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MICRO-SHEAR BOND STRENGTH OF UNIVERSAL ADHESIVES TO DENTAL ENAMEL: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Despite manufacturers' efforts to develop and commercialize new universal adhesives, it remains to be clarified which bonding strategy favors adhesion to tooth enamel. A systematic review was conducted to determine whether the etch-and-rinse or self-etching mode is the best protocol for enamel adhesion by universal adhesives.This work followed the PRISMA guideline and a total of 8 articles were included in the meta-analysis. Two reviewers performed a bibliographic search until June 2020 in four databases: Pubmed, Cochrane Library, Web of Science and Embase. In vitro studies, which evaluated the bond strength using the universal adhesive micro-shear test applied to the enamel by means of etch-and-rinse and self-etching were eligible for selection. Statistical analyzes were performed using the RevMan 5.4 program. A global comparison was performed with random effects models at a significance level of $p < 0.05$.The results showed that the etch-and-rinsemode improves the bond strength to microcutting in theenamelcomparedtothe self etchingmode ($p \leq 0.05$). Based on this meta-analysis, it is concluded that prior enamel etching can be considered the best strategy to optimize the bond strength of universal adhesives and that this strategy would be advisable to optimize adhesion.

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INTRODUCTION

Current adhesives can be classified according to their bonding strategy, into etch-and-rinse and self-etching adhesives (Jacker-Guhr *et al*., 2019; Nagarkar *et al*., 2019; van Meerbeek *et al*., 2020). The etch-and-rinse strategy involves the prior application of an acid, usually a phosphoric acid gel, to the substrate with the objective of completely removing the smear layer and superficial hydroxyapatite. Then, resinous monomers infiltrate these microporosities created by acid conditioning forming the hybrid layer (McLean *et al*., 2015; Pashley *et al*., 2011; van Meerbeek *et al*., 2020). On the other hand, the acid conditioning step is eliminated in self-etching adhesives because they contain monomers with acidic functional groups that partially dissolve the layer smear layer, demineralize the dentin/enamel and simultaneously infiltrate the dental substrate (Jacker-Guhr *et al*., 2019; Nagarkar *et al*., 2019; Pires *et al*., 2019; Sato *et al*., 2018; Siqueira *et al*., 2019; van Meerbeek *et al*., 2020). According to van Meerbeek *et al*., 2020, the two ways of applying the adhesive have been successful in clinical and laboratory research.

The evidence points out that adequate adhesion to dentin can be achieved with the self-etching approach(Cuevas-Suárez *et al*., 2019; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015). However, this strategy revealed some limitations when applying to enamel (Cuevas-Suárez *et al*., 2019; Jacker-Guhr *et al*., 2019; McLean *et al*., 2015). The resistance of the union to the enamel with the adhesive in the self-etching mode has been reported to be inferior to the adhesive applied in the etch-and-rinse mode (Cardenas *et al*., 2016; Cuevas-Suárez *et al*., 2019; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; McLean *et al*., 2015; Perdigão *et al*., 2014; Pires *et al*., 2019; Rosa *et al*., 2015). Although clinical studies suggest that adhesives used in the etch-and-rinse mode have a superior performance under masticatory load (Schwendicke *et al*., 2016), many professionals are looking for simpler and less sensitive materials or strategies(Carrilho *et al*., 2019; Cuevas-Suárez *et al*., 2019; Nagarkar *et al*., 2019). This search encouraged manufacturers to develop adhesive systems easier to use(van Meerbeek *et al*., 2020).The newestones are "universal", "multipurpose" or "multimode" adhesives, which providedentists with the option to choose the adhesion strategy: etch-and-rinse, selfetchconditioning oranalter native enamel selective conditioning, which is a combination ofetch-and-rinseonenamel and self-conditioning ondentine (Cardenas *et al*., 2016; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; McLean *et al*., 2015; Muñoz *et al*., 2013; Pires *et al*., 2019; Rosa *et al*., 2015; Sato *et al*., 2018; Siqueira *et al*., 2019; van Meerbeek *et al*., 2020). Although there is no official definition of universal adhesives, the literatures describe them as a single-bottle, single-step, unmixed, all-in-one adhesive system that incorporates the versatility to adapt well with any adhesion strategy (Chen *et al*., 2015; Rosa *et al*., 2015) and that adequately joins the dental structure and different direct and indirect restorative materials, such as composite resins, vitreous ceramics, zirconia and metals (Hanabusa *et al*., 2012; Nagarkar *et al*., 2019). This ability of multiple approaches allows clinicians to apply the adhesive in any of the joining strategies, depending on the clinical situation and the personal preferences of the operators (Carrilho *et al*., 2019; Cuevas-Suárez *et al*., 2019; Jacker-Guhr *et al*., 2019; Rosa *et al*., 2015; Siqueira *et al*., 2019). Despite manufacturers' efforts to develop and commercialize new universal adhesives, with variation in their composition and pH(Cardenas *et al*., 2016; Diniz *et al*., 2016; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; McLean *et al*., 2015; Pires *et al*., 2019; Rosa *et al*., 2015), it remains to be seen which bonding strategy favors adhesion to the dental substrate. A considerable number of in vitro studies evaluating the bonding effectiveness of these new adhesives applied under different conditioning modes are now available. Thus, the objective of this study was to systematically review the literature to assess whether the bond strength to the enamel micro-shear is favored by universal adhesives applied in the etch-and-rinse mode. The tested hypothesis was that there is no difference in bond strength to enamel when applying universal adhesives in the etch-and-rinse or self-etching mode.

MATERIALS AND METHODS

This systematic review was carried out in accordance with the Guidelines for Preferred Report Items for Systematic Review and Meta Analysis (PRISMA) (Moher *et al*., 2009). The articles were selected according to the following research question: The application of the universal adhesive system in the etch-and-rinse mode or does self-etching influence the bond strength by enamel micro-shear?

Search strategy: Two independent researchers (JKU and SV) examined the material published until June 11, 2020 in the Pubmed, Cochrane Library, Web of Science and Embase databases, using the research strategies described in Table 1. Only articles in English, Spanish orPortuguese. The reviewers manually searched the reference lists of the articles included due to the additional articles, and the cited articles were also tracked using the SCOPUS citation tools. After identifying the articles in the databases, they were imported into the Endnote X9 software (Thompson Reuters, Philadelphia, PA, USA) to remove duplicates.

Inclusion and exclusion criteria and study selection: The inclusionandexclusioncriteria for dataselectionandextraction are described in Table 2. The titles and abstracts of the studies were selected according to the criteria: in vitro studies that evaluated the bond strength by microcutting in enamel of universal adhesive systems. Then, complete copies of all potentially relevant studies were searched using the exclusion criteria: revision studies or studies in animals or clinical follow-up or micro-shear tests that were not performed after 24 hours of immersion in distilled water at 37ºC. All disagreements were resolved in mutual discussion and consensus with a more experienced researcher (J.K.U.). Only articles that m*et al*l the eligibility criteria were included.

Data extraction: Two authors (JKU and SV) extracted data from classified articles using a standardized spreadsheet in Microsoft Office Excel 365 (Microsoft Corporation, Redmond, Washington), with all test documents containing demographic data (year, country), the evaluated results, the number of teeth, the universal adhesive system used, the predominant failure mode and the composite resin used (Table 3). Data related to adhesive resistance to enamel were also tabulated (adhesive resistance to micro-shearing) (Table 4). In the absence of any information, the authors of the selected articles were contacted by email to retrieve the missing data. If no reply was received within 2 weeks of sending the first email, a second email would be sent. If the authors did not respond within a month after the first contact, the missing information was not included in this systematic review.

Quality assessment: The methodological quality of each included study was assessed individually by the two reviewers, adapted from anotheres systematic review of in vitro studies(Sarkis-Onofre *et al*., 2014). Thus, the risk of bias was evaluated according to the description of the articles in the following parameters: dental randomization, caries-free teeth, control group, samples with similar dimensions, micro-shear test, description of the variation coefficient, calculation of the size of the examiner sample and blinding. If the authors reported the parameter, the article received a “Yes” in that specific item, if it was not possible to find the information, the article received a “No”. Articles that reported one to three items were classified as having a high risk of bias, four or five items as a medium risk of bias and six to eight items as a low risk of bias (Table 5).

Statistical analysis: Each possible comparison of the bond strength of the universal adhesive was performed using self-etching and etch-and-rinse techniques. For the enamel, the mode of etch-and-rinse and self-etch conditioning were compared, after storage in distilled water for 24 hours at 37ºC. The combined effect estimates were obtained by comparing the standardized average difference of each universal adhesive and were expressed as the weighted average difference between the groups. A value of $p \leq 0.05$ was considered statistically significant. The statistical heterogeneity of the treatment effect between the studies was assessed by the Cochran Q test and the I2 inconsistency test, in which values above 50% were considered indicative of substantial heterogeneity. The first global analysis of enamel bond strength was performed using a random-effect model and, for adhesives that were evaluated in at least two different studies, the analyzes were performed independently. All analyzes were performed using the Review Manager Software version 5.4 statistical program (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The influence of bonding strategies between studies on bond strength of universal adhesives was analyzed using descriptive statistics.

RESULTS

Search Strategy: A total of 1072 potentially relevant records were identified in all databases. Figure 1 is a flow chart that summarizes the article selection process according to the PRISMA guidelines (Moher *et al*., 2009).

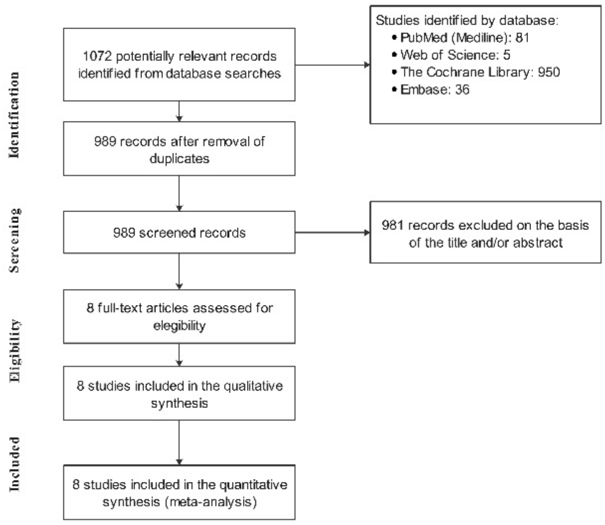


Fig. 1. Search flowchart according to the PRISMA Statement [20]

After removing 83 duplicates, 989 records were examined by titles and abstracts, of which 981 studies were excluded because they did not meet the criteria for eligibility. A total of 8 studies m*et al* the selection criteria and were included in this review.

Descriptive analysis: Seven different types of universal adhesives were evaluated in this review (Table 6). Of the studies included in the review, six evaluated the Single Bond Universal adhesive (3M Espe, St. Paul, MN, USA)(Cardenas *et al*., 2016; Diniz *et al*., 2016; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; Pires *et al*., 2019; Siqueira *et al*., 2019). Four studies evaluated the bond strength of Futurabond U (Voco, Cuxhaven, Germany) (Cardenas *et al*., 2016; Diniz *et al*., 2016; Loguercio *et al*., 2015; Siqueira *et al*., 2019) and three evaluated the bond strength of Clearfil Universal Bond (Kuraray Noritake Dental Inc, Tokyo, Japan) (Cardenas *et al*., 2016; Loguercio *et al*., 2015; Siqueira *et al*., 2019). Otheres universal adhesives evaluated, with two evaluations each, were G-Bond Plus (GC, Tokyo, Japan) (Goracci *et al*., 2013; Perdigão *et al*., 2014), Prime & Bond Elect (Dentsply, Caulk, Milford, DE, USA) (Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015), All-Bond Universal (Bisco, Schaumburg, IL, USA) (Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015) and the iBond Universal (Kulzer; Hanau, Germany) (Jacker-Guhr *et al*., 2019; Siqueira *et al*., 2019). In addition, different types of composite resins were used as restorative materials. Two studies used Filtek Z350 nanoparticle resin (3M Espe, St. Paul, MN, USA) (Cardenas *et al*., 2016; Loguercio *et al*., 2015). One study used Filtek Z250 XT nano-hybrid resin (3M Espe, St. Paul, MN, USA) (Pires *et al*., 2019)and, the another, Venus Diamond (Kulzer, Hanau, Germany) (Jacker-Guhr *et al*., 2019). Other resins used were 3 Filtek Z250 microhybrid resins (3M Espe, St. Paul, MN, USA)(Perdigão *et al*., 2014), Opallis (FGM, Joinville, SC, Brazil)(Siqueira *et al*., 2019) and TPH (Dentsply, Petrópolis, RJ, Brazil)(Diniz *et al*., 2016) and a flow resin G-aenial Universal Flo (GC, Tokyo, Japan)(Goracci *et al*., 2013). Each study used its own protocol to age and store the samples, and most studies stored the samples for 24 hours in distilled water at 37°C. Thermocycling for 10,000 cycles (cyclic immersion at 5ºC / 55ºC, for 30 seconds each bath) was also used by an in vitro study(Jacker-Guhr *et al*., 2019). In this study, the results of bond strength were not different before and after thermocycling.

Meta analysis: A meta-analysis was carried out with 22 data sets, although only eight studies were included(Cardenas *et al*., 2016; Diniz *et al*., 2016; Goracci *et al*., 2013; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; Perdigão *et al*., 2014; Pires *et al*., 2019; Siqueira *et al*., 2019). For the resistance to the micro-shear bonding (μSBS) in enamel, eight studies in which 22 data sets were included in the analysis. One study evaluated the bond strength to enamel with 7 different types of universal adhesives (Loguercio *et al*., 2015). Another two studies evaluated 4 different types (Jacker-Guhr *et al*., 2019; Siqueira *et al*., 2019), another with 3 different types (Cardenas *et al*., 2016), plus one with 2 different types (Diniz *et al*., 2016) and the other studies with 1 type of universal adhesive(Goracci *et al*., 2013; Perdigão *et al*., 2014; Pires *et al*., 2019). In addition, two studies evaluated the adhesive resistance to enamel by applying the adhesive in self-etching mode for 20 and 40 seconds (Cardenas *et al*., 2016; Siqueira *et al*., 2019), another analyzed the passive and active application of the adhesive (Loguercio *et al*., 2015) and another evaluated the adhesive resistance to enamel before and after thermocycling(Jacker-Guhr *et al*., 2019). For of these studies, only the first part of the results of each study were included in the analysis to obtain the overall results (Figure 2). The characteristics of these studies (22 data sets) are summarized in Table 4. The global analysis of the bond strength to the enamel micro-shear bond (Figure 2), of the random effect model, showed that the etch-and-rinse strategy was significantly different from the self-conditioning strategy for the following universal adhesives ($p \leq 0.05$): Single Bond Universal ($p<0.0001$), Futurabond U ($p = 0.0002$), G-Bond Plus ($p = 0.005$), Prime & Bond Elect ($p<0.00001$) and Universal All-Bond ($p = 0.0009$). Considerable heterogeneity was observed in the analysis of Futurabond U ($I^2 = 56\%$), Single Bond Universal ($I^2 = 74\%$) and All-Bond Universal ($I^2 = 73\%$). This heterogeneity was considered low in the analysis of G-Bond Plus ($I^2 = 26\%$) and Prime & Bond Elect ($I^2 = 31\%$). The following universal adhesives ($p \geq 0.05$) did not show a statistically significant difference between etch-and-rinse and self-

Table 1. Research strategy used

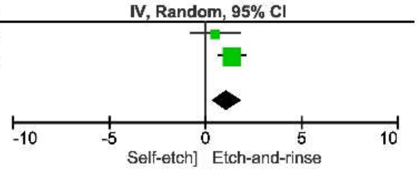
Database	Search Strategy
PubMed	((((((((((universal adhesive) OR (multi purpose adhesive)) OR (multi-purpose adhesive)) OR (multipurpose adhesive)) OR (all in one adhesive)) OR (all-in-one adhesive)) OR (multimode adhesive)) OR (multi-mode adhesive)) OR (multi mode adhesive)) AND (((enamel) OR (resin-enamel)) OR (resin enamel))) AND ((microshear) OR (micro-shear)) ((((((((((universal adhesive) OR (multi purpose adhesive)) OR (multi-purpose adhesive)) OR (multipurpose adhesive)) OR (all in one adhesive)) OR (all-in-one adhesive)) OR (multimode adhesive)) OR (multi-mode adhesive)) OR (multi mode adhesive)) AND (((enamel) OR (resin-enamel)) OR (resin enamel))) AND ((microshear) OR (micro-shear))
Cochrane Library	universal adhesive in Title Abstract Keyword OR multi mode adhesive in Title Abstract Keyword AND enamel in Title Abstract Keyword AND bond strength in Title Abstract Keyword
Web of Science	TS= (universal adhesive OR multimode adhesive OR multi mode adhesive OR multi mode adhesive) AND TS= (enamel OR resin enamel OR resin enamel) AND TS= (microshear OR micro shear)
Embase	((universal AND adhesive OR (multimode AND adhesive) OR ('multi mode' AND adhesive) OR (multi AND mode AND adhesive)) AND enamel OR (resin AND enamel) OR 'resin enamel') AND microshear AND 'micro shear'

Table 2. Inclusion and exclusion criteria

Inclusion criteria	In vitro study
	Universal, multimode or multipurpose dentin adhesive
	Bond strength to micro shear (μSBS)
	Bond strength to enamel
	Sound enamel
	Direct restorations
	Storage time in distilled water for 24 hours at 37°C
Exclusion criteria	Review studies
	Animal studies
	Studies on primary teeth
	Clinical follow-up studies
	Indirect restorations
	Resin cements
	Storage time in distilled water other than 24h at 37°C
	Adhesion to metallic and ceramic alloys, intraradicular pins
	Plaque inhibitors / antibacterial activity
	Alteration of the enamel surface
	Studies published in languages other than English, Spanish or Portuguese

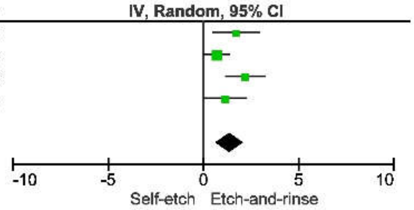
Study (G-Bond Plus)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Perdigão et al.	15.9	2.8	5	14.7	1.1	5	30.0%	0.51 [-0.76, 1.78]	2012
Goracci et al.	15.2	4.4	20	10.1	2.7	20	70.0%	1.37 [0.67, 2.07]	2013
Total (95% CI)			**25**			**25**	**100.0%**	**1.11 [0.34, 1.88]**	

Heterogeneity: Tau² = 0.10; Chi² = 1.35, df = 1 (P = 0.25); I² = 26%
Test for overall effect: Z = 2.82 (P = 0.005)



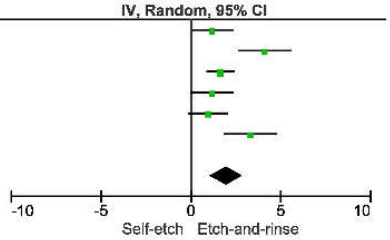
Study (Futurabond U)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Loguercio et al.	17.2	2.6	8	12.5	2.6	8	20.2%	1.71 [0.52, 2.90]	2015
Cardenas et al.	17.1	2	20	15.9	1.3	20	33.4%	0.70 [0.06, 1.34]	2016
Diniz et al.	36.8	4.9	13	28.4	1.9	13	24.1%	2.19 [1.18, 3.19]	2016
Siqueira et al.	17.2	2	8	14.8	1.9	8	22.3%	1.16 [0.08, 2.25]	2019
Total (95% CI)			**49**			**49**	**100.0%**	**1.36 [0.65, 2.08]**	

Heterogeneity: Tau² = 0.29; Chi² = 6.79, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 3.72 (P = 0.0002)



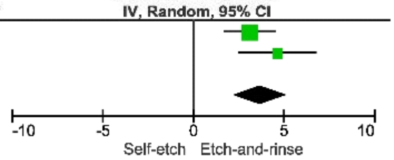
Study (Single Bond Universal)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Loguercio et al.	14	2.4	7	11	2.4	7	16.6%	1.17 [0.00, 2.34]	2015
Cardenas et al.	30.3	3.3	13	18.4	2.2	13	14.5%	4.11 [2.67, 5.54]	2016
Diniz et al.	19.3	1.7	20	16.9	1.1	20	20.2%	1.64 [0.92, 2.37]	2016
Pires et al.	14	2.4	7	11	2.4	7	16.6%	1.17 [0.00, 2.34]	2019
Siqueira et al.	19.4	2.1	8	17.2	2.2	8	17.6%	0.97 [-0.09, 2.02]	2019
Jacker-Guhr et al.	41.2	2.5	10	21.9	7.5	10	14.5%	3.31 [1.87, 4.75]	2019
Total (95% CI)			**65**			**65**	**100.0%**	**1.97 [1.07, 2.86]**	

Heterogeneity: Tau² = 0.89; Chi² = 18.95, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 4.33 (P < 0.0001)



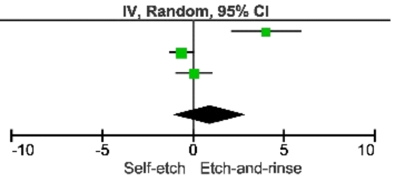
Study (Prime & Bond Elect)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Jacker-Guhr et al.	39.1	7	10	16.1	7.2	10	63.6%	3.10 [1.72, 4.49]	2019
Loguercio et al.	21.4	1.2	8	13.6	1.9	8	36.4%	4.64 [2.55, 6.74]	2019
Total (95% CI)			**18**			**18**	**100.0%**	**3.66 [2.21, 5.11]**	

Heterogeneity: Tau² = 0.36; Chi² = 1.44, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 4.95 (P < 0.00001)



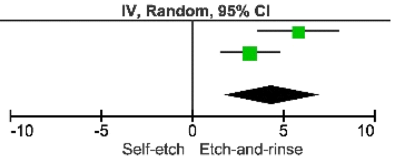
Study (Clearfil Universal Bond)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Loguercio et al.	20.2	2	8	11.9	1.9	8	28.4%	4.02 [2.14, 5.90]	2015
Cardenas et al.	19.1	1.8	20	20.1	1.2	20	36.7%	-0.64 [-1.28, -0.00]	2016
Siqueira et al.	19.5	1.5	8	19.4	2.1	8	34.9%	0.05 [-0.93, 1.03]	2019
Total (95% CI)			**36**			**36**	**100.0%**	**0.93 [-1.06, 2.91]**	

Heterogeneity: Tau² = 2.68; Chi² = 21.32, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 0.92 (P = 0.36)



Study (All-Bond Universal)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Jacker-Guhr et al.	41.6	4.2	10	19.2	3.1	10	45.8%	5.81 [3.62, 8.00]	2019
Loguercio et al.	23.7	3.4	8	14.6	1.8	8	54.2%	3.16 [1.56, 4.76]	2019
Total (95% CI)			**18**			**18**	**100.0%**	**4.38 [1.79, 6.96]**	

Heterogeneity: Tau² = 2.55; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 3.32 (P = 0.0009)



Study (iBond Universal)	Etch-and-rinse Mean	SD	Total	Self-etch Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Jacker-Guhr et al.	33.8	4.8	10	13.4	3.7	10	48.3%	4.56 [2.76, 6.36]	2019
Siqueira et al.	15.3	2	8	14.4	1.9	8	51.7%	0.44 [-0.56, 1.43]	2019
Total (95% CI)			**18**			**18**	**100.0%**	**2.43 [-1.61, 6.46]**	

Heterogeneity: Tau² = 7.95; Chi² = 15.38, df = 1 (P < 0.0001); I² = 93%
Test for overall effect: Z = 1.18 (P = 0.24)

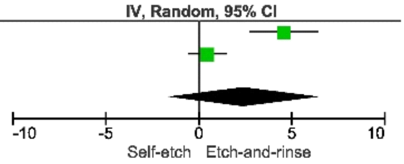


Fig. 2. Results for the analysis of the micro-shear bond strength to enamel using a random-effects model. The etch-and-rinse mode was significantly different than the self-etch strategy (p≤0.05) for Single Bond Universal, Futurabond U, G-Bond Plus, Prime & Bond Elect and All-Bond Universal (p≤0.05). No statistically significant differences between the etch-and-rinse and self-etch strategies for Clearfil Universal Bond and iBond Universal (p≥0.05) were observed

Table 3. Demographic data of the included studies

Study	Year	Country	Number of teeth (pergroup)	Tipo de dente	Primary outcome	Secondary outcome	Predominant failure mode	Universal adhesives	Composite	Type of composite
(Perdigão et al., 2012)	2012	United States	5	Permanent human molars	Enamel µSBS* and dentin µTBS*	Ultra-morphologic evaluation	Adhesive	G-Bond Plus (GC, Tokyo, Japan)	Filtek Z250(3M Espe, St. Paul, MN, USA)	Microhybrid composite
(Goracci et al., 2013)	2013	Italy	20	Bovine incisors	Enamel µSBS	Microleakage measurements and scanning electron microscopy	Adhesive/ mixed	G-Bond Plus (GC, Tokyo, Japan)	G-aenial UniversalFlo (GC, Tokyo, Japan)	Flowable composite
(Loguercio et al., 2015)	2015	Brazil	8	Permanent human molars	Enamel µSBS	Etching pattern and in situ degree of conversion	Adhesive/ mixed	Clearfil Universal Bond (Kuraray Noritake Dental Inc., Tokyo, Japan); Futurabond U (VOCO, Cuxhaven, Germany); G-Bond Plus (GC, Tokyo, Japan); Single Bond Universal (3M Espe, St. Paul, MN, USA); All-Bond Universal (Bisco Inc., Schaumburg, IL, USA); Prime & Bond Elect (Dentsply; Milford, DE, USA).	Filtek Z350 (3M Espe, St. Paul, MN, USA)	Nanocomposite
(Diniz et al., 2016)	2016	Brazil	13	Bovine incisors	Enamel µSBS	Failure pattern	Adhesive	Futurabond U (VOCO, Cuxhaven, Germany); Single Bond Universal (3M Espe, St. Paul, MN, USA)	TPH (Dentsply, Petrópolis, RJ, Brazil)	Microhybrid composite
(Cardenas et al., 2016)	2016	Brazil	20	Permanent human molars	Enamel µSBS	Degree of conversion, failure pattern, enamel etching pattern	Adhesive/ mixed	Clearfil Universal Bond (Kuraray Noritake Dental Inc, Tokyo, Japan); Futurabond U (VOCO, Cuxhaven, Germany); Single Bond Universal (3M Espe, St. Paul, MN, USA)	Filtek Z350 (3M Espe, St. Paul, MN, USA)	Nanocomposite
(Siqueira et al., 2019)	2019	Brazil	8	Permanent human molars	Enamel µSBS	Degree of conversion, failure pattern and scanning electron microscopy	Adhesive/ mixed	Clearfil Universal Bond (Kuraray Noritake Dental Inc., Tokyo, Japan); Futurabond U (VOCO, Cuxhaven, Germany); Single Bond Universal (3M Espe, St. Paul, MN, USA); iBond Universal (Kulzer; Hanau, Germany).	Opallis (FGM, Joinville, SC, Brazil)	Microhybrid composite
(Jacker-Guhr et al., 2019)	2019	Germany	10	Permanent human molars	Enamel and dentin µSBS	Failure pattern and thermocycling	Adhesive/ mixed	Single Bond Universal (3M Espe, St. Paul, MN, USA); Prime & Bond Elect (Dentsply; Milford, DE, USA); All-Bond Universal (Bisco Inc., Schaumburg, IL, USA); iBond Universal (Kulzer; Hanau, Germany)	Venus Diamond (Kulzer, Hanau, Germany)	Nanocomposite
(Pires et al., 2019)	2019	Brazil	7	Permanent human molars	Enamel µSBS	Failure pattern	Adhesive	Single Bond Universal (3M Espe, St. Paul, MN, USA)	Filtek Z250 XT (3M Espe, St. Paul, MN, USA)	Nanocomposite

*µTBS: micro-tensile bond strength; µSBS: micro-shear bond strength.

conditioning strategies: Clearfil Universal Bond ($p = 0.36$) and iBond Universal ($p = 0.24$). However, considerable heterogeneity was observed for both adhesives, $I^2 = 91\%$ and 93% respectively.

Quality assessment: Of the eight studies included, four had a medium risk of bias and another four showed a low risk of bias. The results are described in Table 5, according to the parameters considered in the analysis. The studies had a particularly low score on the following items: calculation of the sample size, description of the coefficient of variation and blinding of the examiner.

DISCUSSION

A systematic review and meta-analysis of the bond strength to micro-shear bonding of universal adhesives applied to the enamel was carried out, in the etch-and-rinse or self-etching mode, based on the published literature until June 2020.

The performance of these universal adhesives evaluated by in vitro studies depended on the were applied. All new adhesive systems evaluated had the same versatility of use in etch-and-rinse and self-conditioning approaches. The reason for the different performances in bond strength evaluated in in vitro studies, may be due to differences in their compositions (Carrilho *et al*., 2019; Diniz *et al*., 2016; Jacker-Guhr *et al*., 2019; McLean *et al*., 2015). Despite the substantial heterogeneity found in this meta-analysis, the literature analysis suggests that previous acid conditioning in Universal adhesives improve the bond strength in the enamel. However, the hypothesis was partially accepted, because in the analysis of the seven adhesives, two (Clearfil Universal Bond and iBond Universal) did not show statistically significant differences. In the others, the acid conditioning prior to the application of the universal adhesive improved the bond strength. In fact, the mechanism of adhesion to enamel is essentially based on superficial demineralization, a result of acid etching. This conditioning creates microporosities on the surface of the prismatic and aprismatic enamel where adhesives penetrate and, after polymerization, establish micromechanical retention (Heintze *et al*., 2015; Jacker-Guhr *et al*., 2019; Rosa *et al*., 2015; Siqueira *et al*., 2019; van Meerbeek *et al*., 2020).

Table 4. Enamel bond strength of universal adhesives with aging/storage procedures

Study	Adhesive system	Aging/ storage	Enamel micro-shear bond strength			
			Etch-and-rinse	SD	Self-etch	SD
(Perdigão et al., 2012)	G-Bond Plus (GC, Tokyo, Japan)	24 h of storage in distilled water at 37°C	15.9	2.8	14.7	1.1
(Goracci et al., 2013)	G-Bond Plus (GC, Tokyo, Japan)	24 h of storage in distilled water at 37°C	15.2	4.4	10.1	2.7
(Loguercio et al., 2015)	Futurabond U (VOCO, Cuxhaven, Germany)	24 h of storage in distilled water at 37°C	17.2	2.6	12.5	2.6
(Cardenas et al., 2016)	Futurabond U (VOCO, Cuxhaven, Germany)	24 h of storage in distilled water at 37°C	17.1	2	15.9	1.3
(Diniz et al., 2016)	Futurabond U (VOCO, Cuxhaven, Germany)	24 h of storage in distilled water at 37°C	36.8	4.9	28.4	1.9
(Siqueira et al., 2019)	Futurabond U (VOCO, Cuxhaven, Germany)	24 h of storage in distilled water at 37°C	17.2	2	14.8	1.9
(Loguercio et al., 2015)	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	22.2	1.3	16.9	1.3
(Cardenas et al., 2016)	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	19.3	1.7	16.9	1.1
(Diniz et al., 2016)	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	30.3	3.3	18.4	2.2
(Pires et al., 2019)	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	14	2.4	11	2.4
(Siqueira et al., 2019)]	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	19.4	2.1	17.2	2.2
(Jacker-Guhr et al., 2019)	Single Bond Universal (3M Espe, St. Paul, MN, USA)	24 h of storage in distilled water at 37°C	41.2	2.5	21.9	7.5
(Siqueira et al., 2019)	Clearfil Universal Bond (Kuraray Noritake Dental Inc., Tokyo, Japan)	24 h of storage in distilled water at 37°C	19.5	1.5	19.4	2.1
(Loguercio et al., 2015)	Clearfil Universal (Kuraray Noritake Dental Inc, Tokyo, Japan)	24 h of storage in distilled water at 37°C	20.2	2	11.9	1.9
(Cardenas et al., 2016)	Clearfil Universal (Kuraray Noritake Dental Inc, Tokyo, Japan)	24 h of storage in distilled water at 37°C	19.1	1.8	20.1	1.2
(Loguercio et al., 2015)	Prime & Bond Elect (Dentsply; Milford, DE, USA)	24 h of storage in distilled water at 37°C	21.4	1.2	13.6	1.9
(Jacker-Guhr et al., 2019)	Prime & Bond Elect (Dentsply; Milford, DE, USA)	24 h of storage in distilled water at 37°C	39.1	7.0	16.1	7.2
(Loguercio et al., 2015)	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	24 h of storage in distilled water at 37°C	23.7	3.4	14.6	1.8
(Jacker-Guhr et al., 2019)	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	24 h of storage in distilled water at 37°C	41..6	4.2	19.2	3.1
(Siqueira et al., 2019)	iBond Universal (Kulzer; Hanau, Germany)	24 h of storage in distilled water at 37°C	15.3	2	14.4	1.9
(Jacker-Guhr et al., 2019)	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	24 h of storage in distilled water at 37°C	33.8	4.8	13.4	3.7

Table 5. Quality assessment and risk of bias

Study	Teeth randomization	Teeth free of caries	Control group	Samples with similar dimensions	Micro-shear bond strength test	Description of coefficient of variation	Sample size calculation	Blinding of the examiner	Risk of bias
Cardenas et al., 2016	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Medium
Diniz et al., 2016	Yes	Yes	Yes	Yes	Yes	No	No	No	Medium
(oracci et al., 2013	Yes	Yes	Yes	Yes	Yes	No	No	No	Medium
Loguercio et al., 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Low
Perdigão et al., 2012	Yes	Yes	Yes	Yes	Yes	No	No	No	Medium
Pires et al., 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Low
Siqueira et al., 2019	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Low
Jacker-Guhr et al., 2019	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Low

Table 6. Composition and classification of universal adhesives

Universal adhesives	Classification according to pH *	Composition
Clearfil Universal Bond (Kuraray Noritake Dental Inc, Tokyo, Japan)	Mild (pH=2.3)	Bis-GMA, HEMA, ethanol, 10-MDP, Hydrophilic aliphatic dimethacrylate, colloidal silica, DLcamphorquinone, silane coupling agent, accelerators, initiators, water
Futurabond U (VOCO, Cuxhaven, Germany)	Mild (pH=2.3)	HEMA, Bis-GMA, HEDMA, acidic adhesive monomer, urethane dimethacrylate, catalyst, silica nanoparticles, ethanol
G-Bond Plus (GC, Tokyo, Japan)	Intermediate strong (pH = 1.5)	Acetone, dimethacrylate, TEGDMA, 4-MET, phosphoric acid estermonomer, silicon dioxide, photoinitiator
Single Bond Universal (3M Espe, St. Paul, MN, USA)	Ultra -mild (pH = 2.7)	10-MDP phosphate monomer, Vitrebond copolymer, HEMA, BISGMA, dimethacrylate resins filler, silane, initiators, ethanol, water
Prime & Bond Elect (Dentsply; Milford, DE, USA)	Ultra-mild (pH = 2.5)	Mono-, di- and trimethacrylate resins, PENTA, diketone, organicphosphine oxide, stabilizers, cetylamine hydrofluoride, acetone, water
All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	Ultra-mild (pH = 3.1 a 3.2)	10-MDP, bis-GMA, HEMA, ethanol, water, initiators
iBond Universal (Kulzer; Hanau, Germany)	Intermediate strong (pH=1.8)	Methacrylate-monomer (4-META, 10-MDP), acetone, water - not listed in the materials MDSD, personal communication with the manufacturer (Kulzer)[2]

- Bis-GMA: bisphenol-A diglycidyl ether dimethacrylate; HEMA: 2-hydroxyethyl methacrylate; 10-MDP: 10-methacryloyloxydecyl dihydrogen phosphate; HEDMA: 2-hydroxyethyl dimethacrylate; TEGDMA: triethylene dimethacrylate; 4-MET: 4-methacryloxyethyl trimellitic acid; PENTA: dipentaerythritol pentaacrylate monophosphate. * Strong (pH<1), intermediar strong (pH=1-2), mild (pH≅2) and ultra-mild (pH≥ 2.5) (Nagarkar et al., 2019; van Meerbeek et al., 2010; van Meerbeek et al., 2020).

Adhesive systems for etch-and-rinse or selective enamel conditioning are characterized by an initial acid etching step, usually with a 32% to 37% phosphoric acid gel, followed by a water spray wash. This conditioning is responsible for the complete removal of the smear layer and for the selective dissolution of the enamel(McLean *et al*., 2015; Pashley *et al*., 2011). This creates macro and microporosities on the enamel surface, which are easily penetrated by the bonding agents through capillary attraction. Afterpolymerization, resin-like tags are formedonthe surface oftheconditionedenamel, providing strong micro mechanical retention (Cuevas-Suárez *et al*., 2019; van Meerbeek *et al*., 2020). It is known that one of the disadvantages of universal adhesives is that they are less acidic than phosphoric acid, thus reducing their potential for enamel demineralization and, consequently, for creating appropriate retentive microporosities(Rosa *et al*., 2015), which reduces the bonding effectiveness on this substrate(Cardenas *et al*., 2016; Cuevas-Suárez *et al*., 2019; Goes *et al*., 2014; Jacker-Guhr *et al*., 2019; Loguercio *et al*., 2015; McLean *et al*., 2015; Perdigão *et al*., 2014; Pires *et al*., 2019; Rosa *et al*., 2015; Sato *et al*., 2018; Siqueira *et al*., 2019; van Meerbeek *et al*., 2020). This has also been observed in relation to the universal adhesives in this meta-analysis. This effect is related to the pH of the adhesive. The lower pH (< 2.5) can potentiate the demineralization mechanism, improving the surface interaction of the adhesive (Nagarkar *et al*., 2019; Siqueira *et al*., 2019) and, consequently, increasing the bond strength by micromechanical retention(McLean *et al*., 2015; Sato *et al*., 2018).

Even the most acidic of the universal adhesives used in the self-etching mode produces only a conditioning pattern involving mainly the ends of the enamel prisms with little effect in the interprismatic regions (Erickson *et al*., 2009). The subsequent penetration of resin monomers is like a negative replica of the demineralization pattern created by acid conditioning, with the resin penetrating the prisms, but not in the slightly demineralized interprismatic regions. This leads to a superficial intercrystalline infiltration of the monomers into the enamel and the formation of shorter, thinner and more fragile interprismatic resin tags (Cardenas *et al*., 2016; Loguercio *et al*., 2015; McLean *et al*., 2015; Nagarkar *et al*., 2019; Perdigão & Geraldeli, 2003). In the enamel, regardless of the pH of the adhesive, the bond strength was improved by prior conditioning with phosphoric acid (Cuevas-Suárez *et al*., 2019). Despite manufacturers' efforts to improve the bond strength to enamel with the new universal adhesives, this meta-analysis revealed that prior acid etching with phosphoric acid is still the best strategy. On the other hand, Cardenas *et al*., 2016 and Siqueira *et al*., 2019 showed that application of the universal adhesive in the self-etching mode for 40 seconds increases the bond strength compared to the application for 20 seconds. It is known that prolonged application times can improve the diffusion and interaction of acid monomers, thus increasing the potential for conditioning and impregnation of the resin in the underlying enamel (Cardenas *et al*., 2016; Loguercio *et al*., 2015; Sato *et al*., 2018; Siqueira *et al*., 2019) Loguercio *et al*., 2015 also showed that the active application of the adhesive universal can increase the external diffusion of the solvent, mainly in adhesives composed with low vapor pressure solvents, such as water / ethanol. Evaporation of the solvent can facilitate changes in the polymer topology, reducing the intrinsic fraction of the nanopores, allowing greater crosslinking and a higher degree of polymerization of the polymer in the enamel. This ends up improving the mechanical properties of the polymer in the hybrid enamel layer (Reis *et al*., 2010), increasing the bond strength (Diniz *et al*., 2016; Loguercio *et al*., 2015; Perdigão&Loguercio, 2014). However, acetone-based solvent adhesives such as iBond Universal, G-Bond Plus and Prime & Bond Elect may not benefit from active application to increase solvent evaporation. Although acetone (200 mmHg at 25ºC) has a higher vapor pressure than ethanol (54.1 mmHg at 25ºC) and water (23.8 mmHg at 25ºC), which theoretically results in a better water evaporation rate due to “azeotropic effect” (Moszner *et al*., 2005), acetone-based adhesives require a longer evaporation time than that recommended by the manufacturer (Luque-Martinez *et al*., 2014). Therefore, the rapid evaporation of acetone increases the concentration of monomers in the adhesives, which decreases the vapor pressure of the others residual solvents, mainly water (Loguercio *et al*., 2015), making it more difficult to evaporate. This residual water negatively affects the degree of polymerization of the adhesive and, consequently, the bond strength (Loguercio *et al*., 2015). In addition to the different application techniques, the different formulations between the adhesive systems can play an important role in the adhesion of the material (see Table 6). Due to the chemistry of universal adhesives, they do not require a prior acid conditioning step because they contain different acid monomers (Jacker-Guhr *et al*., 2019).Most have the functional monomer 10-MDP (10-methacryloyl-oxidecyl-dihydrogen phosphate) or other functional monomers, such as 4 -META, GPDM, PENTA, 4-MET (Muñoz *et al*., 2013). These monomers allow the multimode application of universal adhesives, that is, the mode of etch-and-rinse, self-conditioning or selective enamel conditioning (Sofan *et al*., 2017). Among all functional monomers, 10-MDP is of particular importance because it improves mechanical strength and protects the adhesive interface against hydrolysis, since it forms a stable and water-resistant Ca-MDP salt, created by the reaction of 10- MDP and Ca^{2+} ions of hydroxyapatite(Carrilho *et al*., 2019; Cuevas-Suárez *et al*., 2019; Diniz *et al*., 2016; Jacker-Guhr *et al*., 2019; McLean *et al*., 2015; Pires *et al*., 2019; Yoshida *et al*., 2004). Almost all universal adhesives available on the market contain at least one monomer with potential for chemical bonding with the tooth's calcium; however, some may have two components with this potential (Loguercio *et al*., 2015). An example is the Single Bond Universal which contains 10-MDP and also a copolymer of polyalkenoic acid modified with methacrylate, both with potential for chemical bonding, which ends up contributing to improve bond strength to enamel (Loguercio *et al*., 2015).

The bond strength can also be influenced by the presence or absence of HEMA in the composition of universal adhesives. Although adhesives containing HEMA suffer a more pronounced water sorption(Hosaka *et al*., 2010), which is especially harmful in light of the long-term stability of adhesives in the oral cavity, adhesives without HEMA are highly prone to phase separation at the adhesive interface, increasing permeability. This can be a limiting factor for the best performance of these materials (Loguercio *et al*., 2015). Regarding the quality of the studies included in this systematic review, all of them presented a risk of medium or low bias and demonstrated that the bond strength to enamel is influenced by the way in which the universal adhesive is applied. These results should beinterpreted with caution, duetothe high heterogeneity observed in the different comparisons made and the limitations inherent in laboratory studies, which may not reflect the clinical performance of the evaluated materials. The validity of bond strength tests to predict the clinical performance of dental adhesives is questionable (Armstrong *et al*., 2010; El Mourad, 2018; Heintze *et al*., 2015). However, some studies have shown that clinical results can, to some extent, be predicted by mechanical laboratory tests and that one of these tests would be that of bond strength (Peumans *et al*., 2005). In addition, mechanical tests can provide valuable information in terms of identifying substrate variables, which helps to define guidelines for clinical application procedures (Armstrong *et al*., 2017; Rosa *et al*., 2015). However, some factors that can influence the bond strength in clinical situations must be taken into account, including chewing forces, pH and temperature changes, as well as the humid environment, which can lead to rapid degradation of the adhesive interfa ce(Rosa *et al*., 2015). It is difficult to establish a relationship between the effectiveness of the bond strength measured in the laboratory with the clinical effectiveness determined by randomized clinical trials (van Meerbeek *et al*., 2010), it should be mentioned that the laboratory results of the adhesives coincide with their clinical performance (Cuevas-Suárez *et al*., 2019). As the main causes of failure of composite resin restorations are related to the occurrence of fracture and secondary caries, achieving a stable bonding interface, especially in the long term, makes restorative treatment more predictable in terms of clinical performance (Cuevas-Suárez *et al*., 2019). From the point of view clinical, it appears that the long-term bond stability of an adhesive is more important than achieving immediate high bond strength. This explains why randomized clinical trials concluded that the additional acid attack on the enamel margins is not critical to the clinical performance of self-etching adhesives (Cuevas-Suárez *et al*., 2019; Peumans *et al*., 2010). Future reviews are needed to analyze the long-term laboratory behavior of these universal adhesives stored in water, as well as their association with clinical trials. Considering the results obtained in this review, performing previous acid etching, followed by the application of the universal adhesive, seems to be the best option to achieve the greatest bond strength to the enamel, in comparison with the self-etching application. Finally, systematic reviews are valuable tools for clinical practice, because they provide a critical approach to scientific knowledge on certain subjects. Aims to answer a clinically relevant question based on the best available scientific evidence, point out improvements and indicate standardized methodologies for further research (Linares-Espinós *et al*., 2018).

Conclusion

Although studies have demonstrated heterogeneity, the in vitro literature seems to suggest that the bond strength in enamel is improved by the use of universal adhesives in the etch-and-rinse mode. Based on this meta-analysis, prior enamel etching can be considered the best strategy to optimize the bond strength of universal adhesives.

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