures (roughening and bevelling) were performed in four studies.[29,30,33,36] No preparation procedures were performed in another four studies.[26-28,34]

In total, 11 different adhesives were tested in the included studies. The most tested adhesive without 10-MDP was GC bond, and the most tested system with 10-MDP was Clearfil SE Bond. With regard to the adhesive approach, all studies used one- or two-step, self-etch techniques. Among systems without 10-MDP, six used the one-step, self-etch approach and two used the two-step, self-etch method. Among those with 10-MDP, two used one-step, self-etch and three used the two-step, self-etch approach.

For restoration evaluation, the majority (seven) of the studies used the modified United States Public Health Service (USPHS) criteria,[26,27,29,31,32,35,36] one used the Federation Dentaire Internationale (FDI) criteria,[28] two used the Modified Ryge criteria,[33,34] and one used the Vanherle and others criteria[30] (Table 2).

Assessment of Bias Risk

An assessment of bias risk was performed for the included articles, and the results have been presented in Figure 2. E-mails were sent to all authors, requesting further information, and nine responded.[26,28,30-36] Among the 11 selected studies therefore, two full-text articles[27,29] were classified as having an "unclear risk of bias", in the key domains of the Cochrane bias tool, and nine studies—those listed above whose authors responded to our request for additional information—were considered as having a low risk of bias.

Meta-analysis

The meta-analysis (MA) was conducted with the data available in the "low and unclear risk of bias" studies included in this SR. Only two studies did not provide sufficient data for POS—Kubo and others[29] and Ruschel and others.[32] The group data that had the highest prevalence of failures (events) was used for studies that included more than one group of 10-MDP-containing Zhou and others[36] or 10-MDP-free adhesive systems Van Dijken and others.[35]

Table 3: *Summary of the Studies Selected for this Systematic Review*

Study ID/ Country	Study Design	Subject's Age Mean [Range] (Years)	Adhesive System	Outcomes Evaluated	Evaluation Criteria	
Without 10-MDP (nbaseline)/(nfollow-up)						
Araújo 2015 Brazil	RCT Split-mouth	n.r. [37-53]	AdheSE Rest: (32)/(23)	Clearfil SE Rest: (32)/(30)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity	Modified USPHS
Dalkilic 2012 Turkey	RCT Split-mouth	n.r. [30-70]	Single Bond (total etch) (30) / (17) Xeno III (30) / (20)	Clearfil SE (41) / (32)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity.	Modified USPHS
Jang 2017 Korea	RCT Split-mouth	55[30-73]	Xeno V (81)/(68)	Clearfil SE Bond (83)/(72)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity.	Modified FDI
Kubo 2009 Japan	RCT Split-mouth	61,8 [30-79]	G-Bond (55)/(54)	Clearfil S3 Bond (53)/(52)	retention; marginal discoloration; marginal adaptation; secondary caries;	Modified USPHS
Moretto 2013 Brazil	RCT Split-mouth	n.r. [20-69]	G-Bond (88)/(82)	Clearfil S3 Bond (87)/(75)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity	A set of criteria introduced by Vanherle et al. (1986)
Pena 2016 Brazil	RCT Split-mouth	n.r.	Xeno V (56) / (52)	Clearfil SE Bond (56) / (52)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity	Modified USPHS
Ruschel 2018 Brazil	RCT Parallel	n.r. [21-67]	Prime & Bond Elect (51)/(41)	Scotchbond Universal 50/37	Retention; marginal discoloration; marginal adaptation; secondary caries;	Modified USPHS
Soderholm 2013 USA	RCT Split-mouth	54 [43-77] Female 52 [44-70] Male	iBond SE (42)/(31)	Clearfil SE (42)/(33)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity.	Modified Ryge protocol
Turkun 2005 Turkey	RCT Split-mouth	44 [26-59]	Xeno III (78) / (75)	Clearfil Protect Bond (85) / (85)	Retention; marginal discoloration; marginal adaptation; secondary caries; postoperative sensitivity.	Modified Ryge
Van Dijken 2004 Sweden	RCT Parallel	58 [46-72]	One Coat Bond (46) / (?) Prompt-L Pop (52) / (?)	Clearfil Liner Bond2 (46) / (?)	Retention; marginal discoloration; marginal adaptation; secondary caries;	Modified USPHS

Table 3: *Summary of the Studies Selected for this Systematic Review (ext.)*

Study ID/ Country	Recall Period (Years)	Rubber Dam	Dentin Prepare	Enamel Bevel	Results	Conclusion
With 10-MDP (nbaseline)/(nfollow-up)						
Araújo 2015 Brazil	02	No	No	No	No significant difference was observed between baseline and 2-year for any criteria when adhesives with and without the addition of CHX were compared ($p > 0.05$)	The inclusion of CHX into the primer of both self-etch systems did not add clinical advantages over the 2-year period. Clearfil SE Bond resulted in better retention rate than AdheSE
Dalkilic 2012 Turkey	2	No	No	No	After 2 years: - No significant difference was found between the retention rates of the groups ($p > 0.05$) - Although groups CL and SI showed significantly better marginal adaptation than group XE ($p < 0.05$), no significant difference was found between the marginal adaptation of the groups CL-B, SI-B and XE-B ($p > 0.05$) - No significant difference was observed among the marginal staining results of all groups ($p > 0.05$)	Although all adhesive systems showed similar retention rates, Clearfil SE and Single Bond showed better marginal adaptation than Xeno III after 2 years of follow-up
Jang 2017 Korea	2	No	No	No	Three restorations were dislodged: two in CS / Sof and one in CS / EP. None of the restorations required any repair or retreatment, except those showing retention loss. CS and XE did not show differences in any criteria (p.0.05)	XE, one-step self-etch adhesives showed clinically equivalent performance to CS, two-step self-etch adhesives
Kubo 2009 Japan	2	No	Yes	Yes	One restoration of each adhesive group was lost during two years. Only the marginal integrity at enamel was a minor clinical problem. 11 restorations of both S3 and GB showed slight marginal staining. There was no significant difference in the clinical performance between S3 and GB for each variable	Both adhesive systems showed an acceptable clinical performance up to two years
Moretto 2013 Brazil	3	No	Yes	Yes	Retention rates: CS3 (93.8%) and GB (98.8%). There were no significant differences between the two adhesive systems for all the parameters evaluated. CS3 and GB showed an increased percentage of clinically acceptable marginal discoloration (CS3: 32.9% and GB: 26.8%) and marginal defects (CS3: 35.8% and GB: 26.5%). A severe marginal defect was presented by only one dentin margin of a GB restoration. One CS3 restoration showed caries	Both adhesive materials showed an equally good clinical performance at three years
Pena 2016 Brazil	2	Yes	No	Yes	Significant differences were detected only after 18 months for marginal staining in the groups Clearfil SE non-etch ($p = 0.009$) and Xeno V+ etch ($p = 0.004$). One restoration was lost during the trial (Xeno V+ etch; $p > 0.05$). No sensitivity in any recall period was observed ($p > 0.05$). Secondary caries were not observed in any group ($p > 0.05$)	Overall clinical success of the two self-etching adhesive systems tested in this study was not affected by selective enamel etching in the 24-month evaluation. There was no significant difference between groups tested for retention rate, marginal integrity, secondary caries, and postoperative sensitivity
Ruschel 2018 Brazil	1,5	No	No	No	A statistically significant difference was reached only for the comparison Scotchbond Universal / selfetch (SU_SE) and Prime & Bond Elect / etch and rinse (PBE_E&R) groups ($p = 0.01$), where a restoration with SU_SE was 66% less likely to maintain a score of Alpha for marginal discoloration than a restoration performed with PBE_E&R	Scotchbond Universal and Prime & Bond Elect presented acceptable clinical performance after 18 months of clinical service. However, Scotchbond Universal, when applied with a self-etch approach, did demonstrate a relatively high level of marginal discoloration when compared to the other groups
Soderholm 2013 USA	4	No	Yes	Yes	In relation to retention, marginal integrity and marginal discoloration, there were no significant differences between the two adhesive systems	The performance of the two adhesive systems tested did not differ significantly during four years. The most pronounced problem with these two materials was the development of marginal defects/staining – which may be related to operator problems or to the soluble precipitates formed by the self-etching adhesives at the adhesive interface
Turkun 2005 Turkey	1	No	No	No	At one year, the retention rates for the restorations in the two-step group were 100%. They were 96 percent for the restorations in the one-step group. Of the retained 75 restorations from the one-step group, two had marginal discoloration and slight anatomical form problems. In both groups, color matching ability and postoperative sensitivity remained excellent	The performance of both self-etching adhesive systems was excellent during this one-year clinical trial. However, the two-step system exhibited slightly better retention than the one-step system
Van Dijken 2004 Sweden	2	No	Yes	No	All except three restorations were evaluated over 2 years. No differences were seen between the groups for the acceptable restorations. None of the participants reported postoperative sensitivity	The three systems provide acceptable initial clinical retention, but that the increasing loss rate observed during the 2-year follow-up indicated that the simplification of adhesive systems seems to restrict

For this MA, the overall heterogeneity was not important (I^2=0%). For each parameter, the heterogeneity ranged from 0-53% (53% for RE, 47% for MA, 12% for MD, 0% for CA, and 0% for POS), or from "absent" to "substantial."[38] The 10-MDP-free adhesive group showed 35 failures out of 546 restorations evaluated for the RE parameter, 39 failures out of 511 restorations that were evaluated for MA, 13 failures from 511 restorations that were evaluated for MD, 1 failure out of 511 restorations that were evaluated for CA, and 6 failures from 418 restorations evaluated for POS.

The 10-MDP-containing adhesive group showed 24 failures from a total of 573 restorations evaluated for the RE parameter, 33 failures out of 549 restorations evaluated for MA, 19 failures from 549 restorations evaluated as MD, 1 failure from 549 restorations evaluated as CA, and 5 failures from 461 restorations evaluated for POS. The overall risk difference was −0.00 [−0.01, 0.00] (p=0.77), and was −0.01 [−0.05, 0.02] (p=0.46) for RE, −0.01 [−0.03, 0.02] (p=0.46) for MA, 0.00 [−0.01, 0.01] (p=0.90) for MD, 0.00 [−0.01, 0.01] (p=0.92) for CA, and 0.00 [−0.01, 0.01] (p=0.94) for POS (Figure 3).

This meant that 10-MDP-free and 10-MDP-containing adhesive systems showed statistically similar clinical performance (overall effect) for all isolated parameters, with moderate certainty of evidence for retention and high certainty of evidence for other parameters (MA, MD, CA, POS, and for pooled results). Table 4 lists the detailed GRADE classifications for each parameter.

DISCUSSION

Modern adhesive systems have exhibited good short-term bond ability; however, interface stability is still challenging where long-term behaviour is concerned.[37] Adequate restorative material stability, in terms of its adhesion to the dental substrate, is only possible when high-quality and long-lasting micromechanical and chemical interactions take place between the adhesive system and dental substrate[38,39] in a hybrid layer, as described by Nakabayashi.[40,41] The evidence for this adhesive interaction was based on deep impregnation of dental substrates, especially dentin, by the adhesive system, after strong acid conditioning.[42,43]

Lately, some studies have been published that identified, *inter alia*, problems related to clinical performance. These issues were found as part of middle- and long-terms follow-ups, and were mostly related to inability on the part of the adhesive systems to totally fill the spaces provided by the acid etching. This was seen to have left collagen deprived of mineral protection, leaving it degradation prone, mainly by some enzymes (matrix metalloproteinases) activated during the acid etching.[31,44-47]

Self-etching systems were developed not only to simplify the entire adhesive process but also to allow complete monomer infiltration, allowing tissue conditioning and resin infiltration to take place at the same time.[46,48] In these systems, acidic monomers were added to play this role, and several modifications have been made over time to self-etching adhesive systems. Changes in the number of steps (one or two) and aggressiveness (strong, middle, mild, and ultra-mild) were the principle modifications,[42-44] and, as for etch-and-rinse adhesives, strong self-etch adhesives completely remove hydroxyapatite (HAp) from dentin, resulting in relatively deep dentin hybridization that is several micrometers thick. However, part of the HAp remains in the hybrid layer, where it may negatively influence bond strength. On the other hand, mild self-etch adhesives, due to their less aggressiveness, form only submicron-thick hybrid layers, and the HAp is not attacked as observed for the strong self-etch adhesives, which allows better mechanical and chemical interactions between functional monomers and HAp. [5,49,50]

Conceptually, mild self-etch adhesives bond to tooth tissue through a twofold (micro-mechanical and chemical bonding) mechanism. Partial dentin conditioning occurs, leaving some HAp around collagen fibers within a submicron hybrid layer.[13,42] In the 80's, Kuraray developed and patented 10-MDP, a mild functional monomer, with a hydrophobic methacrylate group at one end, capable of reacting with methacrylate-based restorative materials, and a hydrophilic polar phosphate group at the other end, which was able to react with metals, zirconium, and dental mineralized tissues.[20,21] This monomer also exhibited the interesting property of low hydrophilicity, due to its long molecular chain.[5,51]

Based on the adhesion–decalcification (AD) concept, functional monomers like 10-MDP bond electrostatically to HAp, forming an insoluble MDP-calcium salt CaMHP2,[10,52,53] thereby contributing to the long-term stability of the bond.[50,54] Primary chemical bonding to HAp was first demonstrated using XPS,[5] and later confirmed using X-ray diffraction (XRD) and nuclear magnetic resonance spectroscopy (NMR).[44,45,55] The XRD examination also

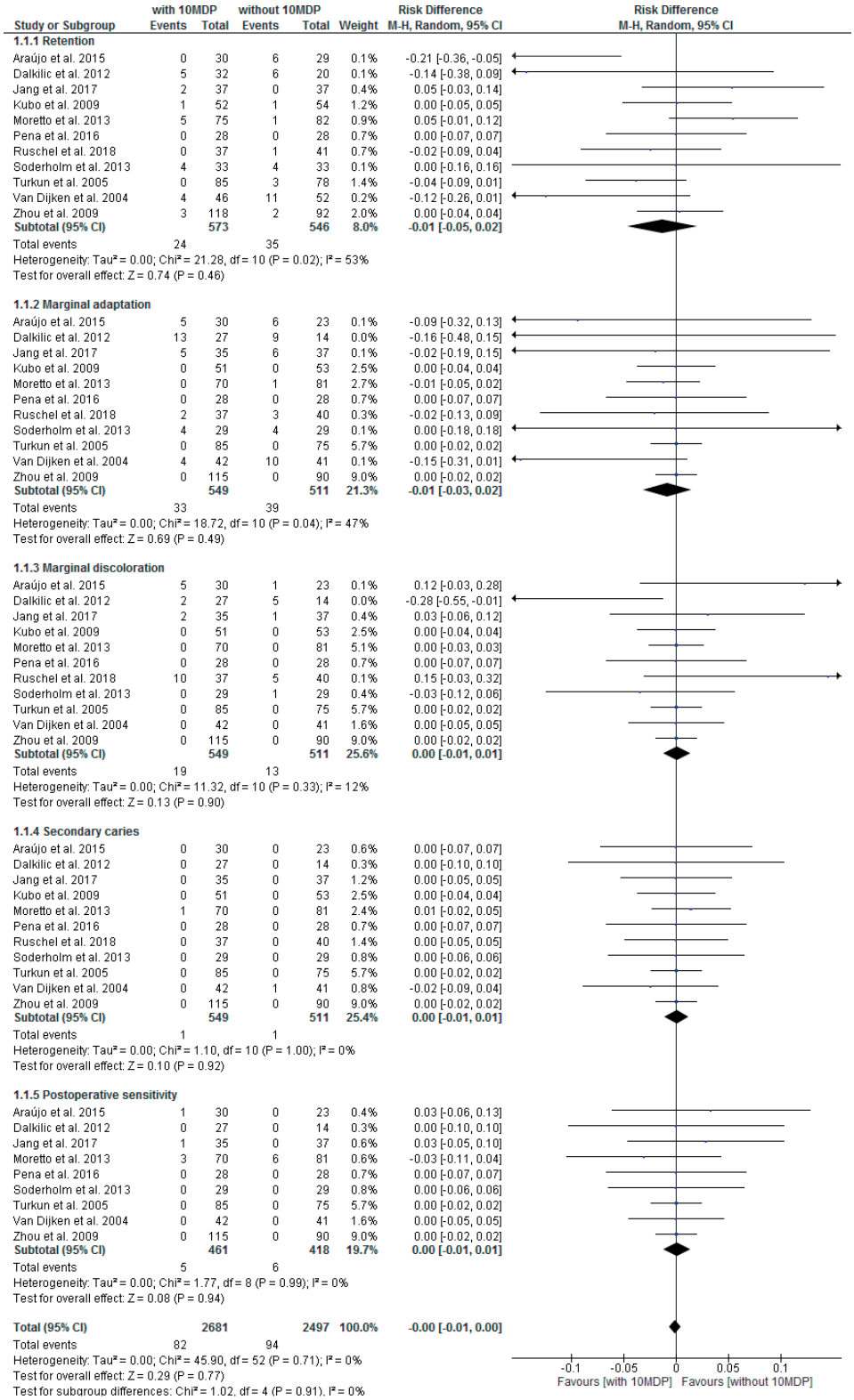

Figure 3. *Meta-analysis (MA).*

showed that 10-MDP bonding to calcium formed a Ca–HAp compound, characterized by a nanolayered structure.[22,42,55] This salt protects the interface against hydrolysis, due to its hydrolytic stability.[48]

The immediate and widespread interest by several manufacturers—including the makers of Clearfil SE Bond, Clearfil S3 Bond, and Clearfil Protect—in adding 10-MDP to adhesive systems was probably

Table 4: *Certainty of Evidence*

Certainty Assessment						Summary of Findings				
Number of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)	Relative effect (95% CI)	Anticipated absolute effects	
With control			With 10-MDP				Risk with control			
Retention										
1119 (11 RCTs)	Not serious	Very serious a, b	Not serious	Serious c	Very strong association	⊕⊕⊕○ MODERATE	35/546 (6.4%)	24/573 (4.2%)	**RD −0.01** (−0.05 to 0.02)	62 per 1000
Marginal adaptation										
1060 (11 RCTs)	Not serious	Serious b	Not serious	Serious c	Very strong association	⊕⊕⊕⊕ HIGH	39/497 (7.8%)	33/525 (6.3%)	**RD -0.01** (−0.03 to 0.02)	76 per 1000
Marginal discoloration										
1060 (11 RCTs)	Not serious	Not serious	Not serious	Serious c	Very strong association	⊕⊕⊕⊕ HIGH	13/511 (2.5%)	19/549 (3.5%)	**RD 0.00** (−0.01 to 0.02)	25 per 1000
Secondary caries										
1060 (11 RCTs)	Not serious	Not serious	Not serious	Serious c	Very strong association	⊕⊕⊕⊕ HIGH	1 / 511 (0.2%)	1/549 (0.2%)	**RD 0.00** (−0.01 to 0.01)	2 per 1000
Postoperative sensitivity										
879 (9 RCTs)	Not serious	Not serious	Not serious	Serious c	Very strong association	⊕⊕⊕⊕ HIGH	6/418 (1.4%)	5/461 (1.1%)	**RD 0.00** (−0.01 to 0.01)	14 per 1000
Pooled results—Clinical performance										
1119 (11 RCTs)	Not serious	Not serious	Not serious	Serious c	Very strong association	⊕⊕⊕⊕ HIGH	79/546 (14.5%)	82/573 (14.3%)	**RD 0.00** (−0.01 to 0.00)	145 per 1000

due to the good results observed when Kuraray systems were tested.[20,21,46] Some laboratory studies demonstrated good performance when bond strength and sealing ability were important.[20-23,39,46] In one of them the adhesive systems were evaluated using mechanical and physical parameters, and the results showed that only systems containing 10-MDP[43,45] were able to protect the bond interface against nanoleakage, and that these systems presented a higher elastic modulus after 1 year.[10,39,45]

Some clinical studies showed favourable short- and mid-term performance when using systems with formulae that included 10-MDP. It is of interest to mention here that, among the 11 RCTs included in this SR, 10 used Kuraray's system (containing 10-MDP in their formulae), compared to other self-etching systems without this functional monomer. Only one study, published in 2018,[32] used different systems, applying Scotchbond Universal (3M) and Prime & Bond Elect (Dentsply Sirona). The RCTs selected normally used retention, marginal degradation and staining, postoperative sensitivity and secondary caries as clinical criteria.

As the MA only accepted paired comparisons, two systems from each RCT were selected—one containing 10-MDP and the other not. In this study, only the adhesion of self-etching systems to dentin was considered. Dentin is a vital substrate, is very dynamic, and has a high water content,[56] and it has also been noted that some pathological changes may occur over time, which make the adhesion process very challenging.[1,57] In this particular SR, neither clinical studies that involved adhesion to enamel nor the total etch technique were included, due to the number of variables that should be considered and discussed, such as self-etch or selective approaches.

Retention is normally used as the primary outcome, and for definition purposes in this study, partial or total loss of restorations was taken as implied by their replacement.[58] The results for this clinical criterion in seven studies[27,28,30,31,33,34,36] did not present significant differences between the two compared groups. On the other hand, statistical differences for retention criteria were reported in two studies.[26,35] When these results were subjected to the MA, however, they did not show any differences when adhesives containing 10-MDP or not were compared. Better clinical performance (retention) had been expected, when 10-MDP was present in the adhesive formulation, once this functional monomer reacted with HAp-forming Ca-MDP salt, which has a hydrolysis protective effect.[54,57-59]

In the present SR, all of the 10-MDP systems included were in commercially available products

with the HEMA monomer in their composition; perhaps this association could explain the MA results in which no significant difference in retention among the adhesive systems were detected. Despite the important role, in a recent SR and MA, the adhesive containing HEMA was compared to HEMA-free adhesives, and a similar clinical behaviour was found.[7] Over time, the high hydrophilicity of this monomer promotes an increase in water acceptance that results in a hydrolytic degradation of the adhesive interface.[60,61]

The presence of HEMA may also interfere with the MDP-Ca nanolayer formation, so thus the retention rate for the 10-MDP-containing systems were not significantly higher, as had been expected.[54,57-59] In a study by Tian and others,[62] several commercial adhesive systems showed little nanolayer formation behaviour at the resin–dentin interface, while more uniform CA-MDP nanolayering was detected for the one system (G-Premio Bond/GC) that did not use HEMA in its formulations. The demineralization rate of HAp by 10-MDP is reduced by HEMA presence, and 10-MDP remains adsorbed onto the HAp surface. Using XRD and NMR to better understand the nanolayering structure in the presence of functional monomer HEMA, Yoshida and others[54] confirmed the chemical interaction between Ca dissociated from HAp and MDP to form the MDP-Ca salt-layered structure. However, when HEMA was added, MDP-Ca salt formation was remarkably decreased and part of the crystalline phase compromised. As XRD analysis can only detect the presence crystalline structures, NMR was used to investigate the chemical interaction of MDP with HAp in HEMA-containing formulations and to unravel the mechanism of how HEMA inhibits nanolayering formations. The NMR analysis showed that when HEMA concentration was increased, the interaction of MDP and HAp decreased. Assessing HEMA-free MDP formulations, shoulder peaks that indicate more consolidated crystalline structures were observed. On the other hand, when HEMA was present in the formulation, weak shoulder peaks were detected that may explain the reduction in the nanolayering formation, probably due to the affinity of HEMA molecules to the HAp, which may compete with the MDP-Ca salt formation. Therefore, one can speculate that this phenomenon could interfere in the retention rates and also in the bond durability.[54]

10-MDP benefits could be demonstrated in laboratory studies, in which the adhesives were synthetized with a high degree of purity and were applied using controlled concentrations. Some studies[21,42,63] have evaluated different 10-MDP concentrations (1%, 3%, 5%, and 15%) with high purity, in terms of Ca-MDP nanolayer formation, and the 15% 10-MDP formulated adhesive exhibited more intense nanolayer deposition. Unfortunately, neither the degree of purity nor the concentration are clearly presented for commercial adhesive systems. On the other hand, Carrilho and others[59] in an SR of 73 laboratory studies stated that commercial adhesives containing 10-MDP had a proven capacity to interact to HAp; however, some clinical steps relating to application of this bonding system must be conducted with due care and attention, because of their influence on the quality of the resulting bond interface. These steps include the selective enamel etching and scrubbing technique used to apply the adhesive systems to dental substrates. The authors also emphasized the importance of allowing sufficient time for the solution to infiltrate, to hybridize, and to form the MDP-Ca salt, protecting collagen fibrils and improving adhesive stability. Perhaps these techniques have not been followed in some clinical studies as precisely as they would have been in laboratory studies, which could also have influenced the results.

Follow-up time is another point to be considered, when reviewing the equity of the various retention rate results described in the RCTs. The longest clinical tracking time was 4 years (Table 3), which may not have been sufficient to detect significant differences.

Secondary outcomes considered in this SR included marginal staining and degradation, and here again, the MA did not detect significant differences when the presence of 10-MDP was considered. Formation of CA-MDP nano layering is more closely related to retention aspects, and so plausible explanations of differences may only show over time, which in some cases may not have been sufficient to detect differences, or to differentiate between variations in the mechanical and physical properties of the restorative materials. Clearly, longer evaluation periods will need to be considered for future studies.

Secondary caries and postoperative sensitivity were also considered as secondary outcomes, and, again, no significant differences were detected in the MA for these effects. The ease with which the restored areas can be kept free of biofilm, and the favourable C-Factors of the NCCLs, may also explain why the different restorative systems showed no significant variations with respect to these characteristics.[7]

Several other aspects may affect the clinical behaviour of dental restorations over time, including the patient, the type of tooth and cavity, the operator, and the restorative system used.[28,56] When the integrity of the adhesive interface is a concern, the type of tooth, cavity, and restorative system may have more impact.[64,65] In this SR, only clinical trials that involved NCCL restorations were included, although for this type of cavity, variation in size and in the amount of exposed dentin would probably not lead to different results. However, we could not affirm the same in cases with different C-factors, or types of occlusion, or with the morphological and/or pathological dentin changes normally present in class II cavities, for instance. The NCCLs that were the subjects of these controlled clinical studies reported little variation in these aspects.[7,31]

Noting that two studies considered for inclusion were regarded as unclear in some review domains, the strength of the data in those studies that were included in this SR was an important aspect that needed to be addressed; and the GRADE approach indicated that the evidence was of high quality for all evaluation criteria, except for retention, which was classified as moderate. This confirmation suggested that it would be unlikely that future studies would arrive at conclusions different from those of the present SR.

CONCLUSION

According to results from this SR and MA, strengthened by application of the GRADE approach to the evidence of selected articles, and considering the follow-up time presented in selected RCTs, the authors were able to conclude that the presence of 10-MDP monomer in self-etch adhesive systems did not influence the clinical performance of NCCL restorations.

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Regulatory Statement

This study protocol was registered at the Prospective Register of Systematic Reviews (PROSPERO - CRD42016050538), and it followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement on the reporting of systematic review.
The approval code issued for this study is PROSPERO CRD42016050538.

Conflict of Interest

The authors of the present study certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in the present article.

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