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Review Article

Impact of Self-Etch Adhesives Increased Application Time on Dental Bond Strength: A Systematic Review and Meta-Analysis

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Abstract
In this systematic review and meta-analysis, it was intended to determine whether increasing the application time of self-etch adhesives and universal adhesives could increase the bond strength between composite resin and enamel/dentin. Electronic databases, such as MEDLINE via PubMed, ISI (Web of Science), and Scopus, were thoroughly searched based on the PICOS strategy in order to gather in vitro articles in English with no publication year limit. Studies assessing the bond strength between enamel/dentin and composite resin were selected and further evaluated using self-etch or universal adhesives. Meta-analysis was performed using a random-effect model to determine the difference in the bond value between the specimens that underwent longer adhesive application and the control groups. Amongst 123 gathered studies, 59 were selected for full-text analysis, and 26 were chosen for inclusion in this review. Overall, 14 studies were included in the meta-analysis, and a random-model effect was used for all but one analysis dependent on the heterogeneity percentage. The meta-analysis demonstrated a significant increase in bond strength subsequent to increasing the application time of the aforementioned bonding systems to an extent. Doubling the application time increased the bond strength to both enamel and dentin. However, tripling the application time seemed to be only beneficial to bond strength between enamel and self-etch/universal adhesive systems. The one-component adhesive systems were more impacted by the increased application time than two-component systems. However, not enough data existed on the effect of the pH level of adhesive systems on bond strength value to draw a reach conclusion. Under the limitations of this review, it was concluded that increasing the application time of self-etch and universal adhesives to a certain extent could increase bond strength to both ground dentin and enamel under in vitro conditions.
Keywords: Self-etch adhesive, Universal adhesive, Bond strength, Application time

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Background
The longevity of restoration depends on many factors, one of which is the adequate adhesion of dental material to tooth structure (1,2). Utilizing adhesive systems in order to form a cohesive bond between the restorative materials and the hard dental tissue is a crucial step in restorative treatments. Without a proficient bonding system or the lack of adequate application of one, the restoration would be prone to microleakage and/or secondary caries (3-5).

Since the development of the first bonding system in the 1970s (6), different generations of bonding systems with diverse compositions and methods of application have emerged (7,8), including total etch/etch and rinse adhesives (TEA), self-etch adhesives (SEA), and universal/multi-mode adhesives (UA) (8,9).

While TEAs use phosphoric acid for complete removal of the smear layer, SEAs utilize acidic monomers to demineralize the smear layer and simultaneously prime the tooth structure (10-12). By eliminating the rinsing step and streamlining the process, SEAs offer advantages, such as reducing technique sensitivity, decreasing contamination risks, and minimizing the risk of postoperative sensitivity (6,13-15). Considering that UAs are also a modified generation of self-etching primers, they possess the main aforementioned advantages (16,17). Nevertheless, the SEAs have shortcomings, since combining diverse functional monomers with varying sizes, weights, and different solvents introduces new forms of technique sensitivity, potentially compromising bonding strength (11,18-21). Furthermore, there are several concerns about bonding to both dentin and enamel, since using acidic monomers instead of phosphoric acid seems to induce less surface roughness in dental tissue and consequently produce less bond strength (11,15,22).

Despite the advancements in the production of SEAs, pH adjustments, and incorporation of various acidic monomers, solvents, initiators, hydrophilic monomers, and crosslinkers, the bonding process remains a subject of controversy. Hence, there remains a need to optimize bonding efficacy by adjusting other clinical factors (23). These methods include but are not limited to reducing moisture by using a rubber dam (20), utilizing proteolytic agents (e.g., sodium hypochlorite) (24), applying multiple coats of adhesive (13,25), texturing the surface of sclerotic dentin using dental burs (26), employing phosphoric acid as a pre-treatment for self-adhesives/universal adhesives (19,27), or altering the application time.

Several studies have explored the impact of modifying the priming time of various adhesive systems. However, these investigations have yielded different outcomes, likely attributed to variations in the adhesive materials employed or whether they were bonding with dentin or enamel (13,15,19,20,28). While some findings stated that alterations in the manufacturer's recommended priming time have no significant impact on bond strength (15,20), others suggested that increasing the application time may result in higher bond strength values (19,24-26).

In light of the aforementioned cases, examining different durations of primer application time may contribute valuable insights to our clinical and technical knowledge, which can result in further improving bond strength values in dental restorative treatments. To the best of our knowledge, no other systematic reviews have been performed based on this query to this extent. Accordingly, the objective of this review and meta-analysis is to investigate whether the adjustments in the conditioning time of SEAs and UAs can affect the bond strength between adhesive systems/resin composite and tooth structure. The null hypothesis posits that altering the application time does not induce a significant alteration in bond strength.

Materials and Methods

This systematic review was conducted based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (29). The research question was as follows:

Does increasing the application time of self-etch adhesives improve the bond strength of composite resins to dentin and enamel?

Protocol and Registration

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews database (under the registration number CRD42022304646), and the method section followed the described methodology of a study that was published in the Journal of Adhesive Dentistry (30).

Information Sources

The last literature search was independently performed by two reviewers on 24 March 2025 without the limitation of publication year. Three databases were investigated, including MEDLINE via PubMed, Web of Science, and Scopus. In addition, a manual search was conducted to find gray literature. The references of included articles were searched for additional papers, and the cited articles were also tracked using Scopus citation tools.

Search Strategy

The PICOS questions were termed as P-population: Self-etch and universal adhesive systems; I-intervention: Increased application time of aforementioned adhesives; C-control: Application time based on the manufacture's instruction; O-outcome: Bond strength of composite to the enamel/dentin specimens; S-study designs: In vitro studies. The following search strategy was employed in the search query box of PubMed, Scopus, and Web of Science databases:

((("self-etch adhesives") OR ("universal adhesives")) AND (("application time") OR ("conditioning time"))) AND (((((((("bond strength") OR ("shear bond strength")) OR ("shear strength")) OR ("micro shear bond strength")) OR ("micro shear strength")) OR ("tensile bond strength")) OR ("tensile strength")) OR ("micro tensile bond strength")) OR ("micro tensile strength")).

Study Selection and Eligibility Criteria

Two reviewers evaluated the titles/abstracts of all of the included studies individually. Articles related to self-etch and universal adhesive systems evaluating dentin and/or enamel bond strength to composite by using SEAs or UAs were chosen for analysis. In vitro studies published in English were subjected to further evaluation. Furthermore, articles whose titles/abstracts suggested to meet the inclusion criteria or articles whose titles/abstracts presented insufficient data in order to make a clear decision were selected for detailed full-text review. Two independent review authors conducted a thorough assessment of the full-text papers. Any disagreements in the eligibility of the included studies were resolved through discussion with a third reviewer. An overview of the aforementioned criteria is provided in Table 1. Studies with a proper control group that demonstrated

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Paper published in English 2. In vitro studies 3. Studies measuring the bond strength of composite resin to enamel/dentin by means of self-etch and universal adhesives in self-etch mode 4. Studies using the bonding agents commercially available and tested by shear/tensile mode on sound enamel/dentin of permanent teeth	1. Enamel/dentin samples, which were contaminated or not treated under clinical conditions before the application of the dentin-bonding agents 2. Studies without data analysis 3. Studies performed on deciduous teeth 4. Papers that did not provide sufficient raw data in the published articles, and attempts to access the data were unsuccessful 5. Studies that compared self-etch bonding systems and etch-and-rinse bonding systems 6. Studies measuring the bond strength to ceramics and other dental materials 7. Studies that measured bond strength to abnormal enamel/dentin (carious, demineralized, sclerotic, and the like)

a standardized method of measurement were further evaluated for use in meta-analysis.

Data Extraction and Collection

The required data were gathered using a form on Microsoft Excel software, and any disagreements concerning the selection of articles were resolved by consulting the third reviewer. The extracted information included demographic information (e.g., first author and year of publication), adhesive systems tested (commercial name and number of steps), source of samples and type of substrate (enamel/dentine), sample size, reported statistical parameters, failure mode, evaluated outcomes, means/standard deviations of bond strength, type of bond strength test (e.g., macro, micro, shear, and tensile), and composite (commercial name and type). In the case of missing data, the authors were contacted to provide unpublished information, and articles that lacked the needed information were excluded from the statistical analysis. Meta-analysis was performed based on the doubling or tripling of advocated primer application time and used substrate (enamel/dentin). Furthermore, the subgroup analysis was conducted according to the mode of adhesive application and their level of acidity (Table 2).

Risk of Bias Assessment

The risk of bias assessment was based on a protocol from a paper depicting Guidelines for Reporting Preclinical in Vitro Studies on Dental Materials (45). The assessment examined the description of several parameters in each section for evaluating the quality of the study, including (1) a structured summary (encompassing trial design, methods, results, and conclusions), (2) scientific background with an explanation of rationale, (2) specific objectives and/or hypotheses, and (3) the intervention per group. Other parameters were (4) completely defined, pre-specified primary and secondary measures of outcome, (5) sample size determination process, (6) method of generation for the random allocation sequence, and (7) method of implementation for the random allocation sequence (describing any steps taken to conceal the sequence until intervention was assigned). Moreover, several other parameters encompassed (8) the implementation of the generator of the random allocation sequence and enroller and assigner of teeth to the intervention, (9) identification of the blinded operator (if performed blind), and (10) statistical methods used to compare groups for primary and secondary outcomes. The remaining explained parameters were (11) precision of primary and secondary outcome, results for each group, and the estimated size of the effect and its precision, (12) trial limitations, addressing sources of potential bias and imprecision, (13) sources of funding, and (14) availability of full trial protocol (Table 3).

Following the method from a previous systematic review (46), the articles were classified into low, high, and unclear risk groups; they had low risk of bias if all criteria were fulfilled, high risk of bias if one or more criteria were not fulfilled, and unclear risk of bias when insufficient data were available for classification as ‘high’ or ‘low’ risk.

Data Analysis

The meta-analysis was conducted using Stata/MP 17.0. Due to high levels of heterogeneity ($I^2 > 50\%$), a random-effects model was used, and the data regarding doubled and tripled conditioning time compared with the manufacturer’s recommended time were assessed accordingly. The high heterogeneity shown in the meta-analyses could be because of the lack of cohesiveness in protocols, different adhesive materials, sample sizes, and the like. Subgroup analysis was performed to evaluate the effect of adhesive acidity and application mode (one step/two steps). Each adhesive system/application time was considered an independent parameter in studies that involved various conditioning times or adhesives.

Results

Study Selection

There were no duplicates, and 123 potentially relevant studies were chosen, 59 of which underwent full-text analysis. Among them, 26 were eligible to be included in the systematic review, and 14 were considered for the meta-analysis (Figure 1).

Risk of Bias

The quality of the involved studies was assessed according to the modified CONSORT form, the results of which are presented in Table 3 (45). According to the 26 in vitro studies, the average score was 74%. All studies obtained a value greater than 47%, except for one that obtained 40% (37). Two studies showed low risk, reaching 100% (15,28),

Table 2. Features of the Included Studies

Author/ Publication Year	Composite Material	Adhesive System/Number of Steps	Source and Substrate	Specimen Number per Group	Bond Strength Test	Failure Mode	Increased Application Time
Karadas 2021 (31)	Filtek Ultimate	All-Bond Universal Scotchbond Universal Tokuyama Universal	Bovine incisor/ enamel	24	Micro-shear	Adhesive	Double
Ostby et al 2021 (32)	---	Transbond Plus SEP/1	Human molars/ enamel	20	Shear	Bracket-adhesive interface	Triple
Karalar and Bayındır 2021 (27)	Voco Grandio Universal Nanohybrid	Single Bond Universal Clearfil Universal Bond Quick One coat 7 Universal	Human molars/ dentin	5	Shear	Adhesive	Double-Triple
Burrer et al 2020 (33)	Filtek supreme	Scotchbond Universal	Human molars/ dentin	10	Microtensile	Adhesive	Double
Ahmed et al 2019 (34)	Clearfil AP-X	Clearfil Universal Bond Quick Scotchbond Universal Clearfil SE Bond 2/2	Human molars/ dentin	40	Microtensile	Adhesive	Double
Zecin-Deren et al 2019 (35)	Flow-Art	Adper Easy One/1 Xeno V/1 Prime & Bond One Select/1 Single Bond Universal	Human molars/ dentin	14	Shear	---	Double-Triple
Saikaew et al 2016 (36)	Clearfil AP-X	G-Premio Bond Clearfil Universal Bond Scotchbond Universal Adhesive	Human molars/ dentin	5	Microtensile	Mixed-Adhesive	Double
Pashaev et al 2017 (37)	Filtek Ultimate Universal	Single-Bond Universal All-Bond Universal Adper Easy One/1	Human molars/ dentin	15	Microtensile	Adhesive	Double
Huang et al 2017 (38)	G-ænial Sculpt	G-Premio Bond	Human molars/ dentin	20	Microtensile	Adhesive	Double
Protásio et al 2016 (39)	---	Transbond Plus Self-Etching Primer/1	Bovine incisor/ enamel	15	Shear	---	Double
Cardenas et al 2016 (25)	Z350	Clearfil Universal Scotchbond Universal Futurabond U	Human molars/ enamel	24	Microshear	Adhesive	Double
Saikaew et al 2018 (28)	Clearfil AP-X	Clearfil Universal G-Premio Bond Scotchbond Universal	Human molars/ dentin	15	Microtensile	Mixed	Double
Amsler et al 2015 (20)	Filtek Z250	Clearfil SE Bond/2 AdheSE/2 Xeno select/1 Scotchbond Universal	Human molars/ dentin	15	Shear	Cohesive-Adhesive	Double
Tekçe et al 2015 (19)	Filtek Z250	Clearfil S3 Bond/1 G-Aenial Bond/1	Human molars/ dentin	47-67	Microtensile	Adhesive-Mixed	Double
Mena-Serrano et al 2013 (26)	Opallis	Adper SE Bond/1 GO/2	Bovine incisor/ dentin	10-14	Microtensile	Adhesive-Mixed	
Kimmes et al 2010 (6)	Z100	Peak SE /(2) Adper Prompt L-Pop/(1) Clearfil SE/(2) Xeno V/(1) AdheSE One Viva Pen/(1) OptiBond All-In-One (1) Clearfil S3/(1) Xeno IV/(1)	Human molar/ dentin /enamel	10	Shear	Adhesive	Double-Triple
Osorio et al 2010 (40)	Tetric Ceram	Prompt-L-Pop/1	Human molars/ dentin	20	Microtensile	Mixed	Double
Tsuchiya et al 2010 (41)	Estelite Quick, Clearfil AP-x, Venus, premise	Bond Force/1 Clearfil Tri-S Bond/1 iBond Self-Etch/1 OptiBond All-in-One/1	Bovine incisor/ enamel	10	Shear	Adhesive	Double-Triple
Erhardt et al 2009 (13)	Tetric Ceram	Clearfil SE Bond/2 Resulcin AquaPrime/2 Etch & Prime/1 One-Up Bond F	Human molars/ dentin	30	Microtensile	Adhesive-Mixed	Double
Barkmeier et al 2009 (42)	Z100	Adper Prompt L-Pop/1 Clearfil SE Bond/2 Clearfil S3 Bond/1 Xeno IV/1	Human molars/ enamel	10	Shear	Adhesive	Triple

Table 2. Continued.

Author/ Publication Year	Composite Material	Adhesive System/Number of Steps	Source and Substrate	Specimen Number per Group	Bond Strength Test	Failure Mode	Increased Application Time
Iijima et al 2009 (43)	---	Transbond Plus/2 Beauty Ortho Bond/2	Human premolars/ enamel	15	Shear	----	Double
Britta et al 2009 (11)	Rok—Lot	Clearfil SE Bond/2 AdheSE/2 Futurabond NR/1 One Up Bond F Plus/1	Human molars/ enamel	16	Microtensile	Mixed	Double
Pivetta et al 2008 (15)	Filtek flow	Clearfil SE Bond/2 Adper Prompt L-Pop/1	Human molars/ enamel	6	Shear	Mixed	Double
Toledano et al 2007 (24)	Arabesk	Futurabond/1	Human molars-bovine incisor/ dentin	30	Microtensile	Adhesive	Double
Velasquez et al 2006 (14)	Z100	Clearfil SE Bond/2 Xeno III/1 AdheSE/2	Human molars/ enamel-dentin	10	Shear	---	Double-Triple
Perdigão et al 2006 (44)	Filtek Z250	Adper prompt Lpop/1 adheSE/2 Clearfil SE Bond/2 Tyrian SPE unit-dose/One-Step Plus/2	Human molars/ enamel	6	Microtensile	---	Double

Table 3. Risk of Bias Assessment

Articles	1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14	Overall Risk
Karadas 2021 (31)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	87%
Ostby et al 2021 (32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	87%
Karalar and Bayındır 2021 (27)	No	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No	53%
Burrer et al 2020 (33)	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	60%
Ahmed et al 2019 (34)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	No	53%
Zecin-Deren et al 2019 (35)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	47%
Saikaew et al 2018 (28)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Pashaev et al 2017 (37)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	40%
Huang et al 2017 (38)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	47%
Protásio et al 2016 (39)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	87%
Cardenas et al 2016 (25)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	93%
Saikaew et al 2016 (36)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	53%
Amsler et al 2015 (20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	93%
Tekçe et al 2015 (19)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	80%
Mena-Serrano et al 2013 (26)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	53%
Kimmes et al 2010 (6)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	93%
Osorio et al 2010 (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	93%
Tsuchiya et al 2010 (41)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	87%
Erhardt et al 2009 (13)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	93%
Barkmeier et al 2009 (42)	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	No	47%
Iijima et al 2009 (43)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	80%
Britta et al 2009 (11)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	80%
Pivetta et al 2008 (15)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Toledano et al 2007 (24)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	93%
Velasquez et al 2006 (14)	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	47%
Perdigão et al 2006 (44)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	87%

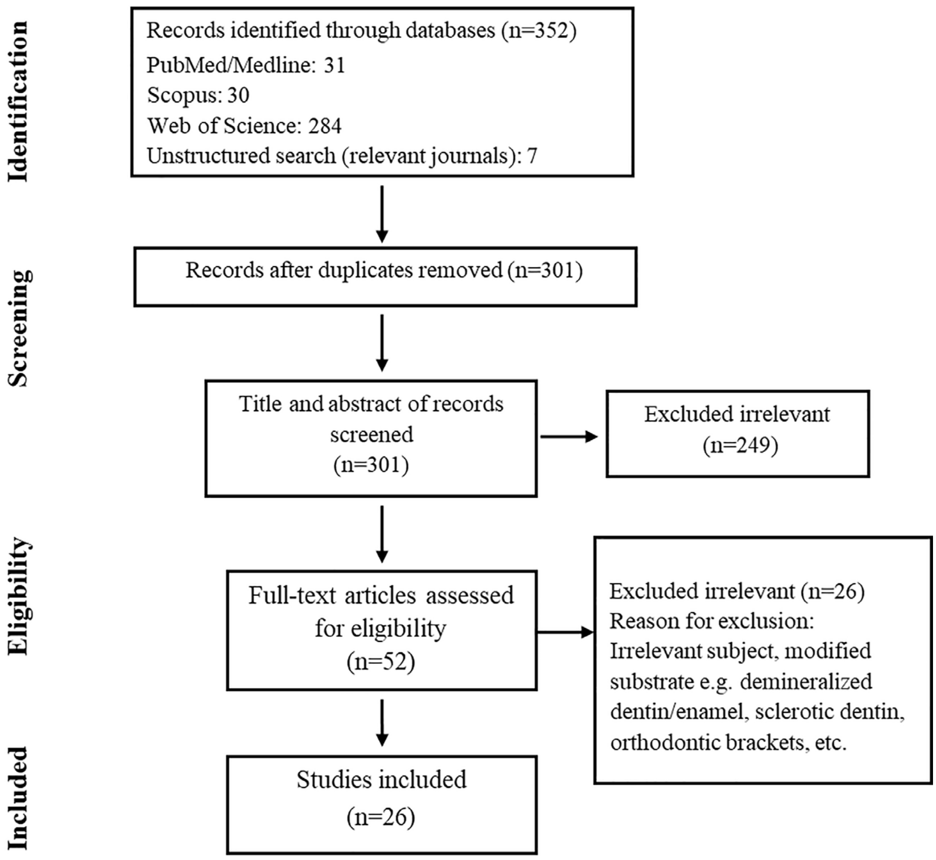

Figure 1. Flowchart of Study Selection for Inclusion in the Systematic Review And Meta-analysis

while others demonstrated moderate or high levels of bias. The least observed parameters were mention of the full trial protocol (Table 3). Concerning the overall risk of included articles, most studies represented moderate to high levels of risk of bias.

Qualitative Analysis

Overall, 26 studies were eligible for this review, all of which were in vitro studies and were performed on extracted teeth. Of this number, 4 (26,31,39,41) and 21 (6,11,13-15,19,20,24,25,27,28,32-38,40,42-44) studies used extracted bovine incisors and extracted human molars, respectively, and one study utilized both human extracted molars and bovine incisors (24). The minimum and maximum number of specimens were reported to be 5 and 34, and all studies employed either self-etch or universal adhesive systems. In all included studies, after the bonding procedure, the samples were stored in 37 °C water for a period of time (minimum 24 hours and maximum 2 years). All the studies performed bond strength tests using a shear/tensile load at a crosshead speed of 0.5 or 1 mm/min, with the exception of one article which reported the crosshead speed of 2 mm/minute. The microtensile bond test was the most commonly used method (13 studies), followed by the shear bond test (11 studies) and micro-shear test (2 studies), respectively.

Meta-Analysis

Meta-analyses were performed using 14 studies that met the required criteria. The results were analyzed using the random-effects model in all but one analysis because I^2 tests showed high heterogeneity (over 50%). In the general analysis of specimens undergoing doubled application time, ground dentin demonstrated higher bond strength compared to the recommended time by manufacturers (95% confidence interval [CI]: -1.509, -0.171, $Z=2.46$, $P=0.014$). Doubling the application time in one-component adhesives induced higher bond strength in ground dentin compared to the recommended time by manufacturers (95% CI: -1.624, -0.225, $Z=2.59$, $P=0.010$). However, by doubling the application time for two-component adhesives, the difference in bond strength was not significant (95% CI: -1.803, 2.088, $Z=0.14$, $P=0.886$, Figure 2). Taking into account the acidity of adhesives, doubling the application time of moderate adhesives seems to have increased the bond strength to the ground dentin (95% CI: -3.035, -0.381, $Z=2.52$, $P=0.012$), while mild (95% CI: -1.374, 0.244, $Z=1.37$, $P=0.171$) and strong (95% CI: -0.002, 1.053, $Z=1.95$, $P=0.057$) adhesives were not impacted as much (Figure 3). According to the overall analysis of adhesives concerning both aforementioned factors (i.e., the number of components and the level of acidity), one-component moderate adhesives seem to increase bond strength to ground dentine following the doubled application time (95% CI: -3.787, -0.734, $Z=2.90$, $P=0.004$). Conversely, other groups either lacked relevant information due to a lack of studies and experiments (i.e., two-component

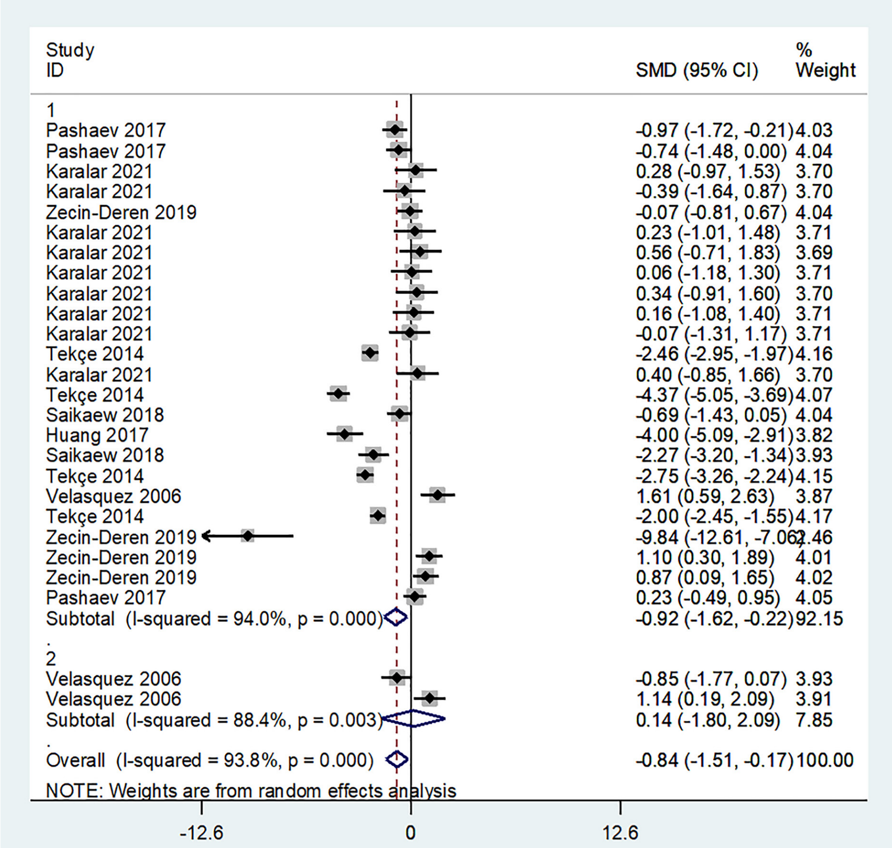

Figure 2. Influence of Doubling the Application Time Compared With Manufacture Recommended Time on Bond Strength to Ground Dentin in One-Component and Two-Component Adhesives

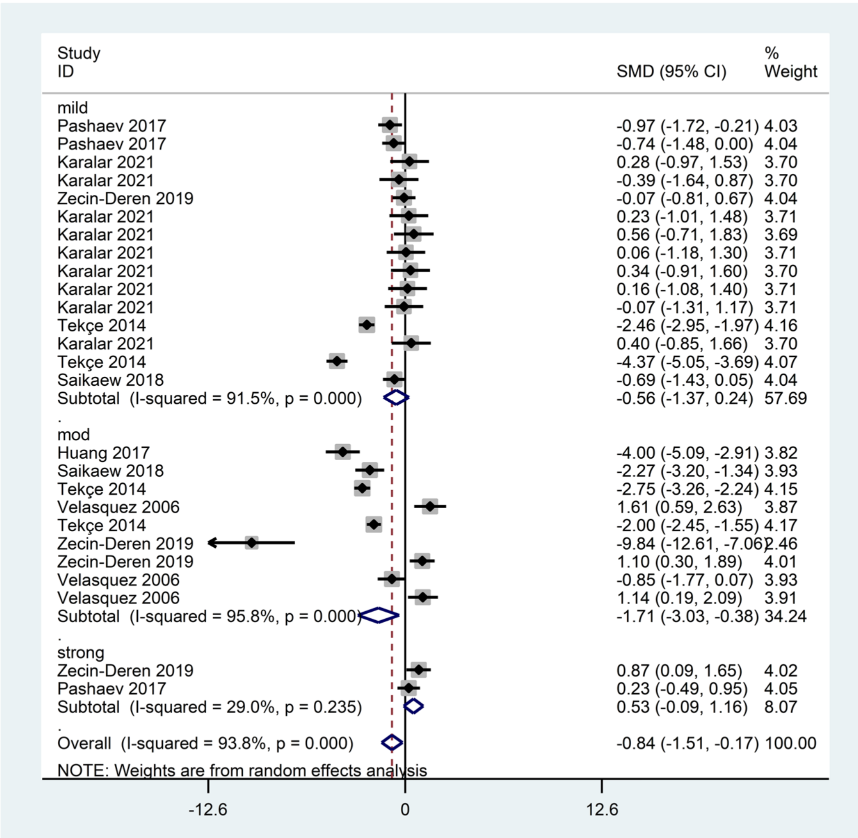

Figure 3. Influence of Doubling the Application Time Compared With Manufacture Recommended Time on Bond Strength to Ground Dentin in Mild, Moderate and Strong Adhesives

mild adhesives and two-component strong adhesives), or the available information indicated that their impact was insignificant (i.e., two-component moderate adhesives) (Figure 4).

In the general analysis of grounded enamel undergoing doubled application time, the specimen showed higher bond strength in comparison to the recommended time by manufacturers (95% CI: -1.287, -0.262, Z = 2.96, *P* = 0.003). Doubling the application time in one-component adhesives could induce higher bond strength in ground enamel compared to the recommended time by manufacturers (95% CI: -1.628, 0.453, Z = 3.47, *P* = 0.001). Contrarily, the difference in bond strength was not significant by doubling the application time for two-component adhesives (95% CI: -0.397, 0.600, Z = 0.40, *P* = 0.690, Figure 5). Based on the level of acidity, doubling the application time of mild adhesives increased the bond strength to the ground enamel (95% CI: -2.051, - 0.292, Z = 2.67, *P* = 0.009), whereas moderate adhesives (95% CI: -1.058, 0.049, Z = 1.79, *P* = 0.074) were not affected by doubled application time (Figure 6). Overall, considering both the number of components and level of acidity, the analysis reported a significant increase in bond strength following the duplication of application time for one-component mild (95% CI: -2.051, -0.292, Z = 2.67, *P* = 0.009) and one-component moderate (95% CI: -1.505, -0.553, Z = 4.24, *P* = 0.000) adhesives. The other subgroups of adhesive material faced the same limitations as the dentin group (Figure S1).

In the general analysis of the specimen undergoing tripled application time, ground dentin displayed no significant increase in bond strength in any of the groups (95% CI: -0.779, -0.270, Z = 0.32, *P* = 0.750). Based on the reports from further specific analysis on one-component (95% CI: -0.927, 0.686, Z = 0.29, *P* = 0.774) and two-component (95% CI: -1.369, 0.895, Z = 041, *P* = 0.682) adhesives, tripling the application time in self-etch and universal adhesives could not induce increased bond strength in grounded dentin (Figure S2). The same results were obtained considering the level of acidity (95% CI: -0.811, 0.584, Z = 0.32, *P* = 0.750) (Figure S3) and thus factors revolving around adhesives and ground dentin (95% CI: -0.811, 0.584, Z = 0.32, *P* = 0.75, Figure S4).

In contrast, the general analysis of grounded enamel undergoing tripled application time revealed a significant increase in bond strength (95% CI: -0.779, -0.270, Z = 4.04, *P* = 0.000) compared to the manufacturer's recommended time. Given that the subgroup analysis of one-component and two-component adhesives produced a low value of heterogeneity ($I^2 < 50\%$), the overall analysis used the fixed model instead of the random model for this specific analysis. Based on the reports from further specific analysis on one-component adhesives using a fixed model ($I^2 = 34.6\%$), tripling the application time induced a significant increase in bond strength to ground enamel (95% CI: -1.180, -0.518, Z = 5.02, *P* = 0.000). Nonetheless, using the fixed model on further analysis of two-component adhesives ($I^2 = 27.7\%$) did not illustrate

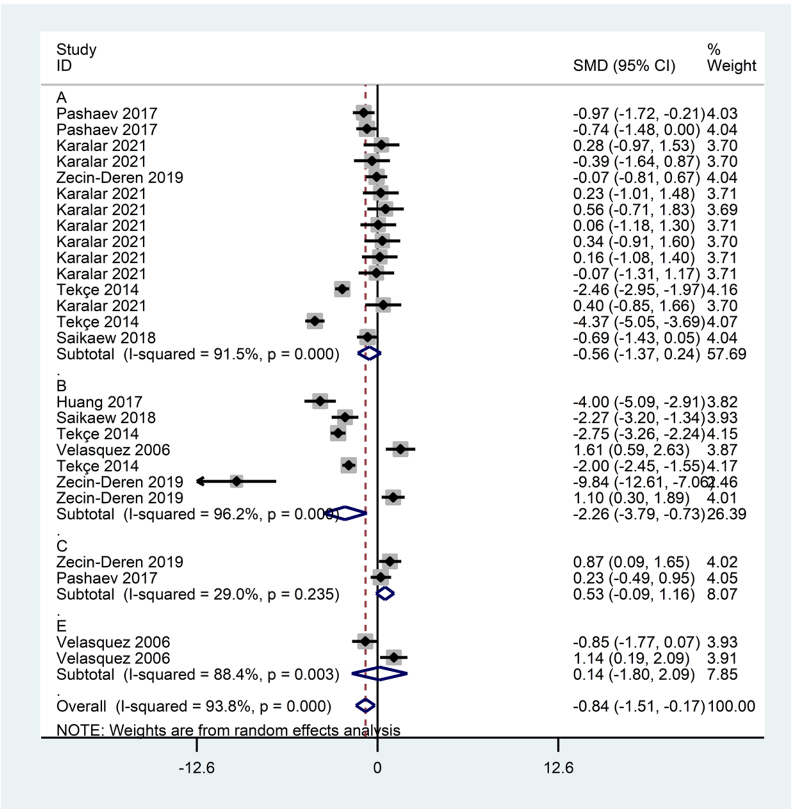

Figure 4. Overall Analysis of the Influence of Doubling the Application Time Compared With Manufacture Recommended Time on Bond Strength to Ground Dentin

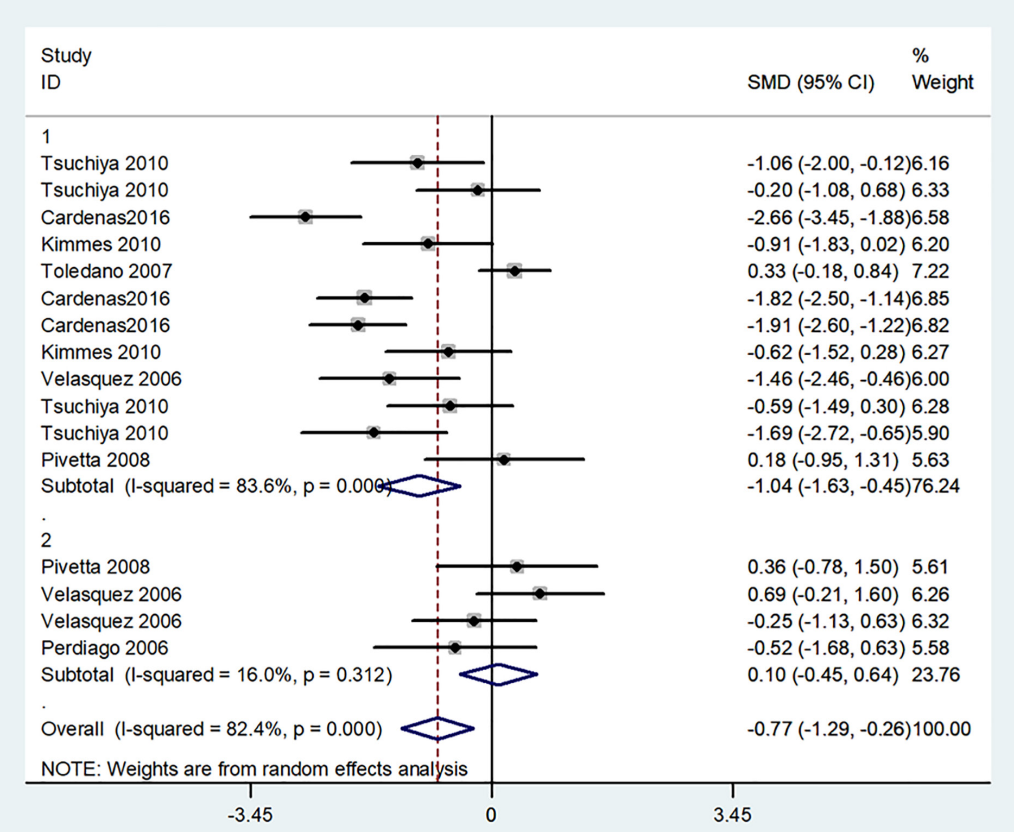

Figure 5. Influence of Doubling the Application Time Compared With Manufacture Recommended Time on Bond Strength to Ground Enamel in One-Component and Two-Component Adhesives

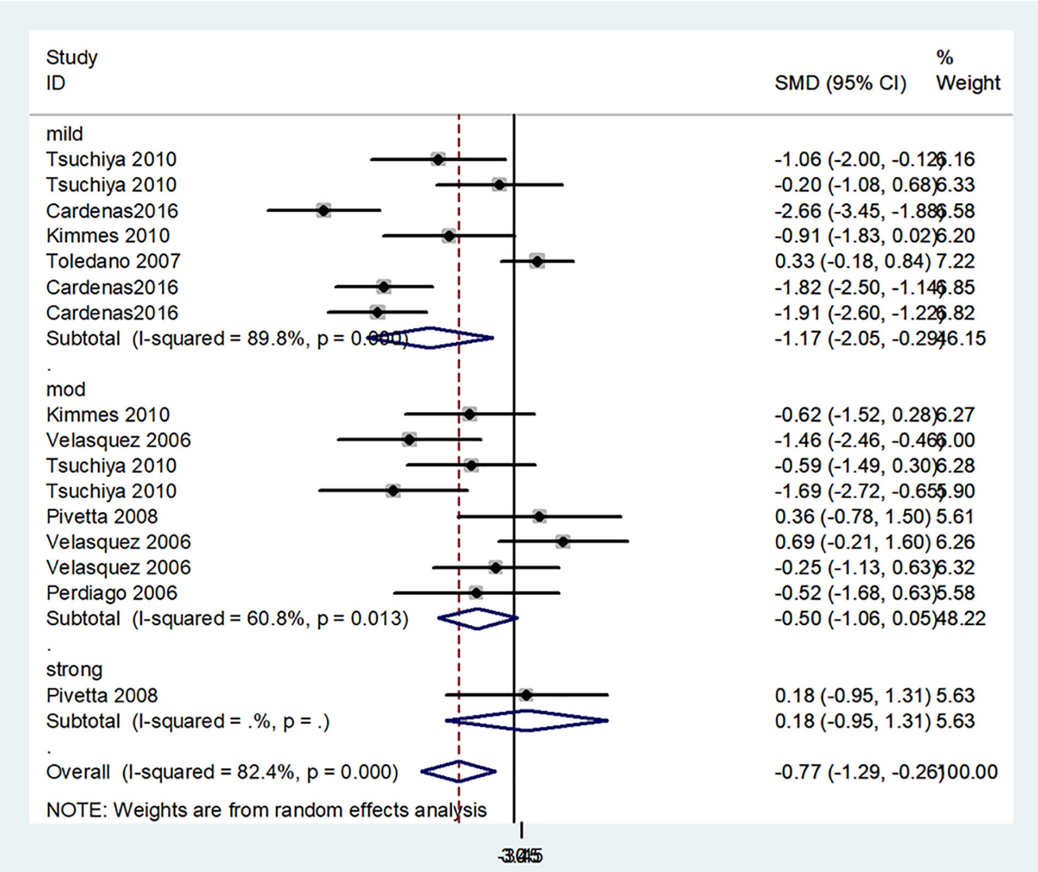

Figure 6. Influence of Doubling the Application Time Compared With Manufacture Recommended Time on Bond Strength to Ground Enamel in Mild, Moderate and Strong Adhesives

any significant increase (95% CI: -0.454, 0.342, Z = 0.28, P = 0.782, Figure S5). Based on the level of acidity, tripling the application time of mild (95% CI: -1.159, - 0.238, Z = 2.97, P = 0.003) and moderate (95% CI: -0.976, -0.012, Z = 2.01, P = 0.045) adhesives could increase the bond strength to ground enamel. Not enough experimental data were available on strong adhesives (Figure S6). In general, considering the number of components and level of acidity, the analysis confirmed a significant increase in bond strength following the duplication of application time for one component mild (95% CI: -1.159, -0.238, Z = 2.97, P = 0.003) and one-component moderate (95% CI: -0.979, -0.012, Z = 2.01, P = 0.045) adhesives. Other subgroups lacked relevant information due to a lack of studies and experiments (i.e., one-component strong adhesives and two-component mild, moderate, and strong adhesives) (Figure S7).

The results of the evaluation of the diffusion pattern using the Egger method revealed that the bias was not significant in any of the meta analyses as follows:

(P = 0.075) for grounded dentin groups with the duplication of primer application time (Figure S8).

(P = 0.944) for grounded enamel groups with the duplication of primer application time (Figure S9).

(P = 0.054) for grounded dentin groups with the triplication of primer application time (Figure S10).

(P = 0.000) for grounded enamel groups with the triplication of primer application time (Figure S11).

Discussion

This systematic review and meta-analysis assessed the impact of increased application time on the bond strength between self-etch/universal adhesive systems and tooth structure. To the best of our knowledge, no other similar systematic review has been conducted so far. A thorough search of existing literature was performed in English, with no publication date restrictions. To conduct the meta-analysis, self-etch and universal adhesive systems were further categorized and independently analyzed based on their pH values (mild, moderate, and strong) and the number of involved components (one or two bottles). This approach was taken to accommodate potential variations in behavior depending on the adhesive system's composition and how different numbers of steps in the clinical application process might influence the outcomes. Subsequently, a complete analysis was conducted, considering both acidity and the number of components.

The null hypothesis was rejected based on the existing data and the performed meta-analysis. Overall, the results indicated that doubling the application time of adhesives could increase the bond strength to dentin or enamel. While tripling the application time did not significantly affect the bond strength between dentin and adhesives, it could increase the bond strength between enamel and SEAs and UAs. However, there were several limitations due to the limited number of available studies in certain subgroups. For instance, there was a lack of data exploring whether tripling the application time in strong adhesive systems could enhance the bond strength to dentin. Similar limitations were observed for 2-component mild adhesives and 2-component strong adhesives.

In relation to doubling the application time of one-component self-etch and universal adhesives, a significant increase was observed in bond strength between these systems and dentin. Our findings align with those of other studies (19,24,47). Considering that the high content of the remaining solvent could compromise the mechanical properties and conversion degree of adhesive systems (48,49), it appears that prolonging the application time would allow for increased solvent evaporation and continued monomer diffusion into the dentin structure. This process could contribute to the formation of a stronger resin-dentin bond strength (37,50). However, the prolonged application time of self-etch and universal adhesive systems may not exhibit a significant increase in all cases, depending on the amount of prolongation (51). These data are in line with our findings considering the tripled application time of one component adhesive and resin-dentin bond strength.

Dentin is a hydrated hard dental tissue, and its composition and structural features are different from those in enamel. While hydroxyapatite minerals compose close to 90% wt of enamel, dentin has a higher organic content (52,53). Acidic monomers in self-adhesive bonding agents interact and partially dissolve the hydroxyapatite minerals in dentin structure, modifying the smear layer as opposed to dissolving it (35,51,54). The residual hydroxyapatite crystals along with smear debris remnants would become part of the final hybrid layer (50,54). Following this step, hydrophilic monomers present in the bond solution would infiltrate and interact with the exposed collagen fibrils (55). As longer exposure of the mineral content to acidic monomers would result in more demineralization, the hydrated collagen matrix might be able to partially maintain its structural height and volume. However, ongoing demineralization might compromise the mechanical support of the matrix (56) and thus likely affect the final bond value. Based on these facts and our statistical results, it is possible to assume that increasing the application time of self-etch adhesives over a certain limit could be destructive to resin-dentin bond strength.

With regard to doubling and tripling the application time of one component adhesive systems on enamel, our findings suggest a significant impact, which is consistent with the results of previous investigations (25,41). According to Cardenas et al (25), since the acidic monomers in self-etch and universal adhesives are not strong enough to create a retentive etching pattern, the prolonged application time might improve the interaction of acidic monomers with the enamel, thereby creating a more retentive pattern and increasing the resin impregnation into the dental tissue. However, the effect of prolonged application time on resin-enamel bond strength has not been substantial in all studies. As reported by Kimmes et al (6), while the enamel bond strength increased slightly with the extended treatment time, it did not induce a significant increase in bond strength compared to the recommended treatment time. Nonetheless, this result might be due to different experimental conditions and materials used. Additionally, because of enamel and dentin chemical and structural differences (57,58), utilizing the same adhesive system might result in different outcomes for dentin and enamel, as certain adhesive systems might yield higher bond strength values for dentin compared to enamel, or conversely (23,59-61).

Recent studies have confirmed the correlation between the pH value of the applied universal adhesives and their bonding performances, highlighting the importance of this knowledge for clinical practitioners (62,63). Self-etch and universal adhesive systems can be classified into ultra-mild (pH > 2.5), mild (2.5 > pH > 2), moderate (1 < pH < 2), and strong (pH < 1) categories based on the pH value (11,15,53). Self-etch adhesives employ acidic monomers for conditioning tooth structures, in contrast to traditional phosphoric acid etching in total-etch methods. However, while strong self-etch adhesives with lower pH values could create demineralization patterns in enamel/dentin similar to that of total-etch systems (64), mild self-etch adhesives did not generate an equivalent level of porosity in enamel surfaces as achieved through phosphoric acid etching. Furthermore, the collateral collapse of collagen fibers in dentin followed by strong adhesive conditioning could result in weaker bond strength to dentin (65,66), leaving the possibility that the resulting bond strength from self-etch adhesives might be related to other bonding factors rather than only the level of pH (15,27,33,55). According to Oliveira et al (56), the bonding mechanism of self-etch adhesives to dentin is largely dependent on the formation of a “hybrid layer”, which is created following the infiltration of resinous monomers in demineralized dentin and the creation of a molecular interaction between the resin and the fibers of collagen (67,68). However, in some self-etch adhesives, the presence of other functional monomers could contribute to the bond strength as well. For example, the ionic interaction of the functional monomer 10-methacryloyloxydecyl dihydrogen phosphate with calcium from the remaining hydroxyapatite around the partially exposed collagen seems to have had a positive impact on the resin-dentin bond value in certain adhesives (13,15,20,21,33).

According to our statistical findings, doubling and tripling the application time of mild one-component self-etch and universal adhesives led to an increase in bond strength to the enamel. However, such variations in the application time had no significant impact on bond strength to dentin. Moreover, the duplication of the application time of one-component moderate adhesive resulted in increased adhesive-dentin bond strength, while tripling the application time produced higher bond strength to the enamel. Nevertheless, it is important to note that there is a limited body of research exploring the relationship between the prolonged application time and the acidity levels of self-etch and universal adhesives and how these factors influence bond strength to dentin and enamel. Consequently, our findings in this specific matter may not offer conclusive clinical guidance due to the current gaps in knowledge.

Most articles stored the samples in water for 24 hours before bond strength tests. However, samples in one study did not undergo water storage (44). The speed per minute of the machine testing the bond strength varied in different machines (0.5, 1, and 2 mm/s) and different bond tests (shear, micro-shear, tensile, and microtensile) used for experimenting. Therefore, the high heterogeneity shown in the meta-analyses could be because of the lack of cohesiveness in protocols, different adhesive materials, sample sizes, and the like. Additionally, the risk of bias was considered medium and high in most studies. Given the identified risk of bias and the observed high heterogeneity, there is an imperative need for standardized experimental methods for further investigations.

Considering the current findings and acknowledged limitations, the prolonged application time of one-component self-etch and universal adhesives could enhance the bond strength of both dentin and enamel. Nevertheless, dental practitioners should interpret these results with caution for clinical purposes. Moreover, further in vitro and clinical investigation is needed to confirm the impact of increased application time of different adhesive systems and provide evidence-based recommendations for clinical practice.

Conclusion

Based on the gathered data and performed analysis, duplicating the application time of self-etch and universal adhesives could increase the bond strength to ground dentine/enamel under in vitro conditions. However, while tripling the application time of self-etch and universal adhesives could increase the bond strength to ground enamel, it did not have the same impact on ground dentin. Furthermore, the overall increased application time of one-component adhesives could result in better bond strength compared to two-component adhesives. Considering the diverse variables affecting the bond strength value and the present limitations in current literature related to this matter, no coherent conclusion could be reached considering the effect of the number of components or the pH level of adhesives on bond strength value.

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Competing Interests
The authors declared that there is no conflict of interests regarding the publication of this paper.

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The data are available upon request from the authors.

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The authors declare the use of generative artificial intelligence in scientific writing upon submission of the paper.

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Not applicable.

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Supplementary Files
Supplementary file 1 contains Figures S1-S11.

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