Can Endodontic Irrigating Solutions Influence the Bond Strength of Adhesives to Coronal Dental Substrates? A Systematic Review and Meta-Analysis of In Vitro Studies

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Purpose: To systematically review the literature to analyze the influence of endodontic irrigating solutions on the bond strength of adhesives to coronal enamel or dentin.

Materials and Methods: The PubMed/MEDLINE, Web of Science and Scopus electronic databases were used to select laboratory studies related to the research question, without publication year or language limits. From 2461 potentially eligible studies, 2451 were selected for full-text analysis, and 97 were included in the systematic review. Two authors independently selected the studies, extracted the data, and assessed the risk of bias. Pooling bond strength data were calculated using RevMan5.1 with random effects model (α = 0.05), comparing control (no endodontic irrigating solution) and experimental groups (one or more endodontic solutions).

Results: No significant difference was found between the control and experimental groups (p = 0.12) in the overall meta-analysis and in the meta-analysis excluding chlorhexidine (p = 0.06). High heterogeneity was found in the meta-analyses. Most included studies in the systematic review were scored as having a high risk of bias.

Conclusion: The different endodontic irrigating solutions evaluated showed no negative influence on the bond strength of dental adhesives to coronal dental substrates.

Keywords: dental bonding, bond strength, adhesive, irrigation.

J Adhes Dent 2018; 20: 481–494.
doi: 10.3290/j.jad.a41633

Submitted for publication: 15.06.18; accepted for publication: 05.11.18

The success of endodontically treated teeth is dependent on the apical sealing after chemomechanical preparation of the root canals, as well as the coronal sealing of bonded restorations.[11,12] When the final restoration fails, microorganisms and their toxins in the root canals may influence the prognosis of endodontic treatment.[39]

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The procedures for obtaining a better cavity seal have been the subject of numerous studies.[30,39] Adhesive restorations are frequently performed in daily clinical practice, as they promote coronal sealing, prevent microleakage of microorganisms, and reinforce tooth structure weakened by endodontic treatment, ensuring the distribution of stress across the bonded interface.[30]

Several irrigants have been used for endodontic treatment. Sodium hypochlorite has broad-spectrum antibacterial properties, as well as a sporicidal and virucidal effect; also, its alkalinity dissolves necrotic tissue. On the other hand, EDTA (R ethylene diamine-tetra-acetic acid) substantially removes the smear layer from the inner walls of the root canal. Its effect is restricted to mineralized dentin, with no effect on collagen fibrils. CHX (chlorhexidine gluconate) has the potential to inhibit proteolytic enzymes called metalloproteinases, but does not remove the smear layer.[15,16,25,58]

A recent systematic review pointed out that the irrigating solution does not interfere with the push-out resistance to dislodgement of root filling materials.[24] However, it is not clear if the irrigation protocol in root canals could jeopardize the longevity of adhesive restorations.

Whereas the endodontic irrigating solutions seem to promote inhibition of polymerization of the resins at the adhesive interface and reduce the physical properties of the dentin substrate,[4,84] a negative effect can be expected on the adhesion of adhesives to previously exposed substrates. Some studies demonstrated that the endodontic irrigating solutions reduced the bond strength of adhesives to dentin.[20,37,84] However, in other studies, endodontic irrigating solutions did not significantly influence bond strength.[9,15,16,59,84]

Thus, questions remain with regard to the effect of endodontic irrigating solutions on the bond strength of adhesives to enamel and dentin. Pooled in vitro data could provide more solid conclusions about this topic. Thus, the aim of this study was to systematically review the literature to evaluate the influence of endodontic irrigating solutions on the bond strength of adhesives to coronal enamel and dentin. The null hypothesis tested was that there would be no difference in the bond strengths of adhesives to enamel and dentin exposed or not to endodontic irrigating solutions. The review aimed to answer the following research question: "Can endodontic irrigating solutions influence the bond strength of adhesives to coronal enamel and dentin?"

MATERIALS AND METHODS

This systematic review was conducted according to the recommendations of the Cochrane Handbook[46] and PRISMA statement (ie, Preferred Reporting Items for Systematic Reviews and Meta-analyses).[61]

Search Strategy

A comprehensive literature search was under taken through PubMed/MEDLINE, Scopus, and Web of Science up to 10 October 2018, to identify literature that evaluated the bond strength of adhesives to enamel or dentin previously treated with any endodontic irrigating solution, without publication year or language limits. The subject search used a combination of specific medical subject headings (MeSH) and keywords as follows: ((((((((((((((tensile strength[MeSH Terms]) OR tensile strength) OR shear strength[MeSH Terms]) OR shear strength) OR tensile) OR shear) OR microshear) OR micro shear) OR microtensile) OR micro tensile) OR bond strength) OR bonding) OR bond*)) AND ((((((((((((((Root Canal Irrigants[MeSH Terms]) OR root canal Irrigant*) OR canal irrigants, root) OR irrigants, root canal) OR root canal Medicament*) OR canal medicaments, root) OR medicaments, root canal) OR irrigant solution*) OR irrigation solution*) OR endodontic solution*) OR endodontic irrigation) OR endodontic irrigant*) OR irrigation regim*) OR edta) OR hypochlorite).

The search strategy developed for PubMed was adapted for the other eletronic databases (Scopus and Web of Science) as follows: ("Root Canal Irrigants" OR "root canal Irrigant" OR "canal irrigants" OR "root canal medicament" OR "canal medicaments" OR "irrigant solution" OR "irrigation solution" OR hypochlorite OR edta).

Selection, Inclusion and Exclusion Criteria

Two authors (PEF and TCB) independently reviewed the titles and abstracts of all eligible studies and in consensus selected publications for full-text reading using the following inclusion criteria: studies that evaluated the influence of any endodontic irrigating solution on the performance of adhesives; in vitro studies that assessed the bond strength to coronal dentin or enamel. If consensus was not reached, the abstract was set aside for further evaluation.

The final decision about inclusion was made on the basis of the full text of the potentially relevant studies in accordance with the following exclusion criteria: did not determine immediate or aged bond strength data; did not present a control group (no endodontic irrigating solution). Papers that did not provide bond strength data (primary outcome), ie, means in MPa and respective standard deviations, were excluded, even after e-mail requests sent to authors (at least twice). Studies that investigated degradation of bond strength but did not describe immediate bond strength data as reference were excluded. When the same bond strength data were reported in different articles (eg, papers with different storage times), only one study was considered to avoid overlapping data. In order to retrieve all relevant papers, two authors (PEF and TCB) screened the reference lists of included papers and related reviews.[59] Disagreements between the reviewers were solved by consultation with a third review (ROR). The eligibility of studies between the authors showed excellent agreement, with a kappa score of 0.90.

Data Extraction

Two authors (PEF and TCB) performed the data extraction of the included studies using a customized extraction form. For each paper, the following data were systematically extracted: authors, publication year, country, endodontic irrigating solution, origin and type of teeth, sample size, adhesive and manufacturer, bond strength test, substrates evaluated, bond strength means and standard deviations. Missing or unclear information was requested from the corresponding authors by e-mail twice at a one-week interval. If no information was provided, the study was excluded from the systematic review.

Risk of Bias Assessment

Risk of bias assessment was based on and adapted from previous systematic reviews of in vitro studies,[57,99] considering the following items: randomization of the teeth for experimental groups, sample size calculation, specimens with similar cross section, failure mode evaluation, materials used according to the manufacturers' instructions, adhesive and testing procedures performed by a single operator, and specimen tested by a blinded operator. If the authors reported the parameter, the paper had a Y (yes) on that specific parameter; if it was not possible to find the information, the paper received an N (no). The risk of bias was classified according to the sum of "yes" received as follows: 1 to 3 = high; 4 to 5 = medium; 6 to 7 = low risk of bias. For the final classification of risk of bias, disagreements between the reviewers (PEF and TCB) were solved by consensus.

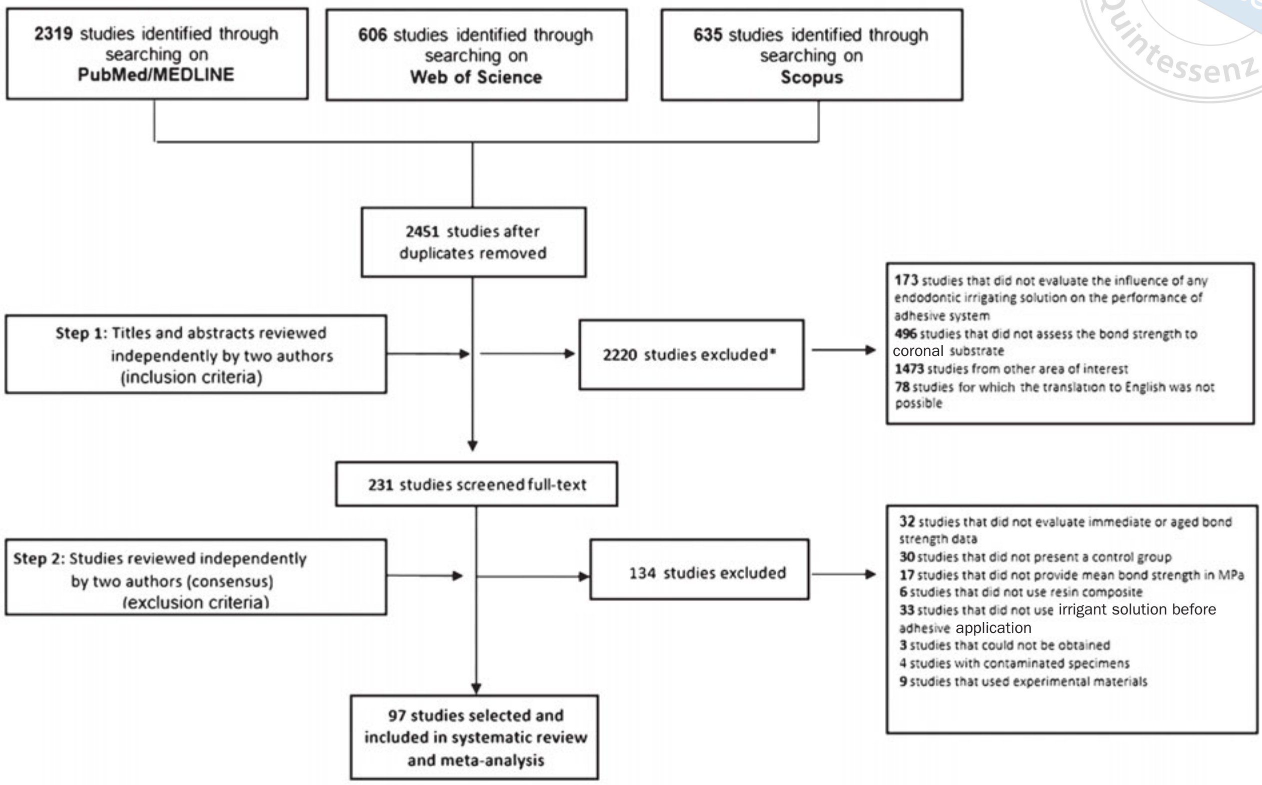

Fig 1 Flowchart diagram of study selection according to PRISMA statement.

Data Analyses

Meta-analyses were performed using Review Manager software (RevMan version 5.3 software, Cochrane Collaboration; Copenhagen, Denmark) and the mean difference with a 95% confidence interval was calculated for the bond strength means from each primary included study, considering two groups: experimental (substrate treated with endodontic irrigating solution) and control (no endodontic irrigating solution was used prior to bonding procedures). Using the inverse variance method and random effect model, $p \leq 0.05$ (Z test) was considered significant. For the studies that evaluated more than one endodontic irrigating solution, adhesive or substrate, one mean of bond strength of each treatment (experimental and control) was calculated using a formula according to the Cochrane Statistical Guidelines.[46] Only immediate bond strengths were considered for analyses and the number of specimens was considered as the number of experimental units.

The same statistical methods were used to estimate the effect of endodontic irrigating solutions excluding chlorhexidine as treatment (subgroup analysis). Forest plots were created to illustrate the meta-analyses. A modified chi-squared test (Cochran Q test) with a threshold $p > 0.1$ was used to assess the statistical homogeneity (I^2) of the treatment effect among studies. Values up to 60% were considered as not important in moderating heterogeneity.

RESULTS

Search and Selection

Figure 1 depicts a flowchart summarizing the study selection process. From 2451 potentially eligible studies, 97 were included in the systematic review. The main reasons for the exclusion of studies were: did not evaluate immediate bond strength data; did not present a control group (no endodontic irrigating solution); did not provide bond strength means in MPa; did not use composite or test any endodontic irrigating solution before adhesive application.

Descriptive Analysis

Table 1 shows descriptive data extracted from the studies included in the review. All studies were published in English between 1992 and 2018, with 50 papers published after 2010. [3,6,7,9,15-17,20,21,26-28,31,32,36,37,42-44,47,52-55,60,62-67,70,75,76,78-80,83,85,91-94,97,98,102-105,115] The majority of the studies were conducted in Brazil (n = 27),[5,7,8,10,15-17,22,25,26,29,36,40,60,64,65,72,78,82,83,85,91,94,95,98,100,108] and Japan (n = 12).[45,48,53-55,67,75,76,86,101,107,109]

Among the included studies, 16 different endodontic irrigating solutions were evaluated. As expected, the most commonly used endodontic irrigant was sodium hypochlorite (72 studies). The majority of the studies evaluated the effect of only one endodontic irrigant (69 studies), while the

Table 1 Characteristics of the studies included in the systematic review

Authors/year	Country*	Endodontic irrigating solution#	Number of samples per group	Origin and type of teeth	Substrate	Adhesive	Bond strength test
Adebayo et al 2007[2]	Australia	EDTA	21	Human molars	Enamel	Clearfil SE Bond Adper Single Bond	Microshear
Adebayo et al 2008[1]	Australia	EDTA	22	Human molars	Dentin	Clearfil SE Bond G-Bond	Microshear
Alici et al 2018[3]	Turkey	NaOCl CHX	10	Human molars	Dentin	Clearfil S3 Bond Plus All-Bond Universal	Microshear
Arias et al 2005[5]	Brazil	NaOCl	15	Bovine incisors	Dentin	Gluma One Bond Prime&Bond Prime&Bond NT Adper Single Bond	Shear
Arslan et al 2011[6]	Turkey	NaOCl CHX	12	Human third molars	Dentin	Filtek Silorane Primer + Adhesive	Shear
Augusto et al 2018[7]	Brazil	NaOCl	10	Bovine incisors	Dentin	Futurabond M+	Microtensile
Barbosa et al 2005[8]	Brazil	NaOCl	50	Human third molars	Dentin	Adper Single Bond Prime&Bond One Coat Bond	Microtensile
Barutcigil et al 2012[9]	Turkey	EDTA	10	Human third molars	Dentin	Adper Single Bond Multi-Purpose Clearfil S3 Bond	Microtensile
Baseggio et al 2009[10]	Brazil	NaOCl	38	Human third molars	Dentin	Adper Single Bond	Microtensile
Benderli and Yucel 1999[13]	Turkey	Na- EDTA	6	Human third molars	Dentin	Prisma Universal Bond 2	Shear
Blomlöf et al 2001[14]	Sweden	EDTA	14	Human third molars	Dentin	All Bond 2 Prime&Bond NT	Shear
Carvalho et al 2017[15]	Brazil	NaOCl + EDTA CHX + saline solution + EDTA	22/23/ 24/33/34	Human molars	Dentin/ enamel	Clearfil SE Bond Adper Single Bond	Microshear
Cecchin et al 2010[16]	Brazil	NaOCl NaOCl + EDTA	10	Human third molars	Dentin	Xeno III	Microshear
Cecchin et al 2011[17]	Brazil	NaOCl EDTA	10	Human third molars	Dentin	Adper Single Bond	Microtensile
Cederlund et al 2001[19]	Sweden	EDTA	15	Human third molars	Dentin/ enamel	All Bond 2	Shear
Cederlund et al 2002[18]	Sweden	EDTA NaOCl + EDTA NaOCl	15	Human third molars	Dentin	All Bond 2	Shear
Cha and Shin 2016[20]	South Korea	NaOCl CHX	15	Human third molars	Dentin	Scotchbond Universal	Shear
Chauhan et al 2015[21]	India	NaOCl	10	Human premolar	Dentin	Adper Single Bond	Shear
Chaves et al 2002[22]	Brazil	EDTA	10	Human third molars	Dentin	Clearfil Mega Bond Etch & Prime 3.0 Prime&Bond NT	Microtensile
Coli et al 1999[23]	Sweden	EDTA	15	Human third molars	Dentin	All Bond 2	Shear
Correr et al 2004[25]	Brazil	NaOCl	15	Human primary molars	Dentin	Adper Single Bond Clearfil SE Bond Prime&Bond 2.1	Shear
Di Francescantonio et al 2015[26]	Brazil	NaOCl	5	Human third molars	Dentin	One Step Plus Clearfil Photo Bond Clearfil SE Bond	Microtensile
Dikmen et al 2015[28]	Turkey	NaOCl	5	Human third molars	Dentin	Adper Single Bond	Microtensile
Dikmen et al 2018[27]	Turkey	NaOCl CHX EDTA + NaOCl NaOCl + sodium ascobate	5	Human third molars	Dentin	Adper Single Bond Clearfil SE Bond Xeno 3	Microtensile
dos Santos et al 2005[29]	Brazil	NaOCl	15	Bovine incisors	Dentin	Adper Single Bond	Shear
Ekambaram et al 2017[31]	China	NaOCl	10	Human primary molars	Enamel	Adper Single Bond	Microshear
Elkassas et al 2014[32]	Egypt	NaOCl MTAD Tubulicid red CHX	10	Human molars	Dentin	Clearfil S3 Bond Adper Single Bond	Microshear
Ercan et al 2009[33]	Turkey	NaOCl H2O2 CHX	10	Human third molars	Dentin	Clearfil SE Bond Prime&Bond NT	Shear
Erhardt et al 2008[35]	Spain	EDTA CHX	30	Human third molars	Dentin	Adper Scotchbond 1	Microtensile
Erhardt et al 2008[34]	Spain	NaOCl	10	Human third molars	Dentin	Clearfil SE Bond One-Up Bond F Etch & Prime	Shear
Farina et al 2011[36]	Brazil	NaOCl NaOCl + EDTA EDTA CHX CHX + EDTA	40	Human third molars	Dentin	Clearfil SE Bond	Microtensile

Table 1 (cont'd)

Fawzi et al 2010[37]	Egypt	NaOCl NaOCl + EDTA NaOCl + Tubulicid NaOCl + MTAD NaOCl + MTAD not rinsed	10	Human molars	Dentin	Clearfil S3 Bond Adper Single Bond	Microshear
Fawzy et al 2008[38]	Egypt	NaOCl	8	Human third molars	Dentin	Excite AdheSE	Tensile
Gonçalves et al 2009[40]	Brazil	NaOCl	60	Bovine teeth	Dentin	Prime&Bond NT	Microtensile
Gwinnett 1994[41]	USA	NaOCl	10	Human molars	Dentin	All Bond 2 Optibond Dual Cure Scotchbond Multi Purpose	Shear
Gönülol et al 2015[42]	Turkey	NaOCl NaOCl + ascorbato de sódio	15	Human third molars	Dentin	Clearfil SE Bond	Microtensile
Harleen et al 2011[43]	India	NaOCl	20	Human molars	Enamel	Adper Single Bond	Shear
Hasija et al 2017[44]	India	NaOCl	10	Human primary molars	Enamel	Prime&Bond NT	Shear
Hayakawa and Horie 1992[45]	Japan	EDTA Acid citric	6/7/9/10/ 11/12/14	Human incisors	Dentin/ enamel	Clearfil Photobond	Tensile
Ibrahim et al 2010[47]	Egypt	EDTA	10	Human premolars	Enamel	Adper Prompt L-Pop AdheSE Frog	Shear
Inai et al 1998[48]	Japan	NaOCl	6	Human third molars	Dentin	Prime&Bond One Step Scotchbond MP Adper Single Bond	Shear
Kanca and Sandrik 1998[50]	USA	NaOCl	10	Human teeth	Dentin	One Step	Shear
Kim et al 2017[52]	Korea	NaOCl CHX	12	Human molars	Dentin	Scotchbond Universal	Microtensile
Kunawarote et al 2010[54]	Japan	NaOCl	10/11/12	Human molars	Dentin	Clearfil SE Bond	Microtensile
Kunawarote et al 2011[53]	Japan	NaOCl	12	Human molars	Dentin	Clearfil SE Bond	Microtensile
Kusunoki et al 201055	Japan	EDTA	10	Human teeth	Dentin	Clearfil Photobond	Shear
Lai et al 2001[56]	China	NaOCl Sodium Ascorbate	13/14/15/16	Human third molars	Dentin	Adper Single Bond Excite	Microtensile
Machnick et al 2003[59]	USA	NaOCl + EDTA NaOCl + MTAD MTAD	10	Human molars	Dentin/ enamel	Opti Bond Solo Plus	Shear
Martini et al 2017[60]	Brazil	EDTA	5	Bovine Teeth	Dentin	Scotchbond Universal Prime&Bond Elect	Microtensile
Martini et al 2017 A[60]	Brazil	EDTA	10	Human third molars	Enamel	Scotchbond Universal Prime&Bond Elect	Microshear
Mokhtari et al 2017[62]	Iran	CHX NaOCl	10	Human third molars	Dentin	Clearfil SE Bond	Microtensile
Monjarás-Ávila et al 2017[63]	Mexico	NaOCl	20	Human molars	Dentin	Optibond Versa	Microtensile
Montagner et al 2015[65]	Brazil	NaOCl	5	Human third molars	Dentin	G-Bond Clearfil SE Bond Adper Single Bond Adper SE Plus	Push out
Montagner et al 2015 A[64]	Brazil	NaOCl CHX	30	Human molars	Dentin	Adper Single Bond	Microtensile
Muratovska et al 2018[66]	Macedonia	NaOCl	20	Human molars	Dentin	Clearfil SE Protect primer	Microtensile
Nakatani et al 2017[67]	Japan	NaOCl	5	Human third molars	Dentin	Clearfil Bond SE ONE	Microtensile
Nassif and El Korashy 2009[68]	Egypt	NaOCl	6	Human third molars	Dentin	One Coat of Selfpriming	Shear
Osorio et al 2005[69]	Spain	EDTA	20	Human third molars and bovine incisors	Dentin	Adper Scotchbond Clearfil SE Bond	Microtensile
Osorio et al 2010[70]	Spain	NaOCl	30	Human third molars	Dentin	Prompt L-Pop	Microtensile
Phrukkanon et al 2000[71]	Australia	NaOCl	12	Bovine incisors	Dentin	Adper Single Bond One Coat Bond	Tensile
Pimenta et al 2004[72]	Brazil	NaOCl	15	Bovine incisors	Dentin	Adper Single Bond	Shear
Pioch et al 1999[73]	Germany	NaOCl	15	Human molars	Dentin	Gluma CPS Prime&Bond Syntac	Tensile
Prasansuttiporn et al 2012[76]	Japan	NaOCl	14	Human third molars	Dentin	Clearfil Protect Bond Clearfil S3 Bond Bond Force	Microtensile
Prasansuttiporn et al 2011[75]	Japan	NaOCl NaOCl + sodium ascorbate	14	Human third molars	Dentin	Clearfil Protect Bond	Microtensile
Prati et al 1999[77]	Italy	NaOCl	12	Human third molars	Dentin	Optibond FL Prime&Bond Adper Singler Bond Scotchbond MP	Shear

Authors/year	Country*	Endodontic irrigating solution#	Number of samples per group	Origin and type of teeth	Substrate	Adhesive	Bond strength test
Pucci et al 2016[78]	Brazil	NaOCl	24	Human molars	Dentin	Dentastic Uno Prime&Bond NT Adper Single Bond	Shear
Puspitasari et al 2017[79]	Indonesia	CHX	8	Human premolars	Dentin	Clearfil SE Bond Clearfil Tri S Bond	Shear
Reddy et al 2013[80]	India	NaOCl CHX	10	Human posterior teeth	Dentin	Adper SE Plus Adper Easy One	Shear
Saber and El-Askary 2009[81]	Egypt	NaOCl CHX	10	Human molars	Dentin	Clearfil S3 Bond	Shear
Saboia et al 2008[82]	Brazil	NaOCl	10	Human third molars	Dentin	XP Bond	Microtensile
Sacramento et al 2011[83]	Brazil	NaOCl	12	Human primary molars	Dentin	Adper Single Bond Clearfil Protect Bond Adper Prompt L-Pop	Microtensile
Saraceni et al 2013[85]	Brazil	NaOCl	10	Human third molars	Dentin	Adper Single Bond Prime&Bond	Tensile
Sato et al 2005[86]	Japan	NaOCl	15	Bovine incisors	Dentin	Adper Single Bond	Shear
Sauro et al 2009[87]	England	NaOCl EDTA	30	Human third molars	Dentin	Scotchbond 1 Optibond Solo Plus	Microtensile
Say et al 2004[88]	Turkey	EDTA CHX	7	Human third molars	Dentin	One Step Optibond Solo	Shear
Say et al 2004 A[88]	Turkey	EDTA CHX	7	Human third molars	Dentin	One Step Optibond Solo	Tensile
Sebold et al 2017[91]	Brazil	EDTA	8	Human third molars	Dentin	XP Bond	Microtensile
Shafiei et al 2016[92]	Iran	NaOCl EDTA	10	Human third molars	Dentin	Optibond All-in-one	Shear
Sharafeddin et al 2017[93]	Iran	NaOCl	10	Human maxillary premolars	Dentin	Adper Single Bond	Shear
Silva et al 2009[95]	Brazil	NaOCl	12	Human third molars	Dentin	Dentastic Uno Prime&Bond NT Adper Single Bond	Shear
Silva et al 2015[94]	Brazil	CHX	12	Human third molars	Dentin	Adper Single Bond Ambar	Microshear
Singh et al 2015[97]	India	EDTA	10	Human third molars	Dentin	G-Bond Optibond All-in-one	Shear
Siqueira et al 2018[98]	Brazil	NaOCl	53/60/62/53/ 64/65/68/69	Human molars	Dentin	Adper Single Bond 2 Scothbond Universal	Microtensile
Spazzin et al 2009[100]	Brazil	NaOCl	10	Human third molars	Dentin	Prime&Bond 2.1	Microtensile
Taniguchi et al 2009[101]	Japan	NaOCl	12	Human third molars	Dentin	Clearfil Protect Bond Bond Force	Microtensile
Tekçe et al 2016[102]	Turkey	EDTA CHX	5	Human third molars	Dentin	Single Bond Universal All Bond Universal	Microtensile
Toledano et al 2007[106]	Spain	NaOCl	30	Human third molars and bovine incisors	Dentin/ enamel	Futura Bond	Microtensile
Toledano et al 2012[104]	Spain	EDTA	30	Human third molars	Dentin	Adper Single Bond	Microtensile
Toledano et al 2015[103]	Spain	EDTA	4	Human third molars	Dentin	Adper Single Bond Plus	Microtensile
Toledano et al 2017[105]	Spain	EDTA	18	Human third molars	Dentin	Adper Single Bond Plus	Microtensile
Torii et al 2003[107]	Japan	EDTA	10	Bovine incisors	Dentin	Adper Single Bond One-up Bond F Clearfil SE Bond Reactmer Bond	Tensile
Uceda-Gómez et al 2003[108]	Brazil	NaOCl	68	Human third molars	Dentin	One Step	Microtensile
Uno and Finger 1995[109]	Japan	NaOCl	5	Human third molars	Dentin	Gluma 3 Primer Gluma 4 Sealer	Shear
Vongphan et al 2005[110]	Thailand	NaOCl NaOCl + sodium ascorbate	10	Human third molars	Dentin	Adper Single Bond	Microtensile
Wahl et al 2002[111]	USA	NaOCl ethanol	10	Human third molars	Dentin	Adper Single Bond	Shear
Yamazaki et al 2008[112]	USA	NaOCl	20	Bovine incisors	Dentin	Adper Single Bond One Step Plus Scotchbond Multi-Purpose All-Bond 2	Microtensile
Yiu et al 2002[113]	China	NaOCl	56/61/62/ 63/70	Human third molars	Dentin	One Step Gluma Confort Bond	Tensile
Yurdagüven et al 2009[114]	Turkey	NaOCl + EDTA MTAD	34	Human third molars	Dentin	Clearfil SE Bond XP Bond	Microtensile
Zhou et al 2015[115]	China	NaOCl	7	Human third molars	Dentin	Xeno V G-Bond Clearfil S3 Bond	Microtensile

*Country of the first author. # EDTA: ethylene diamine tetra acetic acid; NaOCl: sodium hypochlorite; CHX: chlorhexidine digluconate; Na-EDTA: sodium EDTA; MTAD: mixture of tetracycline isomer, acid and detergent (Biopure, Dentsply Tulsa Dental; Tulsa, OK USA); Tubulicid Red: benzalkonium chloride based (Global Dental Products; Bellmore, NY, USA); H_2O_2: hydrogen peroxide.

other studies evaluated two or more irrigants, each one used either as a single solution or combined in irrigating protocols. Only 5 (5.15%) studies evaluated the effect of endodontic irrigating solutions on bond strength to enamel,[2,31,43,44,47] whereas 86 (88.66%) to dentin,[1, 3,5-10,13,14,16-18,20-23,25-29,32-37,39-42,48,50,52-56,62-73,75-83,85-88,91-95,97,98,100-105,107-115] and 6 (6.18%) to both substrates.[15,19,45,59,60,106] Ten studies used bovine teeth,[5,7,29,40,60,71,72,86,107,112] one used human incisors,[45] 80 studies used human molars or premolars,[1-3,6,8-10,13-23,25-28,32-38,41-43,47,48,52-54,56,59,60,62-68,70,73,75-82,85,87,88,91-95,97,98,100-105,108-115] 2 studies used human teeth without information about tooth type,[50,55] 3 studies used bovine and human teeth[60,69,106] and 4 studies used primary teeth.[25,31,44,83] Regarding sample size, the number ranged from 5 to 70 samples per group.

In total, 62 commercial adhesives were considered, including universal adhesives. Adper Single Bond (3M Oral Care; St Paul, MN, USA) and Clearfil SE Bond (Kuraray Noritake; Tokyo, Japan) were the materials most used in 34 studies,[2,5,8,10,15,17,21,25,27-29,31,32,37,43,48,56,64,65,71,72, 78,83,85,86,93-95,98,104,107,110-112] and 18 studies,[1,2,15,26,27,33,34, 36,42,53,54,62,65,69,79,107,114] respectively. The shear bond strength test was the most commonly employed method for evaluating bond strength (36 studies),[5,6,13,14,18-21,23,25,33,34,41,43,44,47,48,50,55,59,68,72,77-81,86,88,92,93,95,97,109,111] followed by microtensile bond strength testing (44 studies).[7-10,17,22,26-28,35,36,40,42,52-54,56,60,62-64,66,67,69,70,75,76,82,83, 87,91, 98,100-106,108,110,114,115]

Meta-Analyses

The meta-analyses were performed considering the global analysis (regardless of substrate, adhesive or endodontic irrigating solution) and considering one subgroup analysis (excluding data from studies that used chlorhexidine as irrigant), as summarized in Figs 2 and 3, respectively.

No significant difference was found between control and experimental groups ($p = 0.12$) in the overall meta-analysis and in the meta-analysis excluding chlorhexidine ($p = 0.06$), showing no evidence that these solutions could jeopardize the bonding to coronal dental substrates. High heterogeneity was found in the meta-analyses ($I^2 > 80\%$).

Risk of Bias

The majority of the included studies were scored as having a high risk of bias (72.16%) (Table 2). The most frequent items that received "no" in the analysis were: sample size calculation (98.97% of studies); single operator responsible for the application of adhesives (94.84%); and operator blinded to experimental condition during the bond strength test (98.97%). Only one study[64] presented a low risk of bias; it only did not report the sample size calculation.

DISCUSSION

This systematic review and meta-analysis is the first to verify the pooled effect of data from in vitro studies that evaluated the effect of endodontic irrigating solutions on bond strength of adhesives to coronal enamel and dentin. The overall statistical analysis showed that irrigants did not affect the bond strength of adhesives to enamel and dentin. Therefore, the null hypothesis cannot be rejected.

In this review, 16 different irrigating solutions were evaluated, used as a single solution or combined with each other. Sodium hypochlorite was the most frequently used solution in the included studies, probably due to its antibacterial effect and ability to dissolve organic substrates.[53] Considering that sodium hypochlorite is a nonspecific proteolytic agent, this effect on dentin is related to the removal of collagen, which could favor resin infiltration, thus minimizing collagen degradation.[98] On the other hand, a possible negative effect is related to the collagen fibril removal by sodium hypochlorite, which could impair optimal hybrid layer formation.[52] The use of EDTA in endodontics seems to be important for removing the smear layer from the inner walls of the root canal. On dentin, EDTA does not increase the roughness or the diameter of the tubule entrance, with minimal changes in the dentin mineral content.[104] This effect is thus not similar to phosphoric acid-etching.[91]

Moreover, dentin was the substrate considered in the majority of the studies, since bonding to dentin is still more sensitive due to its more heterogeneous composition.[106] Furthermore, in endodontic treatment, dentin is probably the substrate that remains in longer contact with the irrigating solution; hence, the effect of these solutions on dentin should be more intense than on enamel. Only four studies[25,31,44,83] evaluated the effect of irrigating solutions using primary teeth. Because a recent meta-analysis showed lower bond strength in primary than permanent dentin,[101] the current authors suggest conducting studies on the effect of endodontic solutions on bonding to primary dentin.

Meta-analysis was performed considering a subgroup analysis excluding chlorhexidine as an endodontic irrigating solution; in this case, the irrigating solutions also did not affect the bond strength of adhesives to enamel and dentin. This subgroup analysis was performed because the literature reports that chlorhexidine has no effect on the immediate bond strength of adhesives to dentin.[58,84] However, it is valid to consider that chlorhexidine can be used in endodontic protocols not only as a solution but also in gel form, in contrast to the studies that considered its effect as a metalloproteinase inhibitor.[6,20,27,32,35,36,64,80,81,88,94,102]

The shear bond test was the test most often employed in the studies evaluated. One explanation for this is that this test is often used to analyze dental adhesives, and it is also described in ISO guideline WP 11405.[19,49] On the other hand, the use of several bonding tests may be one of the reasons for the high heterogeneity observed in meta-analyses of in vitro studies.

Several commercial adhesives were tested in the studies included in this review. However, there was a predominance

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adebayo et al 2007	28	3.4	19	23.04	6.13	41	1.1%	4.96 [2.54, 7.38]
Adebayo et al 2008	13.6	5.71	158	14.65	6	87	1.1%	-1.05 [-2.59, 0.49]
Alici et al 2018	15.06	6.17	40	12.67	1.82	20	1.1%	2.39 [0.32, 4.46]
Arias et al 2005	15.6	5.07	120	13.58	4.99	60	1.1%	2.02 [0.47, 3.57]
Arslan et al 2011	13.46	1.33	24	14.55	1.67	12	1.1%	-1.09 [-2.17, -0.01]
Augusto et al 2018	27.31	5.62	80	17.14	7.85	120	1.1%	10.17 [8.30, 12.04]
Barbosa et al 2005	52.41	13.12	195	46.46	14.5	193	1.1%	5.95 [3.20, 8.70]
Barutcigil et al 2012	29.09	8.68	80	38.86	9.89	20	0.9%	-9.77 [-14.50, -5.04]
Baseggio et al 2009	40.63	801	120	50.38	3.4	42	0.0%	-9.75 [-153.07, 133.57]
Benderli, Yucel 1999	6.35	1.11	12	9.6	4.04	12	1.1%	-3.25 [-5.62, -0.88]
Blomlöf et al 2001	9.72	4.98	29	7.09	3.26	29	1.1%	2.63 [0.46, 4.80]
Carvalho et al 2017	26.75	6.56	225	26.17	5.16	112	1.1%	0.58 [-0.70, 1.86]
Cecchin et al 2010	15.37	6.44	80	11.89	4.22	40	1.1%	3.48 [1.56, 5.40]
Cecchin et al 2011	4.24	4.98	20	8.41	3.51	10	1.0%	-4.17 [-7.25, -1.09]
Cederlund et al 2001	15.54	3.51	75	5.6	2.1	15	1.1%	9.94 [8.61, 11.27]
Cederlund et al 2002	9.07	3.39	45	10.4	3.4	15	1.1%	-1.33 [-3.32, 0.66]
Cha, Shin 2016	13.4	4.81	60	16.74	5.14	15	1.0%	-3.34 [-6.21, -0.47]
Chauhan et al 2015	15.94	4.7	10	14.24	3.17	10	1.0%	1.70 [-1.81, 5.21]
Chaves et al 2002	30.2	12.14	30	24.1	12.47	30	0.8%	6.10 [-0.13, 12.33]
Coli et al 1999	7.89	4.09	60	9.4	5.28	69	1.1%	-1.51 [-3.13, 0.11]
Correr et al 2004	11.75	2.36	45	13.14	2.68	45	1.1%	-1.39 [-2.43, -0.35]
Di Francescantonio et al 2015	37.32	6.02	30	45.22	7.21	30	1.0%	-7.90 [-11.26, -4.54]
Dikmen et al 2015	23.6	7.55	10	29.48	6.86	5	0.7%	-5.88 [-13.50, 1.74]
Dikmen et al 2018	23.94	8.53	65	32.47	9.85	15	0.9%	-8.53 [-13.93, -3.13]
dos Santos et al 2005	4.8	1.63	30	6.54	1.63	30	1.1%	-1.74 [-2.56, -0.92]
Ekambaram et al 2017	27.21	3.3	10	29.5	5.2	10	1.0%	-2.29 [-6.11, 1.53]
Elkassas et al 2014	12.85	5.77	80	13.79	4.55	20	1.1%	-0.94 [-3.30, 1.42]
Ercan et al 2009	18.91	3.76	80	20.85	3.76	20	1.1%	-1.94 [-3.78, -0.10]
Erhardt et al 2008	27.7	4.44	60	31.9	3.3	30	1.1%	-4.20 [-5.83, -2.57]
Erhardt et al 2008 A	20.37	14.5	40	20.65	10.56	40	0.9%	-0.28 [-5.84, 5.28]
Farina et al 2011	20.66	7.78	200	26.88	3.81	40	1.1%	-6.22 [-7.82, -4.62]
Fawzi et al 2010	17.67	7.12	100	18.1	8.39	20	1.0%	-0.43 [-4.36, 3.50]
Fawzy et al 2008	6.05	2.22	16	4.24	1.32	16	1.1%	1.81 [0.54, 3.08]
Gonçalves et al 2009	50.62	11.87	120	32.43	16.59	120	1.0%	18.19 [14.54, 21.84]
Gwinnett 1994	28.21	5.01	90	28.31	5.77	90	1.1%	-0.10 [-1.68, 1.48]
Gönülol et al 2015	33.62	6.96	60	37.34	8.87	15	0.9%	-3.72 [-8.54, 1.10]
Harleen et al 2011	15.06	6.22	20	13.51	5.72	20	1.0%	1.55 [-2.15, 5.25]
Hasija et al 2017	13.94	4.04	10	12.16	2.4	10	1.0%	1.78 [-1.13, 4.69]
Hayakawa, Horie 1992	5.65	3.21	19	10.32	7.07	19	1.0%	-4.67 [-8.16, -1.18]
Ibrahim et al 2010	7.2	4.54	30	7.77	4.15	30	1.1%	-0.57 [-2.77, 1.63]
Inai et al 1998	15.81	12.39	54	22.79	6.39	30	1.0%	-6.98 [-11.00, -2.96]
Kanka, Sandrik 1998	30.8	4.6	10	33.2	2.5	10	1.0%	-2.40 [-5.64, 0.84]
Kim et al 2017	28.42	5.12	24	33.12	4.05	12	1.0%	-4.70 [-7.77, -1.63]
Kunawarote et al 2010	37.35	7.04	136	41.26	6.32	13	1.0%	-3.91 [-7.54, -0.28]
Kunawarote et al 2011	41.33	5.68	34	41.56	5.39	12	1.0%	-0.23 [-3.83, 3.37]
Kusunoki et al 2010	7.28	1.71	10	3.37	0.65	10	1.1%	3.91 [2.78, 5.04]
Lai et al 2001	44.35	11.55	144	47.4	9.56	30	1.0%	-3.05 [-6.96, 0.86]
Machnick et al 2003	25.85	9.27	60	3.65	3.84	20	1.0%	22.20 [19.31, 25.09]
Martini et al 2017	42.77	6.52	20	30.6	3.04	10	1.0%	12.17 [8.75, 15.59]
Martini et al 2017 A	12.77	3.28	40	12.35	3.36	20	1.1%	0.42 [-1.37, 2.21]
Mokhtari et al 2017	34.32	11.19	40	41.4	13.35	20	0.8%	-7.08 [-13.88, -0.28]
Monjarás-Ávila et al 2017	12.67	10.67	90	15.02	11.43	90	1.0%	-2.35 [-5.58, 0.88]
Montagner et al 2015	10.78	4.5	60	9.55	4.1	60	1.1%	1.23 [-0.31, 2.77]
Montagner et al 2015 A	24.08	10.5	120	20.75	11.34	60	1.0%	3.33 [-0.10, 6.76]
Muratovska et al 2018	56.3	7.9	20	57	16.4	20	0.7%	-0.70 [-8.68, 7.28]
Nakatani et al 2017	35.17	13	15	34.13	10.93	15	0.7%	1.04 [-7.56, 9.64]
Nassif, El-Korashy 2009	31.5	4.76	24	19.5	2.5	6	1.1%	12.00 [9.24, 14.76]
Osorio et al 2005	18.35	9.73	40	25.4	15.47	40	0.9%	-7.05 [-12.71, -1.39]
Osorio et al 2010	17.87	8.97	60	22.03	13.93	60	1.0%	-4.16 [-8.35, 0.03]
Phrukkanon et al 2000	18.23	5.05	72	16.1	4.42	24	1.1%	2.13 [0.01, 4.25]
Pimenta et al. 2004	11.9	4.67	30	16.3	4.28	30	1.1%	-4.40 [-6.67, -2.13]
Pioch et al 1999	3.88	4.03	45	4.84	3.3	45	1.1%	-0.96 [-2.48, 0.56]
Prasansuttiporn et al 2012	34.7	8.11	42	41.33	7.9	42	1.0%	-6.63 [-10.05, -3.21]
Prasansuttiporn et al 2011	44.23	4.88	42	50.5	4.8	14	1.0%	-6.27 [-9.19, -3.35]
Prati et al 1999	12.35	5.96	48	13.5	6.22	48	1.1%	-1.15 [-3.59, 1.29]
Pucci et al 2016	23.72	9.69	144	8.65	8.69	144	1.1%	15.07 [12.94, 17.20]
Puspitasari et al 2017	10.93	1.73	16	10.45	1.41	16	1.1%	0.48 [-0.61, 1.57]
Reddy et al 2013	14.15	1.72	40	17.82	2.53	20	1.1%	-3.67 [-4.90, -2.44]
Saber, El-Askary 2009	18.85	8.35	40	24.63	7.04	30	1.0%	-5.78 [-9.39, -2.17]
Saboia et al 2008	14.5	6.31	20	42.55	1.95	20	1.0%	-28.05 [-30.94, -25.16]
Sacramento et al 2011	22.67	4.62	72	24.5	7.09	72	1.1%	-1.83 [-3.78, 0.12]
Saraceni et al 2013	18.05	6.99	20	20.25	4.89	20	1.0%	-2.20 [-5.94, 1.54]
Sato et al 2005	5.03	3.46	45	18.2	3.2	15	1.1%	-13.17 [-15.08, -11.26]
Sauro et al 2009	49.72	21.72	180	59.2	12.79	60	0.9%	-9.48 [-14.01, -4.95]
Say et al 2004	15.85	3.58	28	16.42	4.95	14	1.0%	-0.57 [-3.48, 2.34]
Say et al 2004 A	12.36	4.02	28	13.34	4.23	14	1.1%	-0.98 [-3.65, 1.69]
Sebold et al 2017	19	10.7	32	35.6	7.44	16	0.9%	-16.60 [-21.80, -11.40]
Shafiei et al 2016	6.73	3.44	20	7.53	2.4	10	1.1%	-0.80 [-2.92, 1.32]
Sharafeddin et al 2017	17.24	2.26	20	19.76	2.53	20	1.1%	-2.52 [-4.01, -1.03]
Silva et al 2009	22.37	11.43	72	11.12	8.05	72	1.0%	11.25 [8.02, 14.48]
Silva et al 2015	12.7	7.54	48	9.48	5.26	48	1.1%	3.22 [0.62, 5.82]
Singh et al 2015	30.23	9.59	40	26.43	7.72	40	1.0%	3.80 [-0.02, 7.62]
Siqueira et al 2018	35.92	7.53	254	34.29	10.82	491	1.1%	1.63 [0.30, 2.96]
Spazzin et al 2009	18.5	7.44	20	11.75	6.74	20	1.0%	6.75 [2.35, 11.15]
Taniguchi et al 2009	37.62	7.91	48	42.45	5.23	24	1.0%	-4.83 [-7.89, -1.77]
Tekçe et al 2016	41.09	6.53	40	37.84	6.61	40	1.0%	3.25 [0.37, 6.13]
Toledano et al 2007	19.15	8.97	60	22	10.28	60	1.0%	-2.85 [-6.30, 0.60]
Toledano et al 2012	36.8	7.9	30	38.4	8.3	30	1.0%	-1.60 [-5.70, 2.50]
Toledano et al 2015	27.8	7.46	8	33.07	6.05	8	0.8%	-5.27 [-11.93, 1.39]
Toledano et al 2017	21.75	2.34	18	23.49	2.99	18	1.1%	-1.74 [-3.49, 0.01]
Torii et al 2003	18.2	5.17	30	19.4	5.1	10	1.0%	-1.20 [-4.86, 2.46]
Uceda-Gómez et al 2003	25.17	9.94	183	29.31	11.26	197	1.1%	-4.14 [-6.27, -2.01]
Uno, Finger 1995	16	3.68	10	12.7	2	5	1.0%	3.30 [0.42, 6.18]
Vongphan et al 2005	27.27	11.5	40	30.1	10.4	10	0.7%	-2.83 [-10.20, 4.54]
Wahl et al 2002	22.35	5.97	20	21.2	4.1	10	1.0%	1.15 [-2.50, 4.80]
Yamazaki et al 2008	32.13	9.77	160	39.94	8.95	160	1.1%	-7.81 [-9.86, -5.76]
Yiu et al 2002	41.99	10.35	251	49.85	7.6	123	1.1%	-7.86 [-9.72, -6.00]
Yurdagüven et al 2009	40.58	17.05	136	49.51	16.23	68	0.9%	-8.93 [-13.74, -4.12]
Zhou et al 2005	23.28	7.12	42	27.33	6.45	42	1.0%	-4.05 [-6.96, -1.14]
Total (95% CI)			**6092**			**4265**	**100.0%**	**-0.87 [-1.97, 0.23]**

Heterogeneity: $Tau^2 = 27.87$; $Chi^2 = 2313.03$, df = 98 ($p < 0.00001$); $I^2 = 96\%$
Test for overall effect: Z = 1.55 ($p = 0.12$)

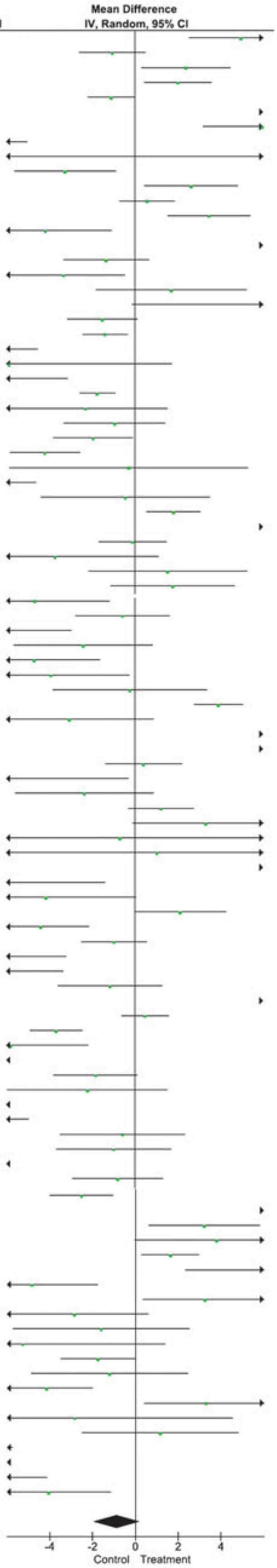

Fig 2 Forest plot for the overall meta-analysis.

Fig 3 Forest plot for the meta-analysis excluding chlorhexidine.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Adebayo et al 2007	28	3.4	19	23.04	6.13	41	1.2%	4.96 [2.54, 7.38]
Adebayo et al 2008	13.6	5.71	158	14.65	6	87	1.2%	-1.05 [-2.59, 0.49]
Alici et al 2018	20.3	4.39	20	12.67	1.82	20	1.2%	7.63 [5.55, 9.71]
Arias et al 2005	15.6	5.07	120	13.58	4.99	60	1.2%	2.02 [0.47, 3.57]
Arslan et al 2011	13.17	1.35	12	14.55	1.67	12	1.2%	-1.38 [-2.59, -0.17]
Augusto et al 2018	27.31	5.62	80	17.14	7.85	120	1.2%	10.17 [8.30, 12.04]
Barbosa et al 2005	52.41	13.12	195	46.46	14.5	193	1.2%	5.95 [3.20, 8.70]
Barutcigil et al 2012	29.09	8.68	80	38.86	9.89	20	1.0%	-9.77 [-14.50, -5.04]
Baseggio et al 2009	40.63	801	120	50.38	3.4	42	0.0%	-9.75 [-153.07, 133.57]
Benderli, Yucel 1999	6.35	1.11	12	9.6	4.04	12	1.2%	-3.25 [-5.62, -0.88]
Blomlöf et al 2001	9.72	4.98	29	7.09	3.26	29	1.2%	2.63 [0.46, 4.80]
Carvalho et al 2017	26.4	6.3	112	26.17	5.16	112	1.2%	0.23 [-1.28, 1.74]
Cecchin et al 2010	15.37	6.44	80	11.89	4.22	40	1.2%	3.48 [1.56, 5.40]
Cecchin et al 2011	4.24	4.98	20	8.41	3.51	10	1.1%	-4.17 [-7.25, -1.09]
Cederlund et al 2001	15.54	3.51	75	5.6	2.1	15	1.2%	9.94 [8.61, 11.27]
Cederlund et al 2002	9.07	3.39	45	10.4	3.4	15	1.2%	-1.33 [-3.32, 0.66]
Cha, Shin 2016	12.2	4.19	30	16.74	5.14	15	1.1%	-4.54 [-7.54, -1.54]
Chauhan et al 2015	15.94	4.7	10	14.24	3.17	10	1.1%	1.70 [-1.81, 5.21]
Chaves et al 2002	30.2	12.14	30	24.1	12.47	30	0.9%	6.10 [-0.13, 12.33]
Coli et al 1999	7.89	4.09	60	9.4	5.28	69	1.2%	-1.51 [-3.13, 0.11]
Correr et al 2004	11.75	2.36	45	13.14	2.68	45	1.2%	-1.39 [-2.43, -0.35]
Di Francescantonio et al 2015	37.32	6.02	30	45.22	7.21	30	1.1%	-7.90 [-11.26, -4.54]
Dikmen et al 2015	23.6	7.55	10	29.48	6.86	5	0.9%	-5.88 [-13.50, 1.74]
Dikmen et al 2018	20.05	6.15	30	32.47	9.85	15	1.0%	-12.42 [-17.87, -6.97]
dos Santos et al 2005	4.8	1.63	30	6.54	1.63	30	1.2%	-1.74 [-2.56, -0.92]
Elkassas et al 2014	12.91	6.76	60	13.79	4.55	20	1.2%	-0.88 [-3.51, 1.75]
Ercan et al 2009	18.01	3.8	40	20.85	3.76	20	1.2%	-2.84 [-4.87, -0.81]
Erhardt et al 2008	28.1	4.2	30	31.9	3.3	30	1.2%	-3.80 [-5.71, -1.89]
Erhardt et al 2008 A	20.37	14.5	40	20.65	10.56	40	1.0%	-0.28 [-5.84, 5.28]
Farina et al 2011	16.95	3.58	120	26.88	3.81	40	1.2%	-9.93 [-11.27, -8.59]
Fawzi et al 2010	17.67	7.12	100	18.1	8.39	20	1.1%	-0.43 [-4.36, 3.50]
Fawzy et al 2008	6.05	2.22	16	4.24	1.32	16	1.2%	1.81 [0.54, 3.08]
Gonçalves et al 2009	50.62	11.87	120	32.43	16.59	120	1.1%	18.19 [14.54, 21.84]
Gwinnett 1994	28.21	5.01	90	28.31	5.77	90	1.2%	-0.10 [-1.68, 1.48]
Gönülol et al 2015	33.62	6.96	60	37.34	8.87	15	1.0%	-3.72 [-8.54, 1.10]
Harleen et al 2011	15.06	6.22	20	13.51	5.72	20	1.1%	1.55 [-2.15, 5.25]
Hayakawa, Horie 1992	5.65	3.21	19	10.32	7.07	19	1.1%	-4.67 [-8.16, -1.18]
Ibrahim et al 2010	7.2	4.54	30	7.77	4.15	30	1.2%	-0.57 [-2.77, 1.63]
Inai et al 1998	15.81	12.39	54	22.79	6.39	30	1.1%	-6.98 [-11.00, -2.96]
Kanka, Sandrik 1998	30.8	4.6	10	33.2	2.5	10	1.1%	-2.40 [-5.64, 0.84]
Kim et al 2017	25.86	4.46	12	33.12	4.05	12	1.1%	-7.26 [-10.67, -3.85]
Kunawarote et al 2010	37.35	7.04	136	41.26	6.32	13	1.1%	-3.91 [-7.54, -0.28]
Kunawarote et al 2011	41.33	5.68	34	41.56	5.39	12	1.1%	-0.23 [-3.83, 3.37]
Kusunoki et al 2010	7.28	1.71	10	3.37	0.65	10	1.2%	3.91 [2.78, 5.04]
Lai et al 2001	44.35	11.55	144	47.4	9.56	30	1.1%	-3.05 [-6.96, 0.86]
Machnick et al 2003	25.85	9.27	60	3.65	3.84	20	1.1%	22.20 [19.31, 25.09]
Mokhtari et al 2017	32.76	11.96	20	41.4	13.35	20	0.8%	-8.64 [-16.50, -0.78]
Monjarás-Ávila et al 2017	12.67	10.67	90	15.02	11.43	90	1.1%	-2.35 [-5.58, 0.88]
Montagner et al 2015	10.78	4.5	60	9.55	4.1	60	1.2%	1.23 [-0.31, 2.77]
Montagner et al 2015 A	25.45	11.05	60	20.75	11.34	60	1.1%	4.70 [0.69, 8.71]
Muratovska et al 2018	56.3	7.9	20	57	16.4	20	0.8%	-0.70 [-8.68, 7.28]
Nassif, El-Korashy 2009	31.5	4.76	24	19.5	2.5	6	1.2%	12.00 [9.24, 14.76]
Osorio et al 2005	18.35	9.73	40	25.4	15.47	40	1.0%	-7.05 [-12.71, -1.39]
Osorio et al 2010	17.87	8.97	60	22.03	13.93	60	1.1%	-4.16 [-8.35, 0.03]
Phrukkanon et al 2000	18.23	5.05	72	16.1	4.42	24	1.2%	2.13 [0.01, 4.25]
Pimenta et al. 2004	11.9	4.67	30	16.3	4.28	30	1.2%	-4.40 [-6.67, -2.13]
Pioch et al 1999	3.88	4.03	45	4.84	3.3	45	1.2%	-0.96 [-2.48, 0.56]
Prasansuttiporn et al 2012	34.7	8.11	42	41.33	7.9	42	1.1%	-6.63 [-10.05, -3.21]
Prasansuttiporn et al 2011	44.23	4.88	42	50.5	4.8	14	1.1%	-6.27 [-9.19, -3.35]
Prati et al 1999	12.35	5.96	48	13.5	6.22	48	1.2%	-1.15 [-3.59, 1.29]
Pucci et al 2016	23.72	9.69	144	8.65	8.69	144	1.2%	15.07 [12.94, 17.20]
Reddy et al 2013	13.65	1.64	20	17.82	2.53	20	1.2%	-4.17 [-5.49, -2.85]
Saber, El-Askary 2009	12.92	2.21	20	24.63	7.04	30	1.2%	-11.71 [-14.41, -9.01]
Saboia et al 2008	14.5	6.31	20	42.55	1.95	20	1.1%	-28.05 [-30.94, -25.16]
Sacramento et al 2011	22.67	4.62	72	24.5	7.09	72	1.2%	-1.83 [-3.78, 0.12]
Saraceni et al 2013	18.05	6.99	20	20.25	4.89	20	1.1%	-2.20 [-5.94, 1.54]
Sato et al 2005	5.03	3.46	45	18.2	3.2	15	1.2%	-13.17 [-15.08, -11.26]
Sauro et al 2009	49.72	21.72	180	59.2	12.79	60	1.1%	-9.48 [-14.01, -4.95]
Say et al 2004	16.28	3.22	14	16.42	4.95	14	1.1%	-0.14 [-3.23, 2.95]
Say et al 2004 A	12.21	3.5	14	13.34	4.23	14	1.1%	-1.13 [-4.01, 1.75]
Sebold et al 2017	19	10.7	32	35.6	7.44	16	1.0%	-16.60 [-21.80, -11.40]
Shafiei et al 2016	6.73	3.44	20	7.53	2.4	10	1.2%	-0.80 [-2.92, 1.32]
Silva et al 2009	22.37	11.43	72	11.12	8.05	72	1.1%	11.25 [8.02, 14.48]
Singh et al 2015	30.23	9.59	40	26.43	7.72	40	1.1%	3.80 [-0.02, 7.62]
Siqueira et al 2018	35.92	7.53	254	34.29	10.82	491	1.2%	1.63 [0.30, 2.96]
Spazzin et al 2009	18.5	7.44	20	11.75	6.74	20	1.1%	6.75 [2.35, 11.15]
Taniguchi et al 2009	37.62	7.91	48	42.45	5.23	24	1.1%	-4.83 [-7.89, -1.77]
Tekçe et al 2016	43	5.54	20	37.84	6.61	40	1.1%	5.16 [1.98, 8.34]
Toledano et al 2007	19.15	8.97	60	22	10.28	60	1.1%	-2.85 [-6.30, 0.60]
Toledano et al 2012	36.8	7.9	30	38.4	8.3	30	1.1%	-1.60 [-5.70, 2.50]
Toledano et al 2015	27.8	7.46	8	33.07	6.05	8	0.9%	-5.27 [-11.93, 1.39]
Torii et al 2003	18.2	5.17	30	19.4	5.1	10	1.1%	-1.20 [-4.86, 2.46]
Uceda-Gómez et al 2003	25.17	9.94	183	29.31	11.26	197	1.2%	-4.14 [-6.27, -2.01]
Uno, Finger 1995	16	3.68	10	12.7	2	5	1.1%	3.30 [0.42, 6.18]
Vongphan et al 2005	27.27	11.5	40	30.1	10.4	10	0.9%	-2.83 [-10.20, 4.54]
Wahl et al 2002	22.35	5.97	20	21.2	4.1	10	1.1%	1.15 [-2.50, 4.80]
Yamazaki et al 2008	32.13	9.77	160	39.94	8.95	160	1.2%	-7.81 [-9.86, -5.76]
Yiu et al 2002	41.99	10.35	251	49.85	7.6	123	1.2%	-7.86 [-9.72, -6.00]
Yurdagüven et al 2009	40.58	17.05	136	49.51	16.23	68	1.0%	-8.93 [-13.74, -4.12]
Zhou et al 2005	23.28	7.12	42	27.33	6.45	42	1.1%	-4.05 [-6.96, -1.14]
Total (95% CI)			**5335**			**4098**	**100.0%**	**-1.24 [-2.53, 0.05]**

Heterogeneity: $Tau^2 = 35.39$; $Chi^2 = 2514.60$, df = 89 ($p < 0.00001$); $I^2 = 96\%$

Test for overall effect: Z = 1.89 ($p = 0.06$)

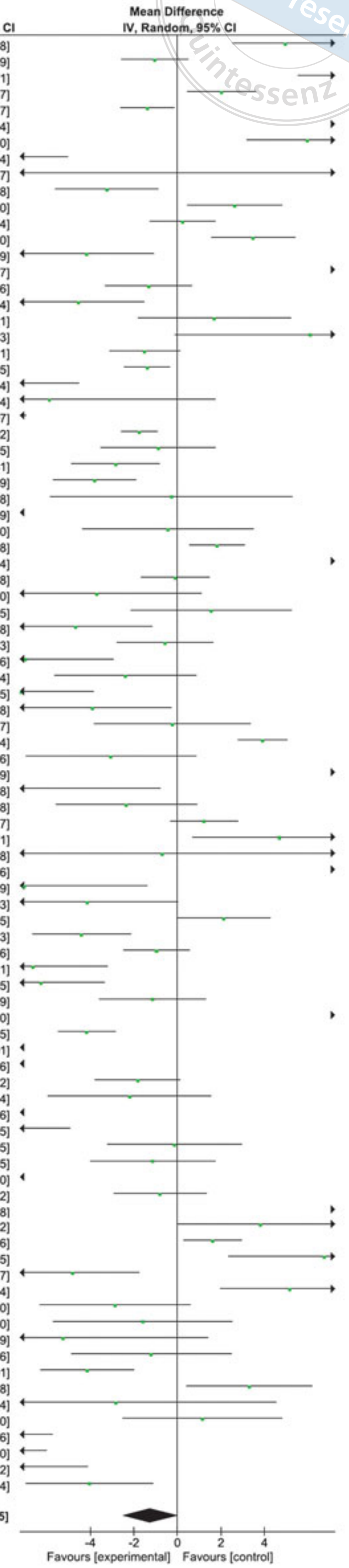

Table 2 Risk bias of the studies (see also Materials and Methods)

Study	Randomization	Sample size calculation	Specimen with similar cross section	Failure mode evaluation	Manufacturer's instructions	Single operator	Operator blinded	Risk of bias
Adebayo et al 2007[2]	N	N	Y	Y	Y	N	N	high
Adebayo et al 2008[1]	Y	N	Y	Y	Y	N	N	medium
Alici et al 2018[3]	Y	N	Y	N	Y	N	N	high
Arias et al 2005[5]	Y	N	Y	N	N	N	N	high
Arslan et al 2011[6]	Y	N	Y	N	Y	N	N	high
Augusto et al 2018[7]	Y	Y	Y	Y	Y	N	N	medium
Barbosa et al 2005[8]	Y	N	Y	N	N	N	N	high
Barutcigil et al 2012[9]	N	N	Y	Y	Y	N	N	high
Baseggio et al 2009[10]	Y	N	Y	N	N	N	N	high
Benderli and Yucel 1999[13]	N	N	Y	N	N	N	N	high
Blomlöf et al 2001[14]	Y	N	Y	N	Y	N	N	high
Carvalho et al 2017[15]	Y	N	Y	Y	Y	Y	N	medium
Cecchin et al 2010[16]	Y	N	Y	N	Y	N	N	high
Cecchin et al 2011[17]	Y	N	Y	N	Y	N	N	high
Cederlund et al 2001[19]	Y	N	Y	N	Y	N	N	high
Cederlund et al 2002[18]	Y	N	Y	N	Y	N	N	high
Cha, Shin 2016[20]	Y	N	Y	N	Y	N	N	high
Chauhan et al 2015[21]	N	N	Y	N	Y	N	N	high
Chaves et al 2002[22]	Y	N	Y	N	Y	N	N	high
Coli et al 1999[23]	Y	N	Y	Y	Y	N	N	medium
Correr et al 2004[25]	Y	N	Y	Y	Y	N	N	medium
Di Francescantonio et al 2015[26]	N	N	Y	N	Y	N	N	high
Dikmen et al 2015[28]	N	N	Y	Y	Y	N	N	high
Dikmen et al 2018[27]	Y	N	Y	Y	Y	N	N	medium
dos Santos et al 2005[29]	Y	N	Y	Y	N	N	N	high
Ekambaram et al 2017[31]	Y	N	Y	Y	Y	N	N	medium
Elkassas et al 2014[32]	Y	N	Y	Y	Y	N	N	medium
Ercan et al 2009[33]	Y	N	Y	Y	N	N	N	high
Erhardt et al 2008[35]	N	N	Y	Y	Y	N	N	high
Erhardt et al 2008 A[34]	N	N	Y	Y	Y	N	N	high
Farina et al 2011[36]	Y	N	Y	Y	Y	N	N	medium
Fawzi et al 2010[37]	Y	N	Y	N	Y	N	N	high
Fawzy et al 2008[38]	N	N	Y	N	Y	N	N	high
Gonçalves et al 2009[40]	Y	N	Y	Y	Y	N	N	medium
Gwinnett 1994[41]	N	N	Y	N	Y	N	N	high
Gönülol et al 2015[42]	Y	N	Y	Y	Y	N	N	medium
Harleen et al 2011[43]	Y	N	Y	N	Y	N	N	high
Hasija et al 2017[44]	N	N	Y	N	N	N	N	high
Hayakawa and Horie 1992[45]	N	N	Y	N	N	N	N	high
Ibrahim et al 2010[47]	N	N	Y	Y	Y	N	N	high
Inai et al 1998[48]	N	N	Y	N	Y	N	N	high
Kanca and Sandrik 1998[50]	Y	N	Y	N	N	N	N	high
Kim et al 2017[52]	Y	N	Y	N	Y	N	N	high
Kunawarote et al 2010[54]	Y	N	Y	Y	Y	N	N	high
Kunawarote et al 2011[53]	Y	N	Y	Y	Y	N	N	medium
Kusunoki et al 2010[55]	N	N	Y	Y	N	N	N	high
Lai et al 2001[56]	N	N	Y	Y	N	N	N	high
Machnick et al 2003[59]	Y	N	Y	Y	Y	N	N	high
Martini et al 2017[60]	Y	N	Y	Y	Y	Y	N	medium
Martini et al 2017 A[60]	Y	N	Y	Y	Y	Y	N	medium
Mokhtari et al 2017[62]	Y	N	Y	Y	N	N	N	high
Monjarás-Ávila et al 2017[63]	Y	N	Y	Y	Y	N	N	medium
Montagner et al 2015[65]	Y	N	Y	Y	Y	Y	N	medium
Montagner et al 2015 A[64]	Y	N	Y	Y	Y	Y	Y	low
Muratovska et al 2018[66]	Y	N	Y	Y	Y	N	N	medium
Nakatani et al 2017[67]	Y	N	Y	Y	Y	N	N	medium
Nassif, El-Korashy 2009[68]	Y	N	Y	N	Y	N	N	high
Osorio et al 2005[69]	N	N	Y	Y	Y	N	N	high
Osorio et al 2010[70]	N	N	Y	Y	N	N	N	high
Phrukkanon et al 2000[71]	N	N	Y	Y	Y	N	N	high
Pimenta et al 2004[72]	Y	N	Y	Y	Y	N	N	medium
Pioch et al 1999[73]	N	N	Y	N	Y	N	N	high
Prasansuttiporn et al 2012[76]	N	N	Y	Y	Y	N	N	high
Prasansuttiporn et al 2011[75]	N	N	Y	Y	Y	N	N	high
Prati et al 1999[77]	N	N	Y	Y	N	N	N	high
Pucci et al 2016[78]	N	N	Y	Y	Y	N	N	high
Puspitasari et al 2017[79]	N	N	Y	N	Y	N	N	high

Table 2 (cont'd)

Reddy et al 2013[80]	Y	N	Y	Y	N	N	N	high
Saber and El-Askary 2009[81]	N	N	Y	N	Y	N	N	high
Saboia et al 2008[82]	Y	N	Y	Y	Y	N	N	medium
Sacramento et al 2011[83]	Y	N	Y	Y	Y	N	N	medium
Saraceni et al 2013[85]	N	N	Y	Y	Y	N	N	high
Sato et al 2005[86]	N	N	Y	Y	Y	N	N	high
Sauro et al 2009[87]	N	N	Y	Y	N	N	N	high
Say et al 2004[88]	Y	N	Y	Y	N	N	N	high
Say et al 2004 A[88]	Y	N	Y	Y	N	N	N	high
Sebold et al 2017[91]	Y	N	Y	Y	Y	N	N	medium
Shafiei et al 2016[92]	Y	N	Y	Y	Y	N	N	medium
Sharafeddin et al 2017[93]	Y	N	Y	N	Y	N	N	high
Silva et al 2009[95]	N	N	Y	Y	Y	N	N	high
Silva et al 2015[94]	Y	N	Y	Y	Y	N	N	medium
Singh et al 2015[97]	Y	N	Y	Y	N	N	N	high
Siqueira et al 2018[98]	Y	N	Y	Y	Y	N	N	medium
Spazzin et al 2009[100]	Y	N	Y	Y	Y	N	N	medium
Taniguchi et al 2009[101]	N	N	Y	Y	Y	N	N	high
Tekçe et al 2016[102]	N	N	Y	Y	Y	N	N	high
Toledano et al 2007[106]	N	N	Y	Y	N	N	N	high
Toledano et al 2012[104]	Y	N	Y	Y	N	N	N	high
Toledano et al 2015[103]	N	N	Y	Y	Y	N	N	high
Toledano et al 2017[105]	N	N	Y	Y	Y	N	N	high
Torii et al 2003[107]	N	N	Y	Y	Y	N	N	high
Uceda-Gómez et al 2003[108]	N	N	Y	Y	N	N	N	high
Uno, Finger 1995[109]	N	N	Y	Y	N	N	N	high
Vongphan et al 2005[110]	N	N	Y	Y	Y	N	N	high
Wahl et al 2002[111]	N	N	Y	Y	Y	N	N	high
Yamazaki et al 2008[112]	Y	N	Y	Y	Y	N	N	medium
Yiu et al 2002[113]	N	N	Y	Y	N	N	N	high
Yurdagüven et al 2009[114]	N	N	Y	Y	N	N	N	high
Zhou et al 2015[115]	Y	N	Y	Y	Y	N	N	medium

If the authors reported the parameter, the paper had a Y (yes) on that specific parameter; if it was not possible to find the information, the paper received an N (no).

of a particular two-step etch-and-rinse adhesive (Adper Single Bond, 3M Oral Care) and a two-step self-etch adhesive (Clearfil SE Bond, Kuraray Noritake). This should be taken into account in the extrapolation of the results.

High heterogeneity was found in all statistical analyses carried out. Considering the methodological variability among studies, heterogeneity is unavoidable. Except one paper,[64] all included studies had a medium or high risk of bias. This finding is common in systematic reviews of laboratory studies.[24,57,99] Lack of information about sample size calculation, number of operators performing adhesive procedures, and operator blinding to the test machine are the main reasons for this, and should be carefully considered in future in vitro studies.

A possible limitation of this study is that it only focused on PubMed/MEDLINE, Scopus and Web of Science databases. EMBASE and gray literature can result in a wider search, but it also results in higher number of false positives (unnecessarily identified studies)[46] and incomplete data, respectively. Furthermore, gray literature seems to have an unclear impact on meta-analysis results in medical research.[89] Moreover, most of bond strength data included in the meta-analyses were from short-term evaluations (immediate). Therefore, further studies evaluating the effect of endodontic irrigating solutions on long-term bond strength of adhesives to dental substrates are required. Although this meta-analysis was conducted based on in vitro studies because of the considered outcome, the parameters taken into account in this study may affect clinical practice, mitigating concern about the effect of endodontic irrigating solutions on bonding to dental substrates.

CONCLUSION

Despite the high heterogeneity found, in vitro literature indicates that the use of endodontic irrigating solutions does not negatively influence bond strength of adhesives to coronal enamel and dentin.

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Clinical relevance: The success of endodontic treatment depends on appropriate apical sealing provided by the root canal filling as well as the marginal seal of the coronal restoration. Irrigants used in endodontic treatment have no influence on the bond strength of adhesives used in coronal dental substrates.