Influence of the Use of Irrigation Solution Inhibitors in Improving Dentine Adhesion: A Systematic Review and Meta-Analysis

Keywords

Sodium Thiosulfate
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ABSTRACT

Introduction: This systematic review examined the effect of neutralizing agents on bond strength after irrigation with sodium hypochlorite and their existing protocols in literature. Methods: This present study adhered to the PRISMA guidelines and was registered at PROSPERO. Five electronic databases were searched (sept-2020/jan-2021) in English, Spanish, and Portuguese, without any restrictions on publication date. Cases reports, editorials and literature reviews were not included. The risk of bias was assessed using the Cochrane Collaboration tool. From the initial 7,147 studies, 2,745 were removed as duplicates and 4,382 were excluded after a title/abstract screen. Results: Seventeen in vitro studies were included. The results showed that the higher the concentration of sodium hypochlorite, the lower the bond strength at dentine/restoration interface (p<0.01). Among the studies, sodium ascorbate was the most widely used neutralizer and showed the most significant results in increasing bond strength (p<0.01). The bond strength values were found to increase with longer application time of the neutralizing substances (p<0.01). Conclusions: The use of sodium ascorbate as a neutralizing agent can reverse the negative effects of the sodium hypochlorite and improve the bond strength between dentine and resin cement, however, it isn't possible to determine the best protocol for use.

INTRODUCTION

Cleaning and modeling root canals is made difficult due to the complex system of root canals, maintaining places with a large bacterial quantity without the touch of mechanized or manual instrumentation. Therefore, the use of irrigation solutions with antibacterial capacity is necessary. Sodium hypochlorite is the most used irrigating agent during the treatment of root canals due to its action on the decomposition of organic matter, which is not seen in other agents such as chlorhexidine.[1] However, the irrigating agents used during endodontic treatment have adverse effects on the resin-dentine bond strength which have been previously investigated and confirmed.[2–6] One reason is that the remnants and by-products of NaOCl oxidation, for example, exhibit a negative effect on the polymerization of dental adhesive systems.[4–6] The removal of organic matter by sodium hypochlorite, in which there is a break in the connection between collagen fibrils, prevents the formation of a consistent hybrid layer.[7] On the other hand, the bond strength compromised by the dentine treated with NaOCl could be restored by applying an antioxidant solution before the adhesive procedure, resulting in neutralization and reversion of the oxidizing effect of the treatment carried out with NaOCl on the dentine surface.[6,8–10]

Sodium ascorbate is used as a neutralizing agent in the sodium hypochlorite solution, but it has low stability,[8,9] which favored the search for other solutions, such as sodium thiosulfate, a neutralizer and antioxidant which can be applied after the use of sodium hypochlorite and which has been shown to overcome the limitations of sodium ascorbate.[11] Studies show that the use of sodium ascorbate provides at least 50% resistance to the original bond to resin-based cements.[12,13] The authors explain this fact due to the reducing action of sodium ascorbate on root dentine.[4] Sodium thiosulfate is a powerful antioxidant in the neutralization of oxidizing agents by means of a redox reaction on the surface treated with sodium hypochlorite, improving the polymerization of the resin on the dentine surface, in turn being able to generate a stable product neutralizing unpaired electron.[13] However, the concentration and application time of sodium thiosulfate varies among studies, which can compromise the reestablishment of adhesion between dentine and resin.[11,14,15]

Added to this, endodontically treated teeth often require intra-radicular reinforcement such as a glass fiber post. This has been recommended because it presents similar corrosion resistance and elasticity modulus to that of dentine, decreasing the fracture rates of the dental remnant.[16] In addition, the similar elasticity module gives the post a better distribution of occlusal forces, which leads us to observe that the highest failure rate in fiberglass posts is in the adhesion between post and cement or between cement and dentine.[17] Therefore, the use of an irrigating solution which impairs the resin adhesion tends to impair the adhesion of the fiber post, and so it is interesting to use a neutralizing solution between these two steps.

The purpose of this systematic review was to determine the effectiveness of using neutralizing agents in overcoming the reduction in adhesion between dentine and resin materials caused by sodium hypochlorite during root canal preparation in endodontic treatment, and to identify the best clinical protocol for cleaning dentine surfaces before cementing posts. The review took into consideration factors such as type of specimen, neutralizer concentration and duration of action, type of test, and concentration of irrigating sodium hypochlorite. The hypothesis was that using neutralizing agents would result in a significant improvement in bond strength.

METHOD

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines[18] and registered at the International Prospective Register of Systematic Reviews - University of York (PROSPERO) ID: CRD42020204136.

REVIEW QUESTION

The focused question was: Do inhibitors for sodium hypochlorite irrigation solution improve the dentine adhesion?

The search strategy was based on the PICO framework (P=population/patient/problem; I=intervention; C=comparison; O=outcome), in which "P" corresponded to dentine; "I" was about the sodium hypochlorite, neutralizing agents and resin cemented; and "O" to adhesive strength.

SEARCH STRATEGY

A search based on the question in this review was conducted to identify potential studies that would substantiate and answer the proposed question. The review was performed from September 2020 to January 2021 (with respect to the monthly alerts received with the update of new published articles), and the search was carried out in the PubMed/MEDLINE, The Cochrane Library, Web of Science, Scopus, LILACS, and the Opengrey databases, covering English, Spanish and Portuguese, without any restrictions on publication date. Cases reports, editorials and literature reviews were not included. The search used the Medical Subject Headings (MeSH) terms with several combinations, and the search strategy was adapted according to the specifications of each database. The search strategy is shown in Table 1. The condition addressed by the search was focused on root canals, restorations, and adhesion between dentine and cement, according to the following inclusion and exclusion criteria:

- Inclusion: Bonding of resin cement to dentine after using sodium hypochlorite irrigation.
- Exclusion: Cleaning with other solutions. Enamel bonding. Endodontic cement.

STUDY SELECTION

The articles were extract from databases and imported into EndNote X7 reference management software (Clarivate Analytics, Philadelphia, PA). Duplicates were identified and removed. All articles were obtained in full version and analyzed by 3 independent reviewers (PFZ, GLCL MGB), based on the pre-established criteria for this review (following the PICO question). Discussions were held in case of disagreement between the reviewers to establish an inclusion or exclusion agreement for the study in question.

QUALITY ASSESSMENT OF RISK OF BIAS

The risk of bias of the included studies was assessed by 3 independent reviewers (PFZ, GLCL MGB), using the Cochrane collaboration tool adapted for systematic reviews of *in vitro* studies. The assessment was analyzed according to the following items: sample calculation; specimen randomization; the number (n) of specimens is clear; solutions concentration standardized (%); neutralizing freshly prepared; time

Table 1. The search strategy according to each database.

Database	Search Strategy
Pubmed (September 2020 2272 - articles)	(((Permanent Dental Restoration[MeSH Terms]) OR (Dentin[MeSH Terms])) OR (Dentine[Title/Abstract])) OR (Dentin[Title/Abstract]) AND ((((((((((((((“Sodium Hypochlorite”[MeSH Terms]) OR (“Sodium Hypochlorite”[Title/Abstract])) OR (Clorox[Title/Abstract])) OR (Hypochlorite[Title/Abstract])) OR (Chlorhexidine[MeSH Terms])) OR (Chlorhexidine Acetate[Title/Abstract])) OR (Chlorhexidine digluconate[Title/Abstract])) OR (Chlorhexidine gluconate[Title/Abstract])) OR (Endodontics[MeSH Terms])) OR (Ascorbate Peroxidases[MeSH Terms])) OR (Ascorbate Peroxidase[Title/Abstract])) OR (Sodium Ascorbate[Title/Abstract])) OR (Lecithins[MeSH Terms])) OR (Tween 80[Title/Abstract])) OR (Thiosulfates[MeSH Terms])) OR (Sodium Thiosulfate[Title/Abstract]) AND (((((((((((((Dental Restoration Failure[MeSH Terms]) OR (Resins, Synthetic[MeSH Terms])) OR (Adhesive Restoration[Title/Abstract])) OR (Resin Restoration[Title/Abstract])) OR (Resin Cements[MeSH Terms])) OR (Resin Cement[Title/Abstract])) OR (Resin sealer[Title/Abstract])) OR (Resin based sealer[Title/Abstract])) OR (Dental cement[MeSH Terms])) OR (Luting Agent[Title/Abstract])) OR (Adhesive[Title/Abstract])) OR (Adhesion[Title/Abstract])) OR (Adhesiveness[Title/Abstract])) OR (Dentin-bonding agents[MeSH Terms])) OR (Bonding[Title/Abstract])
Scopus (Filter. Dentistry; September 2020 2747 - articles)	TITLE-ABS-KEY (“Permanent Dental Restoration” OR dentin OR dentine) AND TITLE-ABS-KEY (“Sodium Hypochlorite” OR clorox OR hypochlorite OR chlorhexidine OR “Chlorhexidine Acetate” OR “Chlorhexidine digluconate” OR “Chlorhexidine gluconate” OR endodontics OR “Ascorbate Peroxidases” OR “Ascorbate Peroxidase” OR “Sodium Ascorbate” OR lecithins OR “Tween 80” OR thiosulfates OR “Sodium Thiosulfate”) AND TITLE-ABS-KEY (“Dental Restoration Failure” OR “Synthetic Resins “ OR “Adhesive Restoration” OR “Resin Restoration” OR “Resin Cements” OR “Resin Cement” OR “Resin sealer” OR “Resin based sealer” OR “Dental cement” OR “Luting Agent” OR adhesive OR adhesion OR adhesiveness OR “Dentin-bonding agents” OR bonding)
Web of Science (September 2020 1750 - articles)	TS=(“Permanent Dental Restoration” OR dentin OR dentine) AND TS=(“Sodium Hypochlorite” OR clorox OR hypochlorite OR chlorhexidine OR “Chlorhexidine Acetate” OR “Chlorhexidine digluconate” OR “Chlorhexidine gluconate” OR endodontics OR “Ascorbate Peroxidases” OR “Ascorbate Peroxidase” OR “Sodium Ascorbate” OR lecithins OR “Tween 80” OR thiosulfates OR “Sodium Thiosulfate”) AND TS=(“Dental Restoration Failure” OR “Synthetic Resins “ OR “Adhesive Restoration” OR “Resin Restoration” OR “Resin Cements” OR “Resin Cement” OR “Resin sealer” OR “Resin based sealer” OR “Dental cement” OR “Luting Agent” OR adhesive OR adhesion OR adhesiveness OR “Dentin-bonding agents” OR bonding)
Cochrane Library (September 2020 378 - articles)	#1 MeSH descriptor: [Dental Restoration, Permanent] explode all trees #2 MeSH descriptor: [Dentin] explode all trees #3 (Dentine OR Dentin):ti,ab,kw #4 #2 OR #3 #5 #1 OR #4 #6 MeSH descriptor: [Sodium Hypochlorite] explode all trees #7 (“Sodium Hypochlorite” OR Clorox OR Hypochlorite):ti,ab,kw #8 #6 OR #7 #9 MeSH descriptor: [Chlorhexidine] explode all trees #10 (“Chlorhexidine Acetate” OR “Chlorhexidine digluconate” OR “Chlorhexidine gluconate”):ti,ab,kw #11 #9 OR #10 #12 MeSH descriptor: [Endodontics] explode all trees #13 MeSH descriptor: [Ascorbate Peroxidases] explode all trees #14 (“Ascorbate Peroxidase” OR “Sodium Ascorbate”):ti,ab,kw #15 #13 OR #14 #16 MeSH descriptor: [Lecithins] explode all trees #17 (Tween 80):ti,ab,kw #18 #16 OR #17 #19 MeSH descriptor: [Thiosulfates] explode all trees #20 (“Sodium Thiosulfate”):ti,ab,kw #21 #19 OR #20 #22 #8 OR #11 OR #12 OR #15 OR #18 #21 #23 MeSH descriptor: [Dental Restoration Failure] explode all trees #24 MeSH descriptor: [Resins, Synthetic] explode all trees #25 (“Adhesive Restoration” OR “Resin Restoration”):ti,ab,kw #26 #24 OR #25 #27 MeSH descriptor: [Resin Cements] explode all trees #28 (“Resin Cement” OR “Resin sealer” OR “Resin based sealer”):ti,ab,kw #29 #27 OR #28 #30 MeSH descriptor: [Dental Cements] explode all trees #31 (“Luting Agent” OR “Adhesive” OR “Adhesion” OR “Adhesiveness”):ti,ab,kw #32 #30 OR #31 #33 MeSH descriptor: [Dentin-Bonding Agents] explode all trees #34 (Bonding):ti,ab,kw #35 #33 OR #34 #36 #23 OR #26 OR #29 OR #32 OR #35 #37 #5 AND #22 AND #36
Lilacs (September 2020 0 article)	(MH: “permanent dental restoration” OR “restauración dental permanente” OR “restauração dentária permanente” OR MH: dentin OR dentina OR dentine OR dentin) AND (MH: “sodium hypochlorite” OR “hipoclorito de sodio” OR “hipoclorito de sódio” OR “sodium hypochlorite” OR clorox OR hypochlorite OR hipoclorito OR MH: chlorhexidine OR clorhexidina OR clorexidina OR “chlorhexidine acetate” OR “acetato de clorhexidina” OR “acetato de clorexidina” OR “chlorhexidine digluconate” OR “digluconato de clorhexidina” OR “digluconato de clorexidina” OR “chlorhexidine gluconate” OR “gluconato de clorhexidina” OR “gluconate de clorexidina” OR MH: endodontics OR endodoncia OR endodontia OR MH: “ascorbate peroxidases” OR “ascorbato peroxidasas” OR “ascorbato peroxidases” OR “ascorbate peroxidase” OR “ascorbato peroxidasa” OR “ascorbato peroxidase” OR “sodium ascorbate” OR “ascorbato de sodio” OR “ascorbato de sódio” OR MH: lecithins OR lecitinas OR tween 80 OR MH: thiosulfates OR tiosulfatos OR tiossulfatos OR “sodium thiosulfate” OR “tiosulfato de sodio” OR “tiossulfato de sódio”) AND (MH: “dental restoration failure” OR “fracaso de la restauración dental” OR “falha de restauração dentária” OR MH: “resins, synthetic” OR “resinas sintéticas” OR “adhesive restoration” OR “restauración adhesiva” OR “restauração adesiva” OR “resin restoration” OR “restauración de resina” OR “restauração de resina” OR MH: “resin cements” OR “cementos de resina” OR “cimentos de resina” OR “resin cement” OR “cemento de resina” OR “cemento de resina” OR “resin sealer” OR “sellador de resina” OR “selador de resina” OR “resin based sealer” OR “sellador a base de resina” OR “selante à base de resina” OR MH: “dental cements” OR “cementos dentales” OR “cimentos dentários” OR “luting agent” OR “agente de retención” OR “agente cimentante” OR adhesive OR adhesivo OR adesivo OR adhesion OR adhesión OR adesão OR adhesiveness OR viscosidad OR adesividade OR MH: “dentin-bonding agents” OR “recubrimientos dentinarios” OR “adesivos dentinários” OR bonding OR vinculación OR ligação)
Opengrey (September 2020 0 article)	

used; blind analysis, parameters for the mechanical teste. The studies were classified into three levels: high risk (1-3 items included), middle risk (4-5 items included), and low risk (6-8 items included).

HETEROGENEITY AND SUBGROUP ANALYSIS

The variability in results across studies was assessed by using the I^2 statistic and the p-value (> 0.10) for the χ^2 test of heterogeneity. We performed subgroup analyses for the *in vitro* studies, stratifying by use and non-use of neutralizer, type of neutralizer, application time, concentration of sodium hypochlorite, type of bond strength tests, type of specimen and type of resin cemented.

STATISTICAL ANALYSIS

The data were presented as relative risk (RR) for the success rates in clinical studies, and as standardized mean differences (SMD) for bond strength considering the *in vitro* studies. Data entry was adjusted in relation to the population size for studies presenting more than two branches and repeated comparisons to the control group. The RR and SMD were calculated with 95% confidence interval (CI). A random-effects model with the significance of 5% was performed using a comprehensive meta-analysis software program (RStudio Software 1.1.463, Boston, USA).

RESULTS

DATA EXTRACTION AND PRESENTATION

The search using the keywords and the MeSH terms carried out in the databases found 7,147 publications, and 4,436 studies remained after removing the duplicates. In turn, 20 articles were read in full, 3 of which were excluded. The study by Erhardt *et al.* (2011) was excluded because the irrigant application order was after the use of the neutralizer (in an inverse order to the one proposed in this review), and it did not contain compatible data for statistical analysis. The articles by Shrestha *et al.* (2013) and Nassar *et al.* (2011) were also excluded, as they assessed the adhesion of endodontic cement, which did not meet the inclusion criteria of this study. Finally, 17 studies ([4,6,8–12,19–27]) were used in this systematic review after applying the inclusion criteria *(Table 2)*. The flowchart for this systematic review is shown in Figure 1.

QUALITY ASSESSMENT OF RISK OF BIAS

A high level of bias was evident in 2 publications included in this review, a low level of bias was evident in 3 publications included in this review, and 12 publications were considered middle risk of bias. Table 3 shows the quality assessment of the studies and the risk of bias.

The included articles that contributed to the result found in this review prove that the use of neutralizers of irrigating solutions improve dentine adhesion. The forest plots for the analyses of the *in vitro* studies are represented in Figures 2 to 8. The results of *in vitro* studies were categorized according to the proposed subgrouping strategy of the assessed variables.

The bond strength for the use of neutralizing substances after sodium hypochlorite presented higher values when the neutralizing solutions were used when compared to non-use (control group) ($p<0.01$) *(Figure 2)*. Sodium ascorbate and ascorbic acid presented better results in the improvement of dentine adhesion when compared to sodium thiosulfate ($p<0.01$) *(Figure 3)*.

The bond strength presented higher values for the application time of the neutralizing substances when the neutralizing solutions were used in 10 min when compared to applications less than 5 min ($p<0.01$) *(Figure 4)*. The results for the type of the specimen used in each *in vitro* study showed no significant effect on the dentine bond strength ($p>0.01$) *(Figure 5)*.

According to the type of resin cemented used, both dual and self-adhesive presented higher bond strength values when the neutralizing solutions were used when compared to non-use ($p>0.01$) *(Figure 6)*. Regarding the sodium hypochlorite concentration used in the *in vitro* studies, the higher the concentration of the substances, up to 5-6%, the higher the influence on dentine adhesion ($p<0.01$) *(Figure 7)*

Lastly, the pull-out, push-out, microtensile and shear bond strength tests presented higher values when compared to micro shear bond strength test ($p<0.01$) *(Figure 8)*

DISCUSSION

This is the first systematic review which assesses the influence of the use of different types of sodium hypochlorite neutralizers on the adhesion of resinous materials to dentine. The results generally suggested that the use of neutralizers after the action of sodium hypochlorite and before performing the adhesion procedure increases the bond strength at the dentine/restoration interface. It was observed that the most significant articles to obtain this result were the studies related to the adhesion of posts through resin cemented. Sodium ascorbate was the most widely used neutralizer among the studies and obtained the most significant results regarding the increase in adhesive bond strength.[4,12,22,28] In the study carried out by Manimaran *et al.*[23] (2011), an increase in bond strength was observed when proanthocyanidin was used, even surpassing the control group with the use of saline solution and the group in which sodium ascorbate was used. Vongphan *et al.*[8] (2005) concluded that sodium ascorbate increases the bond strength after the use of sodium hypochlorite; however, it is believed that this data was not as significant in this systematic review because the bond strength was lower in one of the groups in which NaOCl (sodium ascorbate and distilled water) was used than when only using NaCl and sodium ascorbate. The author reports that more studies are needed to understand this mechanism.

Table 2. Characteristics of the included studies.

First author (year)	Country	Specimen Type	Irrigant	Neutralizing	Test Type
Lai et al. (2001)	China	Coronary dentin	NaOCl 5%	Sodium ascorbate 10%	Microtensile Bond Strenght (μTBS) – 1mm/min crosshead speed in the universal testing machine (Model 4440; Instron Inc., Canton, MA, USA)
Morris et al. (2001)	USA	Root dentin	NaOCl 5%	Sodium ascorbate 10% / Ascorbic acid 10%	Tensile Bond Strenght (Pull-out) – 0.6mm/min in the Vitrodyne V-1000 universal tester (John Chatillon & Sons, Greensboro, NC)
Soeno et al. (2004)	Japan	Coronary dentin	NaOCl 10%	Ascorbic acid 10%	Tensile Bond Strenght (Pull-out) – 2mm/min crosshead speed in the universal testing machine (Autograph AGS-10kNG, Shimadzu Corp., Kyoto, Japan)
Soeno et al. (2005)	Japan	Coronary dentin	NaOCl 10%	Ascorbic acid 10%	Tensile Bond Strenght (Pull-out) - 2mm/min (not specified)
Vongphan et al. (2005)	Thailand	Coronary dentin	NaOCl 5.25%	Sodium ascorbate 10%	Microtensile Bond Strenght (μTBS) – 1mm/min crosshead speed in the universal testing machine (Instron 5566, Instron Corp., London, UK)
Weston et al. (2007)	USA	Root dentin	NaOCl 5.25%	Sodium ascorbate 10% / Sodium ascorbate 20%	Tensile Bond Strenght (Pull-out) - 0.6mm/min in the Vitrodyne V-1000 universal tester (John Chatillon & Sons, Greensboro, NC)
Celik et al. (2010)	Turkey	Coronary dentin	NaOCl 5.25%	Sodium ascorbate 10%	Shear Bond Strenght - 0.5mm/min crosshead speed in the Universal Testing Machine (Lloyd-LRX; Lloyd Instruments, Fareham, UK)
Cunha et al. (2010)	Brazil	Root dentin	NaOCl 5.25%	Ascorbic acid 10%	Push-out Bond Strenght – 0.5mm/min crosshead speed in the universal testing machine (EMIC, São Jose dos Pinhais, PR, Brazil)
Manimaran et al. (2011)	India	Root dentin	NaOCl 5.25%	Sodium ascorbate 10%	Microtensile Bond Strength (μTBS) – 1mm/min (not specified)
Prasansuttiporn et al. (2011)	Japan	Coronary dentin	NaOCl 6%	Sodium ascorbate 10%	Microtensile Bond Strength (μTBS) – 1mm/min crosshead speed in the universal testing machine (EZ Test, Shimadzu Crop., Kyoto, Japan)
Furuse et al. (2014)	Brazil	Root dentin	NaOCl 5.25%	Ascorbic acid 10%	Push-out Bond Strenght - 0.5mm/min crosshead speed in the universal testing machine (EMIC, São Jose dos Pinhais, PR, Brazil)
Khoroushi & Kachuei (2014)	Iran	Root dentin	NaOCl 2.5%	Sodium ascorbate 10%	Tensile Bond Strength (Pull-out) – 1mm/min crosshead speed in the universal testing machine (HC10, Dartec, Stourbridge, UK)
Stevens (2014)	USA	Coronary dentin	NaOCl 6%	Sodium ascorbate 10%	Shear Bond Strenght – 1mm/min crosshead speed in the universal testing machine (Instron Machine; Instron, Norwood, MA).
Ebrahimi-Chaharom et al. (2015)	Iran	Coronary dentin	NaOCl 5.25%	Sodium ascorbate 10%	Shear Bond Strenght – 1mm/min strain rate in the universal testing machine (Hounsfield Test Equipment, H5k-S Model, Surray, England)
Corrêa et al. (2016)	Brazil	Coronary dentin	NaOCl 5.25%	Thiosulfate 0.5%/ Thiosulfate 5%	Microtensile Bond Strength (μTBS) - 1mm/min crosshead speed in the universal testing machine (EZ Test, Shimadzu Crop., Kyoto, Japan)
Chandrashekhar et al. (2018)	India	Coronary dentin	NaOCl 5.25%	Thiosulfate 5%	Microtensile Shear Bond Strenght – 1mm/min crosshead speed (not specified)
Dikmen & Tarim (2018)	Turkey	Coronary dentin	NaOCl 5.25%	Sodium ascorbate 10%	Microtensile Bond Strength (μTBS) – 0.5mm/min crosshead speed in the universal testing machine (BİSCO Inc., Schaumburg, IL, USA).

Table 2. Characteristics of the included studies.

First author (year)	Treatments Comparison	Conclusion
Lai et al. (2001)	10% Sodium Ascorbate and 10% Hydrogen Peroxide before or after acid-etching for 1 or 10 min	Hydrogen peroxide reduced the bond strengths of both adhesives, while sodium hypochlorite produced reduction in adhesion of only Single Bond. Following treatment with sodium ascorbate, reductions in bond strength were reversed
Morris et al. (2001)	Effect of 5% NaOCl and RC-Prep treatment on the bond strength of a resin cement, C&B Metabond	The results demonstrated that both 5% NaOCl and RC-Prep produced significantly large reductions in resin-dentin bond strengths, and the reductions could be completely reversed by the application of either 10% ascorbic acid or 10% sodium ascorbate
Soeno et al. (2004)	Experimental dentin conditioners of Sodium Ascorbate and Ferric Chloride after application of Sodium Hypochlorite	A novel dentin conditioned with 10 wt% ascorbic acid and 5 wt% ferric chloride improved the bonding between 4-META/ MMA-TBB resin and dentin conditioned with phosphoric acid etching and subsequent NaClO treatment
Soeno et al. (2005)	Experimental dentin primer consisting of Ascorbic Acid and Ferric Chloride after application of Sodium Hypochlorite	The experimental primer consisting of 10 wt% ascorbic acid and 0.075 wt% ferric chloride improved the bonding between Super-Bond C&B and dentin conditioned with phosphoric acid and NaOCl
Vongphan et al. (2005)	Different irrigation protocols before applying the total-etching adhesive system: water for 10 min/ sodium hypochlorite for 10 min/ sodium hypochlorite for 10 min and water for 10 min/ sodium hypochlorite for 10 min and sodium ascorbate for 10 min/ sodium hypochlorite for 10 min, sodium ascorbate for 10 min and water 10 min	Sodium hypochlorite significantly reduced the bond strengths of the adhesive when a total-etching was applied. The application of sodium ascorbate on sodium hypochlorite treated dentine significantly improved the bond strengths
Weston et al. (2007)	Different irrigation protocols before applying the adhesive system: 10% Sodium Ascorbate for 10 min/ 3min/ 1min and 20 % ascorbate for 1 min	5.25% NaOCl irrigation produced significant reduction in resin dentin bond strengths, but this can be reversed by 10% Sodium Ascorbate treatment for 1 min
Celik et al. (2010)	5,25% NaOCl for 10 min with or without 10% Sodium Ascorbate for 10 min before applying different adhesive systems	Although statistically significant differences were no demonstrated in all adhesive resin groups, sodium ascorbate application after NaOCl treatment improved the bond strength values
Cunha et al. (2010)	5% NaOCl for 10 min and 5% NaOCl for 10 min followed by 10 minutes of 10% Ascorbic Acid before self-adhesive or dual-cured cement	Deproteinization reduced bond strengths. Subsequent treatment with ascorbic acid was capable of reversing bond strength value changes to levels similar to those of controls in both cements
Manimaran et al. (2011)	Different irrigation protocols before applying the adhesive system: 5,25% NaOCl + EDTA + 2% CLX (20 min) + 10% Sodium Ascorbate for 10 min / 5,25% NaOCl + EDTA + 2% CLX (20 min) + 5% Proanthocyanidins (PA) for 10 min	The results demonstrated that 5.25% NaOCl caused significant reduction ($P<0.05$) in the bond strength, but this can be reversed by 5% PA significantly more than the 10% sodium ascorbate
Prasansuttiporn et al. (2011)	6% NaOCl for 30 secs + 10% Sodium Ascorbate for 5 secs or 10 secs before adhesive system	The reversal effects of antioxidant/reducing agents on compromised bonding to NaOCl-treated dentin depended on their application times and their redox potential. The 5 or 10 s application times of 10% sodium ascorbate did not significantly increased bond strength to NaOCl-treated dentin
Furuse et al. (2014)	Irrigation of 5% NaOCl 10min/ NaOCl followed by 10 minutes irrigation with 10% Ascorbic Acid before applying different adhesive systems	Only the all-in-one adhesive was influenced by the deproteinization and the subsequent irrigation with ascorbic acid was able to reverse the effect
Khoroushi & Kachuei (2014)	Different irrigation protocols before applying the adhesive system: 2,5% NaOCl for 1 min + 10% rosmarinic acid; 2,5% NaOCl for 1 min + 10% hesperidin; 2,5% NaOCl for 1 min + 10% sodium ascorbate hidrogel	Irrigation with NaOCl during canal preparation decreased bond strength of resin cement to root dentin. Amongst the antioxidants tested, SA had superior results in reversing the diminishing effect of NaOCl irrigation on the bond strength to root dentin
Stevens (2014)	Evaluate the immediate shear bond strength of different categories of resin cements on sodium hypochlorite (NaOCl)-treated dentin and to evaluate if the bond was improved by a subsequent treatment with 10% sodium ascorbate before adhesive procedures	Some resin cements exhibited equal or improved bond strengths ($P < .05$), whereas others exhibited significantly decreased bond strengths ($P < .05$). For the susceptible resin cements, a rinse of 10% sodium ascorbate provided an immediate restoration of at least 50% of the original bond strength ($P < .05$). The efficacy of sodium ascorbate may vary among resin cements
Ebrahimi-Chaharom et al. (2015)	Evaluate the effect of 10% sodium ascorbate on the bond strength of two all-in-one adhesive systems to NaOCl-treated dentin	Use of 10% sodium ascorbate for 10 minutes restored the decreased bond strength of the adhesive systems to that of the control groups
Corrêa et al. (2016)	5,25% NaOCl + 0,5 % and 5% Sodium Thiosulfate (Na2S2O3) at 1 min/ 5min/ 10min before adhesive procedures	The use of Na2S2O3 can significantly increase the bond strength of composite resin to NaOCl/EDTA treated dentin, allowing adhesive restorations to be immediately applied after endodontic treatment. When 5% Na2S2O3 was used for 10 minutes, the bond strength was found to be statistically equal to the negative control and higher than the positive control
Chandrashekhar et al. (2018)	5,25% NaOCl + EDTA + 5% Sodium Thiosulfate (Na2S2O3) for 10 min / 5,25% NaOCl + EDTA + 6,5% proanthocyanidin (PA) for 10 min before adhesive procedures	The use of Na2S2O3 and PA can significantly increase the bond strength of composite resin to NaOCl/EDTA-treated dentin, allowing adhesive restorations to be immediately applied after endodontic treatment.
Dikmen & Tarim (2018)	Different irrigation protocols before applying different adhesive systems: 5,25% NaOCl/ EDTA + 5,25% NaOCl/ 2% CHX/ NaOCl + 10% sodium ascorbate for 10 min	Application of sodium ascorbate improved compromised bond strength to NaOCl-treated dentin ($P < 0.01$)

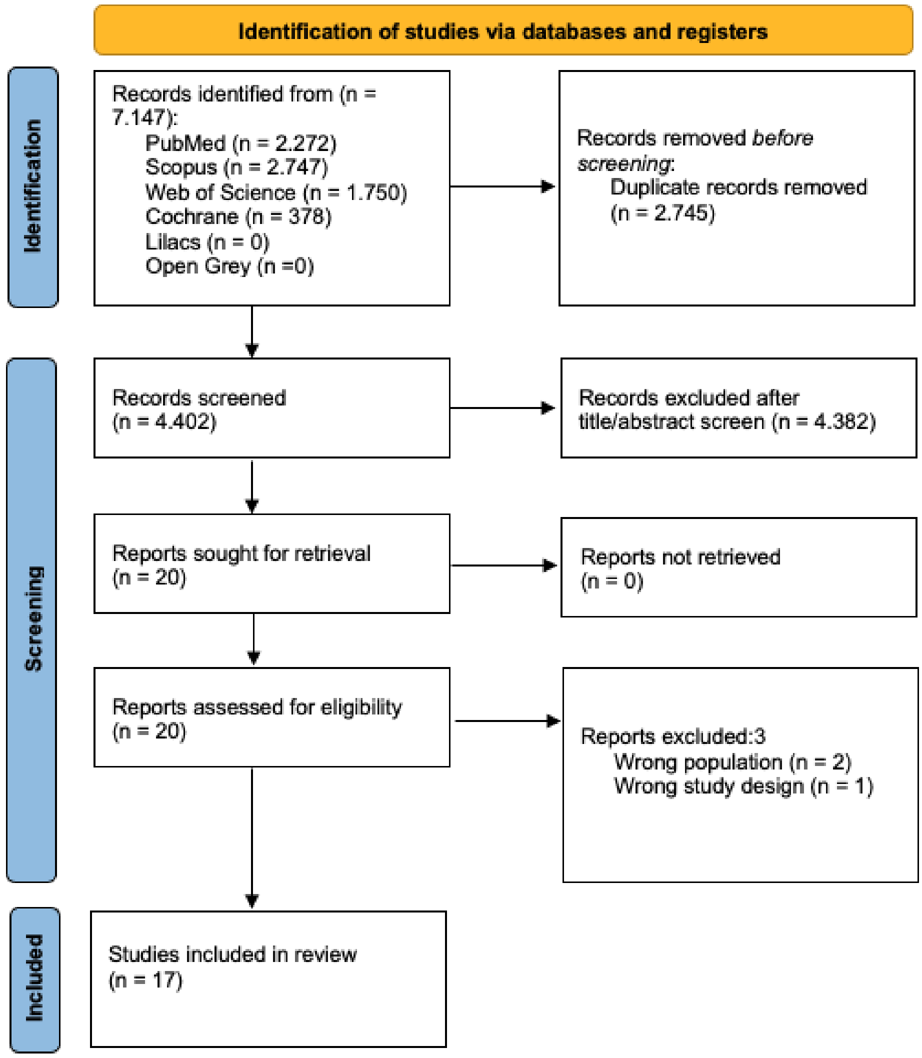

Figure 1: PRISMA flowchart with identification of the studies via databases and registers.

The articles included in this review used sodium ascorbate, sodium thiosulfate and ascorbic acid, all of which are inactivators of sodium hypochlorite. Sodium ascorbate yielded the most favorable results in improving dentine adhesion among the tested substances, followed by ascorbic acid, both which demonstrated statistically significant difference. However, sodium thiosulfate did not exhibit a statistically significant difference in dentin adhesion. This could be attributed to the limited number of studies in the thiosulfate group, with only two articles. The majority of articles contributing to this outcome employed sodium ascorbate as a neutralizer. This discrepancy may have influenced the stronger evidence supporting enhanced adherence by sodium ascorbate as a neutralizing agent. Nonetheless, it is important to note that the lack of effectiveness of thiosulfate cannot be definitively concluded, and further studies, particularly clinical ones, are warranted to obtain more realistic data.

Some articles[21] report that sodium ascorbate causes a dentine surface effect through its chemical reaction which improves adhesion and neutralizes sodium hypochlorite; in addition, they report that the application of ascorbate can neutralize the acidic nature of the adhesive system, changing surface conditions and improving adhesive strength. A study present in this review[22] proves that the oxygen released by NaOCl causes oxidation surface and inhibits the polymerization of resin-based materials, however ascorbic acid was able to restore adhesive strength due to its antioxidant properties. Furthermore, it is non-toxic, and is unlikely to produce any adverse biological effects. The study by Furuse *et al.*[28] (2014) also highlights the antioxidant effect of ascorbic acid as its main action mechanism in inhibiting sodium hypochlorite.

Only two studies in this review[11,26] used sodium thiosulfate as a neutralizer. They defend its action due to the potential to neutralize oxidizing agents through the substrate redox reaction, thus facilitating the complete polymerization of resinous materials; in turn, they can react with oxidizers to neutralize unpaired electrons by easy release of protons to form a stable product.

The studies which contributed to this review used the neutralizer in two different times, up to 5 min and 10 min of application. The use for 10 min obtained better results with statistical difference in comparison to the time less than 5 min, which makes sense because the greater the neutralizer contact with the dentine, the greater its neutralizing effect. This corroborates the study by Corrêa *et al.*[11] (2016), which concludes that the

Table 3. The quality assessment of the studies and the risk of bias.

	Sample calculation	Specimen randomization	The number (n) of specimens is clear	Solutions concentration standardized (%)	Neutralizing freshly prepared	Time used	Blind analysis	Parameters for the mechanical test	Overall risk of bias
Lai et al. (2001)	-	-	?	+	-	+	-	+	High
Morris et al. (2001)	-	+	?	+	-	+	-	?	High
Soeno et al. (2004)	-	+	+	+	-	+	-	+	Medium
Soeno et al. (2005)	-	-	+	+	-	+	-	+	Medium
Vongphan et al. (2005)	-	-	+	+	+	+	-	+	Medium
Weston et al. (2007)	-	+	+	+	-	+	-	?	Medium
Celik et al. (2010)	-	+	+	+	+	+	-	+	Low
Cunha et al. (2010)	-	-	+	+	+	+	-	+	Medium
Manimaran et al. (2011)	-	+	+	+	+	+	-	+	Low
Prasansuttiporn et al. (2011)	-	-	+	+	+	+	-	+	Medium
Furuse et al. (2014)	-	-	+	+	+	+	-	+	Medium
Khoroushi & Kachuei (2014)	-	+	+	+	+	+	-	+	Low
Stevens (2014)	-	-	+	+	-	+	-	+	Medium
Ebrahimi-Chaharom et al. (2015)	-	+	+	+	-	+	-	+	Medium
Corrêa et al. (2016)	-	+	+	+	-	+	-	+	Medium
Chandrashekhar et al. (2018)	-	+	+	+	-	+	-	?	Medium
Dikmen & Tarim (2018)	-	+	?	+	-	+	+	+	Medium

? = Unclear

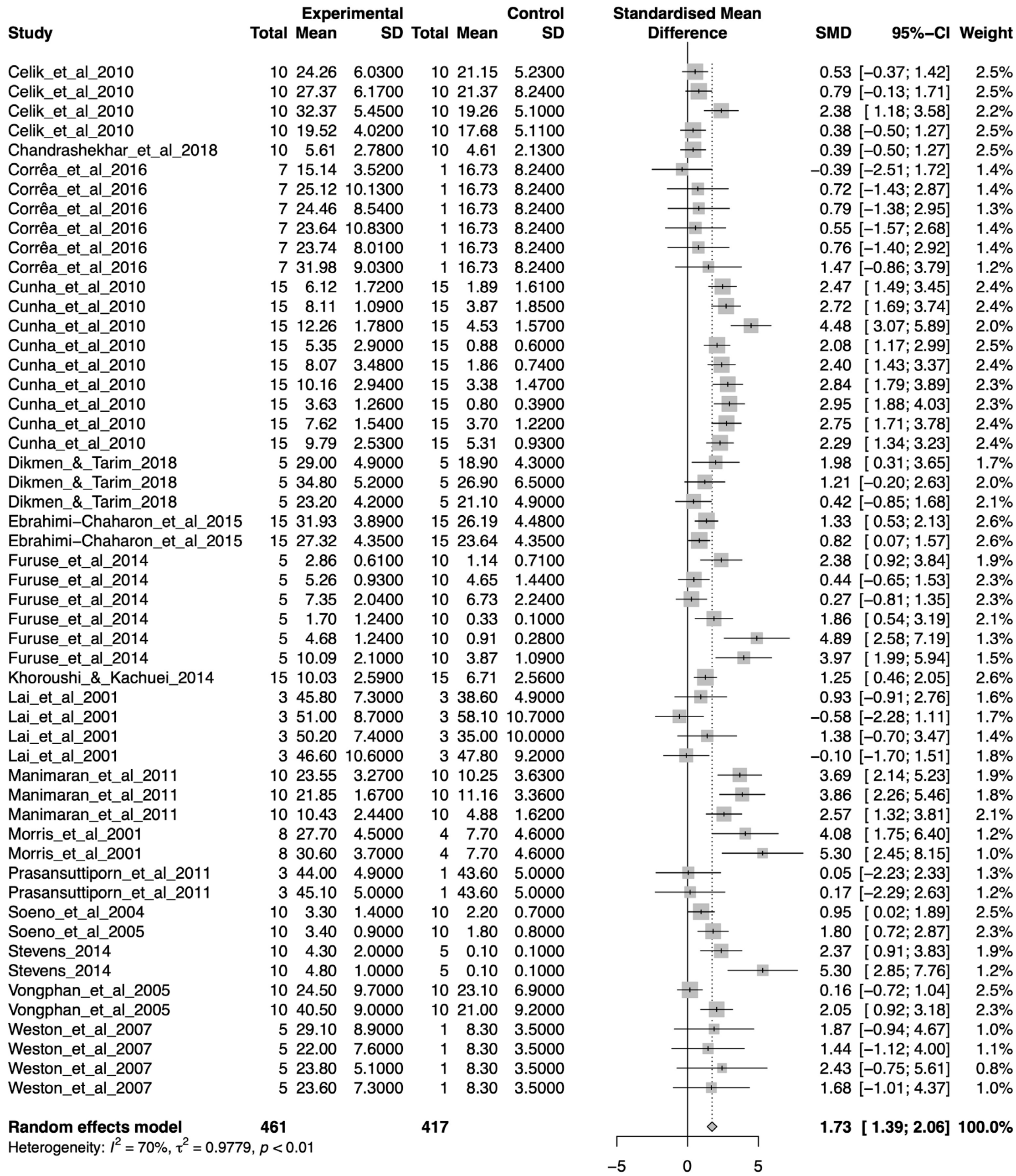

Figure 2: Neutralizing substances after sodium hypochlorite. The bond strength presented higher values when the neutralizing solutions were used when compared to non-use (control group) (p<0.01.)

neutralizer action not only occurs by physical effect, but also chemical; in addition, the same study relates the application time with the neutralizer concentration, and the higher the concentration and the longer the application time, the greater the dentine recovery effect is. Prasansuttiporn *et al.*[10] (2011) applied the neutralizer for 5 and 10 seconds, and did not obtain a significant result, which is explained by their insufficient application time which did not show the benefits of the neutralizer. Based on the literature, the authors also defend that the neutralizer application time must be greater than 1 min when the concentration of 10% is used.

The irrigant concentrations were classified into three different concentrations of between 5-6%, 2.5% and 10% according to the articles which compose this review. Most of the studies used sodium hypochlorite concentration of 5-6%, and therefore this concentration was statistically significant in the influence of adherence when compared with the other concentrations. One study present in this review[22] reports that the concentration and application time of the irrigant influences the result, since the NaOCl oxygen causes superficial oxidation and inhibits the interfacial polymerization of resin-based materials and the residual chemical solutions; furthermore, its by-products are likely to diffuse into dentine, affecting the polymerization of monomers in demineralized dentine and reducing adhesion.

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight
neutralizing = sodium_ascorbate									
Celik_et_al_2010	10	24.26	6.0300	10	21.15	5.2300	0.53	[−0.37; 1.42]	2.5%
Celik_et_al_2010	10	27.37	6.1700	10	21.37	8.2400	0.79	[−0.13; 1.71]	2.5%
Celik_et_al_2010	10	32.37	5.4500	10	19.26	5.1000	2.38	[1.18; 3.58]	2.2%
Celik_et_al_2010	10	19.52	4.0200	10	17.68	5.1100	0.38	[−0.50; 1.27]	2.5%
Dikmen_&_Tarim_2018	5	29.00	4.9000	5	18.90	4.3000	1.98	[0.31; 3.65]	1.7%
Dikmen_&_Tarim_2018	5	34.80	5.2000	5	26.90	6.5000	1.21	[−0.20; 2.63]	2.0%
Dikmen_&_Tarim_2018	5	23.20	4.2000	5	21.10	4.9000	0.42	[−0.85; 1.68]	2.1%
Ebrahimi−Chaharon_et_al_2015	15	31.93	3.8900	15	26.19	4.4800	1.33	[0.53; 2.13]	2.6%
Ebrahimi−Chaharon_et_al_2015	15	27.32	4.3500	15	23.64	4.3500	0.82	[0.07; 1.57]	2.6%
Khoroushi_&_Kachuei_2014	15	10.03	2.5900	15	6.71	2.5600	1.25	[0.46; 2.05]	2.6%
Lai_et_al_2001	3	45.80	7.3000	3	38.60	4.9000	0.93	[−0.91; 2.76]	1.6%
Lai_et_al_2001	3	51.00	8.7000	3	58.10	10.7000	−0.58	[−2.28; 1.11]	1.7%
Lai_et_al_2001	3	50.20	7.4000	3	35.00	10.0000	1.38	[−0.70; 3.47]	1.4%
Lai_et_al_2001	3	46.60	10.6000	3	47.80	9.2000	−0.10	[−1.70; 1.51]	1.8%
Manimaran_et_al_2011	10	23.55	3.2700	10	10.25	3.6300	3.69	[2.14; 5.23]	1.9%
Manimaran_et_al_2011	10	21.85	1.6700	10	11.16	3.3600	3.86	[2.26; 5.46]	1.8%
Manimaran_et_al_2011	10	10.43	2.4400	10	4.88	1.6200	2.57	[1.32; 3.81]	2.1%
Morris_et_al_2001	8	30.60	3.7000	4	7.70	4.6000	5.30	[2.45; 8.15]	1.0%
Prasansuttiporn_et_al_2011	3	44.00	4.9000	1	43.60	5.0000	0.05	[−2.23; 2.33]	1.3%
Prasansuttiporn_et_al_2011	3	45.10	5.0000	1	43.60	5.0000	0.17	[−2.29; 2.63]	1.2%
Stevens_2014	10	4.30	2.0000	5	0.10	0.1000	2.37	[0.91; 3.83]	1.9%
Stevens_2014	10	4.80	1.0000	5	0.10	0.1000	5.30	[2.85; 7.76]	1.2%
Vongphan_et_al_2005	10	24.50	9.7000	10	23.10	6.9000	0.16	[−0.72; 1.04]	2.5%
Vongphan_et_al_2005	10	40.50	9.0000	10	21.00	9.2000	2.05	[0.92; 3.18]	2.3%
Weston_et_al_2007	5	29.10	8.9000	1	8.30	3.5000	1.87	[−0.94; 4.67]	1.0%
Weston_et_al_2007	5	22.00	7.6000	1	8.30	3.5000	1.44	[−1.12; 4.00]	1.1%
Weston_et_al_2007	5	23.80	5.1000	1	8.30	3.5000	2.43	[−0.75; 5.61]	0.8%
Weston_et_al_2007	5	23.60	7.3000	1	8.30	3.5000	1.68	[−1.01; 4.37]	1.0%
Random effects model	216			182			1.46	[1.01; 1.90]	50.9%
Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.7964$, $p < 0.01$									
neutralizing = Thiosulfate									
Chandrashekhar_et_al_2018	10	5.61	2.7800	10	4.61	2.1300	0.39	[−0.50; 1.27]	2.5%
Corrêa_et_al_2016	7	15.14	3.5200	1	16.73	8.2400	−0.39	[−2.51; 1.72]	1.4%
Corrêa_et_al_2016	7	25.12	10.1300	1	16.73	8.2400	0.72	[−1.43; 2.87]	1.4%
Corrêa_et_al_2016	7	24.46	8.5400	1	16.73	8.2400	0.79	[−1.38; 2.95]	1.3%
Corrêa_et_al_2016	7	23.64	10.8300	1	16.73	8.2400	0.55	[−1.57; 2.68]	1.4%
Corrêa_et_al_2016	7	23.74	8.0100	1	16.73	8.2400	0.76	[−1.40; 2.92]	1.4%
Corrêa_et_al_2016	7	31.98	9.0300	1	16.73	8.2400	1.47	[−0.86; 3.79]	1.2%
Random effects model	52			16			0.50	[−0.12; 1.13]	10.6%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.95$									
neutralizing = ascorbic_acid									
Cunha_et_al_2010	15	6.12	1.7200	15	1.89	1.6100	2.47	[1.49; 3.45]	2.4%
Cunha_et_al_2010	15	8.11	1.0900	15	3.87	1.8500	2.72	[1.69; 3.74]	2.4%
Cunha_et_al_2010	15	12.26	1.7800	15	4.53	1.5700	4.48	[3.07; 5.89]	2.0%
Cunha_et_al_2010	15	5.35	2.9000	15	0.88	0.6000	2.08	[1.17; 2.99]	2.5%
Cunha_et_al_2010	15	8.07	3.4800	15	1.86	0.7400	2.40	[1.43; 3.37]	2.4%
Cunha_et_al_2010	15	10.16	2.9400	15	3.38	1.4700	2.84	[1.79; 3.89]	2.3%
Cunha_et_al_2010	15	3.63	1.2600	15	0.80	0.3900	2.95	[1.88; 4.03]	2.3%
Cunha_et_al_2010	15	7.62	1.5400	15	3.70	1.2200	2.75	[1.71; 3.78]	2.4%
Cunha_et_al_2010	15	9.79	2.5300	15	5.31	0.9300	2.29	[1.34; 3.23]	2.4%
Furuse_et_al_2014	5	2.86	0.6100	10	1.14	0.7100	2.38	[0.92; 3.84]	1.9%
Furuse_et_al_2014	5	5.26	0.9300	10	4.65	1.4400	0.44	[−0.65; 1.53]	2.3%
Furuse_et_al_2014	5	7.35	2.0400	10	6.73	2.2400	0.27	[−0.81; 1.35]	2.3%
Furuse_et_al_2014	5	1.70	1.2400	10	0.33	0.1000	1.86	[0.54; 3.19]	2.1%
Furuse_et_al_2014	5	4.68	1.2400	10	0.91	0.2800	4.89	[2.58; 7.19]	1.3%
Furuse_et_al_2014	5	10.09	2.1000	10	3.87	1.0900	3.97	[1.99; 5.94]	1.5%
Morris_et_al_2001	8	27.70	4.5000	4	7.70	4.6000	4.08	[1.75; 6.40]	1.2%
Soeno_et_al_2004	10	3.30	1.4000	10	2.20	0.7000	0.95	[0.02; 1.89]	2.5%
Soeno_et_al_2005	10	3.40	0.9000	10	1.80	0.8000	1.80	[0.72; 2.87]	2.3%
Random effects model	193			219			2.36	[1.85; 2.86]	38.5%
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.7932$, $p < 0.01$									
Random effects model	**461**			**417**			**1.73**	**[1.39; 2.06]**	**100.0%**
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.9779$, $p < 0.01$									
Residual heterogeneity: $I^2 = 63\%$, $p < 0.01$									

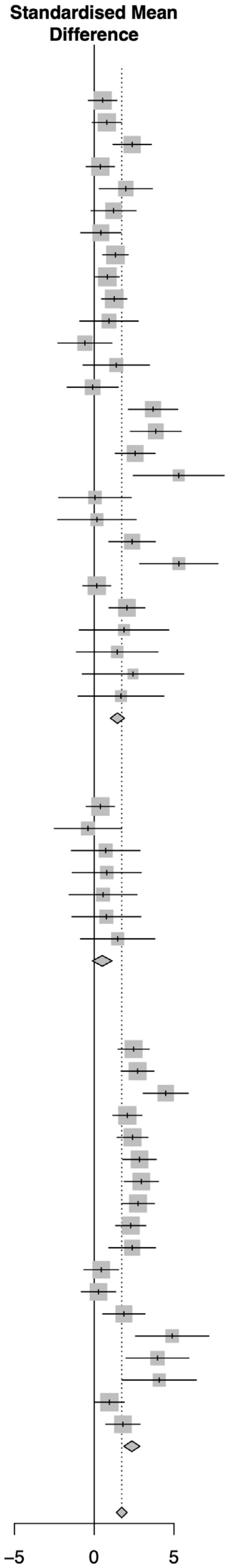

Figure 3: The type of the neutralizing substances. Sodium ascorbate and ascorbic acid presented better results for improving dentine adhesion when compared to sodium thiosulfate (p<0.01.)

The articles that used the push-out and shear bond strength tests had remarkably close results if compared between them and the general average of the subgroup. Of the articles that used the pull-out test, most of the groups analyzed presented higher average values than the general average of the subgroup, while only three were below, two of which were the studies by Soeno *et al.*[19,20] (2004 and 2005), where the neutralizing agent was incorporated into an experimental conditioning agent and an experimental primer, respectively. The best results obtained from the conditioning agent in the 2004 study were with the

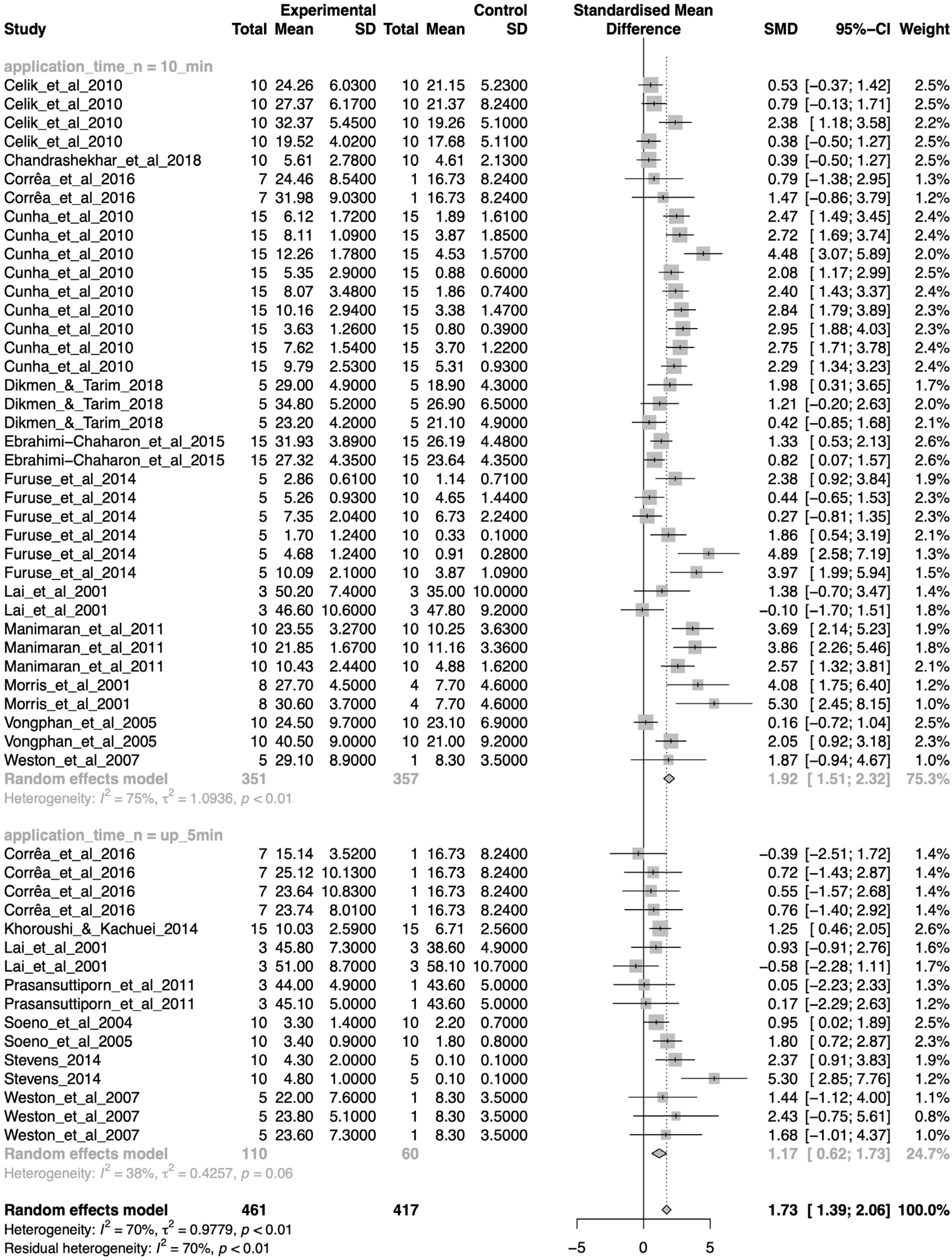

Figure 4: Bond strength according to the application time of the neutralizing substances. Higher values were presented when the neutralizing solutions were used in 10 min when compared to applications less than 5 min (p<0.01).

mixture of 10% ascorbic acid + 5% ferric chloride; however, only the conditioning agent with ascorbic acid was considered in this analysis. These factors may have influenced the results found, in addition to the fact that the specimens were washed after applying the acid, which may have decreased the bond strength, as seen in this condition in other articles.[8] The same occurred with the 2005 study, in which the best results achieved were from the experimental primer of 10% ascorbic acid + 0.075% ferric chloride; however, only the primer with ascorbic acid was incorporated in this analysis.

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight
third = –									
Celik_et_al_2010	10	24.26	6.0300	10	21.15	5.2300	0.53	[−0.37; 1.42]	2.5%
Celik_et_al_2010	10	27.37	6.1700	10	21.37	8.2400	0.79	[−0.13; 1.71]	2.5%
Celik_et_al_2010	10	32.37	5.4500	10	19.26	5.1000	2.38	[1.18; 3.58]	2.2%
Celik_et_al_2010	10	19.52	4.0200	10	17.68	5.1100	0.38	[−0.50; 1.27]	2.5%
Chandrashekhar_et_al_2018	10	5.61	2.7800	10	4.61	2.1300	0.39	[−0.50; 1.27]	2.5%
Corrêa_et_al_2016	7	15.14	3.5200	1	16.73	8.2400	−0.39	[−2.51; 1.72]	1.4%
Corrêa_et_al_2016	7	25.12	10.1300	1	16.73	8.2400	0.72	[−1.43; 2.87]	1.4%
Corrêa_et_al_2016	7	24.46	8.5400	1	16.73	8.2400	0.79	[−1.38; 2.95]	1.3%
Corrêa_et_al_2016	7	23.64	10.8300	1	16.73	8.2400	0.55	[−1.57; 2.68]	1.4%
Corrêa_et_al_2016	7	23.74	8.0100	1	16.73	8.2400	0.76	[−1.40; 2.92]	1.4%
Corrêa_et_al_2016	7	31.98	9.0300	1	16.73	8.2400	1.47	[−0.86; 3.79]	1.2%
Dikmen_&_Tarim_2018	5	29.00	4.9000	5	18.90	4.3000	1.98	[0.31; 3.65]	1.7%
Dikmen_&_Tarim_2018	5	34.80	5.2000	5	26.90	6.5000	1.21	[−0.20; 2.63]	2.0%
Dikmen_&_Tarim_2018	5	23.20	4.2000	5	21.10	4.9000	0.42	[−0.85; 1.68]	2.1%
Ebrahimi−Chaharon_et_al_2015	15	31.93	3.8900	15	26.19	4.4800	1.33	[0.53; 2.13]	2.6%
Ebrahimi−Chaharon_et_al_2015	15	27.32	4.3500	15	23.64	4.3500	0.82	[0.07; 1.57]	2.6%
Khoroushi_&_Kachuei_2014	15	10.03	2.5900	15	6.71	2.5600	1.25	[0.46; 2.05]	2.6%
Lai_et_al_2001	3	45.80	7.3000	3	38.60	4.9000	0.93	[−0.91; 2.76]	1.6%
Lai_et_al_2001	3	51.00	8.7000	3	58.10	10.7000	−0.58	[−2.28; 1.11]	1.7%
Lai_et_al_2001	3	50.20	7.4000	3	35.00	10.0000	1.38	[−0.70; 3.47]	1.4%
Lai_et_al_2001	3	46.60	10.6000	3	47.80	9.2000	−0.10	[−1.70; 1.51]	1.8%
Morris_et_al_2001	8	27.70	4.5000	4	7.70	4.6000	4.08	[1.75; 6.40]	1.2%
Morris_et_al_2001	8	30.60	3.7000	4	7.70	4.6000	5.30	[2.45; 8.15]	1.0%
Prasansuttiporn_et_al_2011	3	44.00	4.9000	1	43.60	5.0000	0.05	[−2.23; 2.33]	1.3%
Prasansuttiporn_et_al_2011	3	45.10	5.0000	1	43.60	5.0000	0.17	[−2.29; 2.63]	1.2%
Soeno_et_al_2004	10	3.30	1.4000	10	2.20	0.7000	0.95	[0.02; 1.89]	2.5%
Soeno_et_al_2005	10	3.40	0.9000	10	1.80	0.8000	1.80	[0.72; 2.87]	2.3%
Stevens_2014	10	4.30	2.0000	5	0.10	0.1000	2.37	[0.91; 3.83]	1.9%
Stevens_2014	10	4.80	1.0000	5	0.10	0.1000	5.30	[2.85; 7.76]	1.2%
Vongphan_et_al_2005	10	24.50	9.7000	10	23.10	6.9000	0.16	[−0.72; 1.04]	2.5%
Vongphan_et_al_2005	10	40.50	9.0000	10	21.00	9.2000	2.05	[0.92; 3.18]	2.3%
Weston_et_al_2007	5	29.10	8.9000	1	8.30	3.5000	1.87	[−0.94; 4.67]	1.0%
Weston_et_al_2007	5	22.00	7.6000	1	8.30	3.5000	1.44	[−1.12; 4.00]	1.1%
Weston_et_al_2007	5	23.80	5.1000	1	8.30	3.5000	2.43	[−0.75; 5.61]	0.8%
Weston_et_al_2007	5	23.60	7.3000	1	8.30	3.5000	1.68	[−1.01; 4.37]	1.0%
Random effects model	266			192			1.13	[0.80; 1.46]	61.7%
Heterogeneity: $I^2 = 46\%$, $\tau^2 = 0.3882$, $p < 0.01$									
third = Apical									
Cunha_et_al_2010	15	6.12	1.7200	15	1.89	1.6100	2.47	[1.49; 3.45]	2.4%
Cunha_et_al_2010	15	5.35	2.9000	15	0.88	0.6000	2.08	[1.17; 2.99]	2.5%
Cunha_et_al_2010	15	3.63	1.2600	15	0.80	0.3900	2.95	[1.88; 4.03]	2.3%
Furuse_et_al_2014	5	2.86	0.6100	10	1.14	0.7100	2.38	[0.92; 3.84]	1.9%
Furuse_et_al_2014	5	1.70	1.2400	10	0.33	0.1000	1.86	[0.54; 3.19]	2.1%
Manimaran_et_al_2011	10	10.43	2.4400	10	4.88	1.6200	2.57	[1.32; 3.81]	2.1%
Random effects model	65			75			2.39	[1.93; 2.85]	13.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.82$									
third = Middle									
Cunha_et_al_2010	15	8.11	1.0900	15	3.87	1.8500	2.72	[1.69; 3.74]	2.4%
Cunha_et_al_2010	15	8.07	3.4800	15	1.86	0.7400	2.40	[1.43; 3.37]	2.4%
Cunha_et_al_2010	15	7.62	1.5400	15	3.70	1.2200	2.75	[1.71; 3.78]	2.4%
Furuse_et_al_2014	5	5.26	0.9300	10	4.65	1.4400	0.44	[−0.65; 1.53]	2.3%
Furuse_et_al_2014	5	4.68	1.2400	10	0.91	0.2800	4.89	[2.58; 7.19]	1.3%
Manimaran_et_al_2011	10	21.85	1.6700	10	11.16	3.3600	3.86	[2.26; 5.46]	1.8%
Random effects model	65			75			2.65	[1.62; 3.67]	12.5%
Heterogeneity: $I^2 = 76\%$, $\tau^2 = 1.1834$, $p < 0.01$									
third = Coronal									
Cunha_et_al_2010	15	12.26	1.7800	15	4.53	1.5700	4.48	[3.07; 5.89]	2.0%
Cunha_et_al_2010	15	10.16	2.9400	15	3.38	1.4700	2.84	[1.79; 3.89]	2.3%
Cunha_et_al_2010	15	9.79	2.5300	15	5.31	0.9300	2.29	[1.34; 3.23]	2.4%
Furuse_et_al_2014	5	7.35	2.0400	10	6.73	2.2400	0.27	[−0.81; 1.35]	2.3%
Furuse_et_al_2014	5	10.09	2.1000	10	3.87	1.0900	3.97	[1.99; 5.94]	1.5%
Manimaran_et_al_2011	10	23.55	3.2700	10	10.25	3.6300	3.69	[2.14; 5.23]	1.9%
Random effects model	65			75			2.83	[1.59; 4.07]	12.4%
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 1.9252$, $p < 0.01$									
Random effects model	**461**			**417**			**1.73**	**[1.39; 2.06]**	**100.0%**
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.9779$, $p < 0.01$									
Residual heterogeneity: $I^2 = 57\%$, $p < 0.01$									

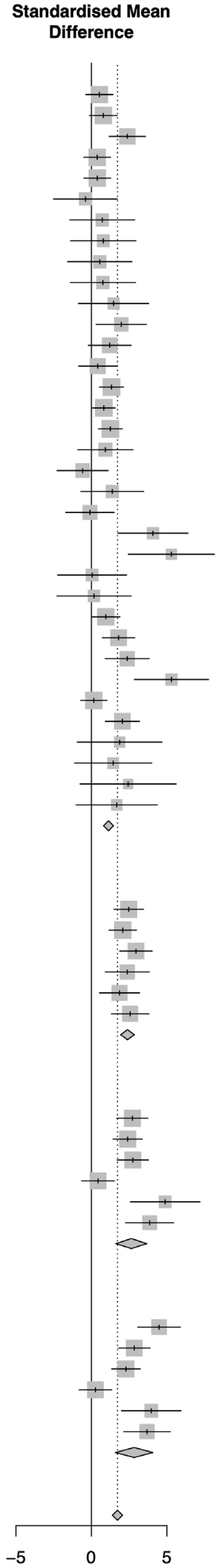

Figure 5: The type of the specimen used in each *in vitro* study, without significant effect of the type of the specimen on the dentine bond strength (p>0.01).

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%–CI	Weight
resin_cement = dual_conventional									
Celik_et_al_2010	10	24.26	6.0300	10	21.15	5.2300	0.53	[−0.37; 1.42]	2.5%
Celik_et_al_2010	10	27.37	6.1700	10	21.37	8.2400	0.79	[−0.13; 1.71]	2.5%
Celik_et_al_2010	10	32.37	5.4500	10	19.26	5.1000	2.38	[1.18; 3.58]	2.2%
Celik_et_al_2010	10	19.52	4.0200	10	17.68	5.1100	0.38	[−0.50; 1.27]	2.5%
Chandrashekhar_et_al_2018	10	5.61	2.7800	10	4.61	2.1300	0.39	[−0.50; 1.27]	2.5%
Corrêa_et_al_2016	7	15.14	3.5200	1	16.73	8.2400	−0.39	[−2.51; 1.72]	1.4%
Corrêa_et_al_2016	7	25.12	10.1300	1	16.73	8.2400	0.72	[−1.43; 2.87]	1.4%
Corrêa_et_al_2016	7	24.46	8.5400	1	16.73	8.2400	0.79	[−1.38; 2.95]	1.3%
Corrêa_et_al_2016	7	23.64	10.8300	1	16.73	8.2400	0.55	[−1.57; 2.68]	1.4%
Corrêa_et_al_2016	7	23.74	8.0100	1	16.73	8.2400	0.76	[−1.40; 2.92]	1.4%
Corrêa_et_al_2016	7	31.98	9.0300	1	16.73	8.2400	1.47	[−0.86; 3.79]	1.2%
Cunha_et_al_2010	15	5.35	2.9000	15	0.88	0.6000	2.08	[1.17; 2.99]	2.5%
Cunha_et_al_2010	15	8.07	3.4800	15	1.86	0.7400	2.40	[1.43; 3.37]	2.4%
Cunha_et_al_2010	15	10.16	2.9400	15	3.38	1.4700	2.84	[1.79; 3.89]	2.3%
Cunha_et_al_2010	15	3.63	1.2600	15	0.80	0.3900	2.95	[1.88; 4.03]	2.3%
Cunha_et_al_2010	15	7.62	1.5400	15	3.70	1.2200	2.75	[1.71; 3.78]	2.4%
Cunha_et_al_2010	15	9.79	2.5300	15	5.31	0.9300	2.29	[1.34; 3.23]	2.4%
Dikmen_&_Tarim_2018	5	29.00	4.9000	5	18.90	4.3000	1.98	[0.31; 3.65]	1.7%
Dikmen_&_Tarim_2018	5	34.80	5.2000	5	26.90	6.5000	1.21	[−0.20; 2.63]	2.0%
Dikmen_&_Tarim_2018	5	23.20	4.2000	5	21.10	4.9000	0.42	[−0.85; 1.68]	2.1%
Ebrahimi−Chaharon_et_al_2015	15	31.93	3.8900	15	26.19	4.4800	1.33	[0.53; 2.13]	2.6%
Ebrahimi−Chaharon_et_al_2015	15	27.32	4.3500	15	23.64	4.3500	0.82	[0.07; 1.57]	2.6%
Furuse_et_al_2014	5	2.86	0.6100	10	1.14	0.7100	2.38	[0.92; 3.84]	1.9%
Furuse_et_al_2014	5	5.26	0.9300	10	4.65	1.4400	0.44	[−0.65; 1.53]	2.3%
Furuse_et_al_2014	5	7.35	2.0400	10	6.73	2.2400	0.27	[−0.81; 1.35]	2.3%
Furuse_et_al_2014	5	1.70	1.2400	10	0.33	0.1000	1.86	[0.54; 3.19]	2.1%
Furuse_et_al_2014	5	4.68	1.2400	10	0.91	0.2800	4.89	[2.58; 7.19]	1.3%
Furuse_et_al_2014	5	10.09	2.1000	10	3.87	1.0900	3.97	[1.99; 5.94]	1.5%
Lai_et_al_2001	3	45.80	7.3000	3	38.60	4.9000	0.93	[−0.91; 2.76]	1.6%
Lai_et_al_2001	3	51.00	8.7000	3	58.10	10.7000	−0.58	[−2.28; 1.11]	1.7%
Lai_et_al_2001	3	50.20	7.4000	3	35.00	10.0000	1.38	[−0.70; 3.47]	1.4%
Lai_et_al_2001	3	46.60	10.6000	3	47.80	9.2000	−0.10	[−1.70; 1.51]	1.8%
Manimaran_et_al_2011	10	23.55	3.2700	10	10.25	3.6300	3.69	[2.14; 5.23]	1.9%
Manimaran_et_al_2011	10	21.85	1.6700	10	11.16	3.3600	3.86	[2.26; 5.46]	1.8%
Manimaran_et_al_2011	10	10.43	2.4400	10	4.88	1.6200	2.57	[1.32; 3.81]	2.1%
Morris_et_al_2001	8	27.70	4.5000	4	7.70	4.6000	4.08	[1.75; 6.40]	1.2%
Morris_et_al_2001	8	30.60	3.7000	4	7.70	4.6000	5.30	[2.45; 8.15]	1.0%
Prasansuttiporn_et_al_2011	3	44.00	4.9000	1	43.60	5.0000	0.05	[−2.23; 2.33]	1.3%
Prasansuttiporn_et_al_2011	3	45.10	5.0000	1	43.60	5.0000	0.17	[−2.29; 2.63]	1.2%
Soeno_et_al_2004	10	3.30	1.4000	10	2.20	0.7000	0.95	[0.02; 1.89]	2.5%
Soeno_et_al_2005	10	3.40	0.9000	10	1.80	0.8000	1.80	[0.72; 2.87]	2.3%
Vongphan_et_al_2005	10	24.50	9.7000	10	23.10	6.9000	0.16	[−0.72; 1.04]	2.5%
Vongphan_et_al_2005	10	40.50	9.0000	10	21.00	9.2000	2.05	[0.92; 3.18]	2.3%
Weston_et_al_2007	5	29.10	8.9000	1	8.30	3.5000	1.87	[−0.94; 4.67]	1.0%
Weston_et_al_2007	5	22.00	7.6000	1	8.30	3.5000	1.44	[−1.12; 4.00]	1.1%
Weston_et_al_2007	5	23.80	5.1000	1	8.30	3.5000	2.43	[−0.75; 5.61]	0.8%
Weston_et_al_2007	5	23.60	7.3000	1	8.30	3.5000	1.68	[−1.01; 4.37]	1.0%
Random effects model	381			347			1.56	[1.22; 1.91]	87.5%
Heterogeneity: $I^2 = 67\%$, $\tau^2 = 0.8574$, $p < 0.01$									
resin_cement = self−adhesive									
Cunha_et_al_2010	15	6.12	1.7200	15	1.89	1.6100	2.47	[1.49; 3.45]	2.4%
Cunha_et_al_2010	15	8.11	1.0900	15	3.87	1.8500	2.72	[1.69; 3.74]	2.4%
Cunha_et_al_2010	15	12.26	1.7800	15	4.53	1.5700	4.48	[3.07; 5.89]	2.0%
Khoroushi_&_Kachuei_2014	15	10.03	2.5900	15	6.71	2.5600	1.25	[0.46; 2.05]	2.6%
Stevens_2014	10	4.30	2.0000	5	0.10	0.1000	2.37	[0.91; 3.83]	1.9%
Stevens_2014	10	4.80	1.0000	5	0.10	0.1000	5.30	[2.85; 7.76]	1.2%
Random effects model	80			70			2.86	[1.83; 3.90]	12.5%
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 1.2209$, $p < 0.01$									
Random effects model	**461**			**417**			**1.73**	**[1.39; 2.06]**	**100.0%**
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.9779$, $p < 0.01$									
Residual heterogeneity: $I^2 = 68\%$, $p < 0.01$									

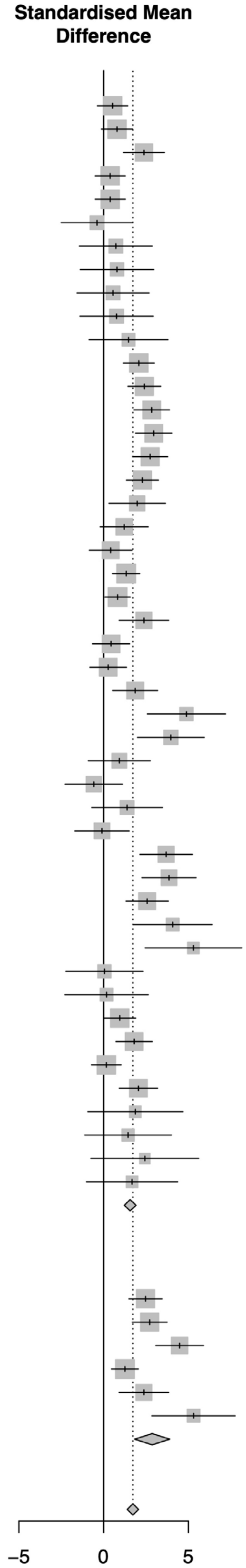

Figure 6: The type of resin cements used in each *in vitro* study. Both dual and self-adhesive presented higher bond strength values when the neutralizing solutions were used when compared to non-use (p>0.01).

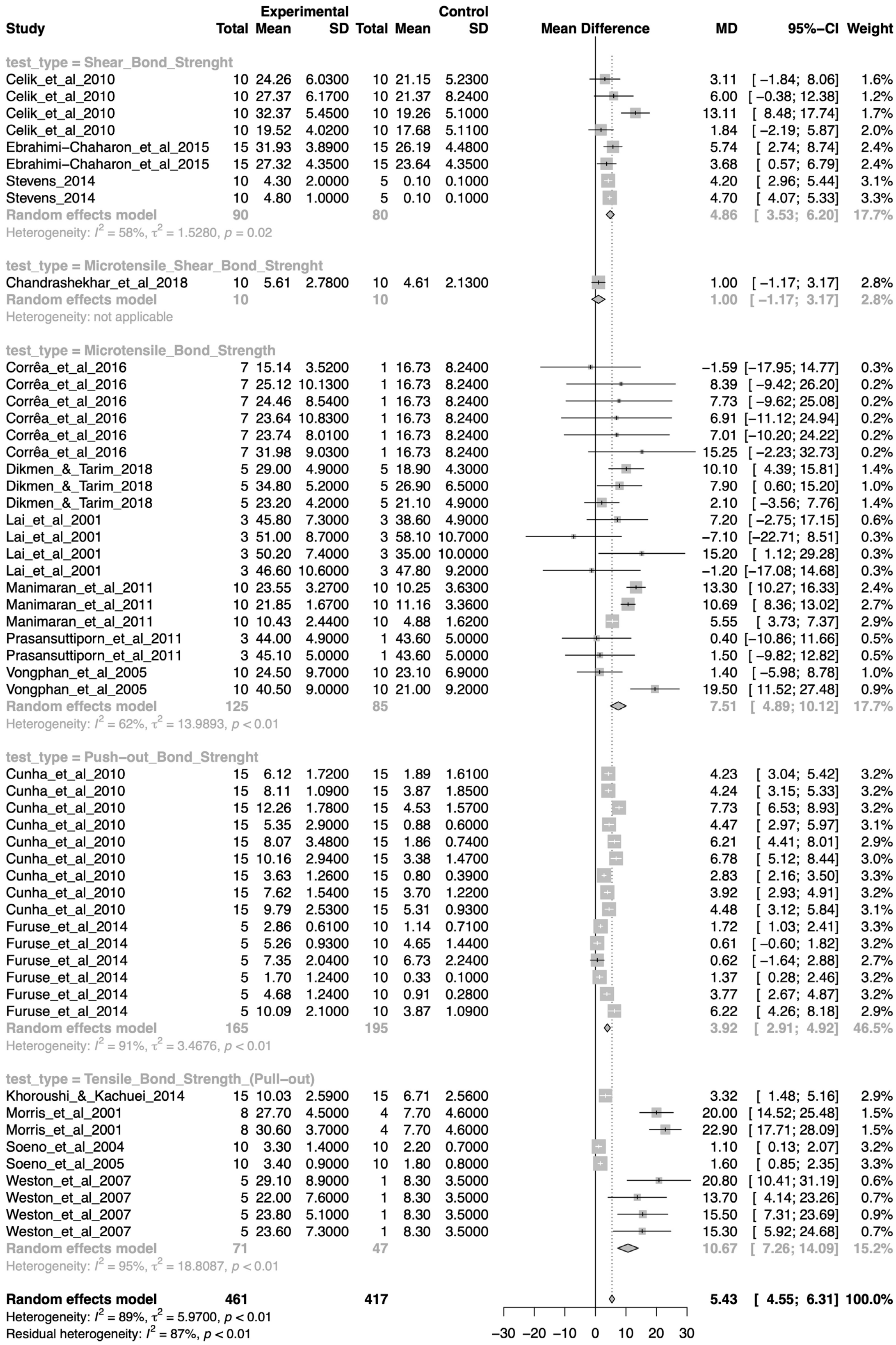

Figure 7: The concentration of sodium hypochlorite used in the *in vitro* studies. The higher the concentration of the substances, up to 5-6%, the higher the influence in dentine adhesion (p<0.01).

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight
irrigant_concentration = 5_to_6_%									
Celik_et_al_2010	10	24.26	6.0300	10	21.15	5.2300	0.53	[−0.37; 1.42]	2.5%
Celik_et_al_2010	10	27.37	6.1700	10	21.37	8.2400	0.79	[−0.13; 1.71]	2.5%
Celik_et_al_2010	10	32.37	5.4500	10	19.26	5.1000	2.38	[1.18; 3.58]	2.2%
Celik_et_al_2010	10	19.52	4.0200	10	17.68	5.1100	0.38	[−0.50; 1.27]	2.5%
Chandrashekhar_et_al_2018	10	5.61	2.7800	10	4.61	2.1300	0.39	[−0.50; 1.27]	2.5%
Corrêa_et_al_2016	7	15.14	3.5200	1	16.73	8.2400	−0.39	[−2.51; 1.72]	1.4%
Corrêa_et_al_2016	7	25.12	10.1300	1	16.73	8.2400	0.72	[−1.43; 2.87]	1.4%
Corrêa_et_al_2016	7	24.46	8.5400	1	16.73	8.2400	0.79	[−1.38; 2.95]	1.3%
Corrêa_et_al_2016	7	23.64	10.8300	1	16.73	8.2400	0.55	[−1.57; 2.68]	1.4%
Corrêa_et_al_2016	7	23.74	8.0100	1	16.73	8.2400	0.76	[−1.40; 2.92]	1.4%
Corrêa_et_al_2016	7	31.98	9.0300	1	16.73	8.2400	1.47	[−0.86; 3.79]	1.2%
Cunha_et_al_2010	15	6.12	1.7200	15	1.89	1.6100	2.47	[1.49; 3.45]	2.4%
Cunha_et_al_2010	15	8.11	1.0900	15	3.87	1.8500	2.72	[1.69; 3.74]	2.4%
Cunha_et_al_2010	15	12.26	1.7800	15	4.53	1.5700	4.48	[3.07; 5.89]	2.0%
Cunha_et_al_2010	15	5.35	2.9000	15	0.88	0.6000	2.08	[1.17; 2.99]	2.5%
Cunha_et_al_2010	15	8.07	3.4800	15	1.86	0.7400	2.40	[1.43; 3.37]	2.4%
Cunha_et_al_2010	15	10.16	2.9400	15	3.38	1.4700	2.84	[1.79; 3.89]	2.3%
Cunha_et_al_2010	15	3.63	1.2600	15	0.80	0.3900	2.95	[1.88; 4.03]	2.3%
Cunha_et_al_2010	15	7.62	1.5400	15	3.70	1.2200	2.75	[1.71; 3.78]	2.4%
Cunha_et_al_2010	15	9.79	2.5300	15	5.31	0.9300	2.29	[1.34; 3.23]	2.4%
Dikmen_&_Tarim_2018	5	29.00	4.9000	5	18.90	4.3000	1.98	[0.31; 3.65]	1.7%
Dikmen_&_Tarim_2018	5	34.80	5.2000	5	26.90	6.5000	1.21	[−0.20; 2.63]	2.0%
Dikmen_&_Tarim_2018	5	23.20	4.2000	5	21.10	4.9000	0.42	[−0.85; 1.68]	2.1%
Ebrahimi−Chaharon_et_al_2015	15	31.93	3.8900	15	26.19	4.4800	1.33	[0.53; 2.13]	2.6%
Ebrahimi−Chaharon_et_al_2015	15	27.32	4.3500	15	23.64	4.3500	0.82	[0.07; 1.57]	2.6%
Furuse_et_al_2014	5	2.86	0.6100	10	1.14	0.7100	2.38	[0.92; 3.84]	1.9%
Furuse_et_al_2014	5	5.26	0.9300	10	4.65	1.4400	0.44	[−0.65; 1.53]	2.3%
Furuse_et_al_2014	5	7.35	2.0400	10	6.73	2.2400	0.27	[−0.81; 1.35]	2.3%
Furuse_et_al_2014	5	1.70	1.2400	10	0.33	0.1000	1.86	[0.54; 3.19]	
Furuse_et_al_2014	5	4.68	1.2400	10	0.91	0.2800	4.89	[2.58; 7.19]	
Furuse_et_al_2014	5	10.09	2.1000	10	3.87	1.0900	3.97	[1.99; 5.94]	
Lai_et_al_2001	3	45.80	7.3000	3	38.60	4.9000	0.93	[−0.91; 2.76]	
Lai_et_al_2001	3	51.00	8.7000	3	58.10	10.7000	−0.58	[−2.28; 1.11]	
Lai_et_al_2001	3	50.20	7.4000	3	35.00	10.0000	1.38	[−0.70; 3.47]	
Lai_et_al_2001	3	46.60	10.6000	3	47.80	9.2000	−0.10	[−1.70; 1.51]	
Manimaran_et_al_2011	10	23.55	3.2700	10	10.25	3.6300	3.69	[2.14; 5.23]	
Manimaran_et_al_2011	10	21.85	1.6700	10	11.16	3.3600	3.86	[2.26; 5.46]	
Manimaran_et_al_2011	10	10.43	2.4400	10	4.88	1.6200	2.57	[1.32; 3.81]	
Morris_et_al_2001	8	27.70	4.5000	4	7.70	4.6000	4.08	[1.75; 6.40]	
Morris_et_al_2001	8	30.60	3.7000	4	7.70	4.6000	5.30	[2.45; 8.15]	
Prasansuttiporn_et_al_2011	3	44.00	4.9000	1	43.60	5.0000	0.05	[−2.23; 2.33]	
Prasansuttiporn_et_al_2011	3	45.10	5.0000	1	43.60	5.0000	0.17	[−2.29; 2.63]	
Stevens_2014	10	4.30	2.0000	5	0.10	0.1000	2.37	[0.91; 3.83]	
Stevens_2014	10	4.80	1.0000	5	0.10	0.1000	5.30	[2.85; 7.76]	
Vongphan_et_al_2005	10	24.50	9.7000	10	23.10	6.9000	0.16	[−0.72; 1.04]	
Vongphan_et_al_2005	10	40.50	9.0000	10	21.00	9.2000	2.05	[0.92; 3.18]	
Weston_et_al_2007	5	29.10	8.9000	1	8.30	3.5000	1.87	[−0.94; 4.67]	
Weston_et_al_2007	5	22.00	7.6000	1	8.30	3.5000	1.44	[−1.12; 4.00]	
Weston_et_al_2007	5	23.80	5.1000	1	8.30	3.5000	2.43	[−0.75; 5.61]	
Weston_et_al_2007	5	23.60	7.3000	1	8.30	3.5000	1.68	[−1.01; 4.37]	
Random effects model	426			382			1.76	[1.40; 2.13]	92.6%
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 1.0996$, $p < 0.01$									
irrigant_concentration = 2,5_%									
Khoroushi_&_Kachuei_2014	15	10.03	2.5900	15	6.71	2.5600	1.25	[0.46; 2.05]	
Random effects model	15			15			1.25	[0.46; 2.05]	2.6%
Heterogeneity: not applicable									
irrigant_concentration = 10_%									
Soeno_et_al_2004	10	3.30	1.4000	10	2.20	0.7000	0.95	[0.02; 1.89]	
Soeno_et_al_2005	10	3.40	0.9000	10	1.80	0.8000	1.80	[0.72; 2.87]	
Random effects model	20			20			1.33	[0.51; 2.16]	4.8%
Heterogeneity: $I^2 = 26\%$, $\tau^2 = 0.0949$, $p = 0.24$									
Random effects model	**461**			**417**			**1.73**	**[1.39; 2.06]**	**100.0%**

Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.9779$, $p < 0.01$
Residual heterogeneity: $I^2 = 71\%$, $p < 0.01$

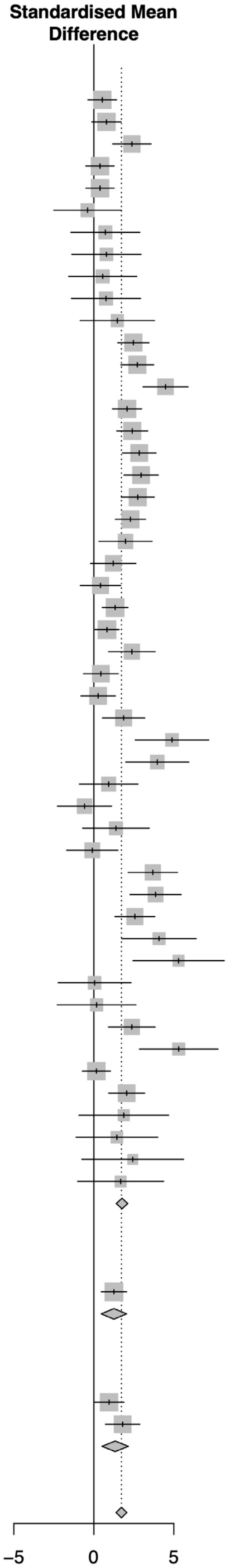

Figure 8: The type of bond strength tests. The pull-out, push-out, microtensile and shear bond strength presented higher values when compared to micro shear bond strength test (p<0.01).

None of the authors of the studies in this review report that the type of specimen used was important for the results, while only Vongphan *et al*.[8] (2005) commented that their results differed from the works of Lai *et al*. (2001) and Morris *et al*.[4,6] (2001); this was perhaps because of the substrate, since they used the pulp chamber wall to perform the tests as this is the region where clinically endodontically treated teeth restorations would be. On the other hand, the other studies used root dentine as a substrate. In the work of Lai[6] (2001), the application of sodium ascorbate did not increase the bond strength when applied after an acid attack on dentine, and this result was seen with the two studied adhesives. The observed drop in bond strength in ascorbate-treated dentine can be explained by the ability of this reducing agent to donate high-energy electrons to eliminate free radicals which are formed during resin polymerization.

Dual and self-adhesive resin cement showed better bond strength when the neutralizing substances were applied after the use of the irrigating solutions ($p<0.01$). Most of the articles included in this systematic review used conventional dual curing resin cements for bonding between dentine and restorations. Only 3 articles[12,22,24] applied the self-adhesive resin cements in their studies. The bonding and cementation protocol differ from each restoration technique chosen for tooth rehabilitations, and dual conventional resin cements is more used for fiber post bonding. Celik *et al*.[21] (2010) compared the dentine bonding effectiveness of different types of adhesive systems and concluded that the sodium ascorbate application improved the bond strength. This can be explained due to the one-step self-etch adhesive containing methacrylated phosphoric and acid-HEMA esters, and so the ascorbate may neutralize the very acidic nature of this adhesive system, change the surface conditions and improve the bond strength values.

The findings of this review would provide guidance to dental surgeons for optimizing adhesion in treatments with endodontically treated teeth, but the heterogeneity of the studies and the lack of publications in vivo about this, do not make clear the best protocol. More studies should be carried out to clinical protocols which help dentists in their daily clinical routine to define and choose the irrigation solution for cleaning and disinfection, together with the neutralizers and a cementation system appropriate to improve the bond strength.

CONCLUSIONS

The results of this meta-analysis showed that sodium ascorbate was the most widely used neutralizer among the studies and obtained the most significant results for increasing the bond strength. The use of a neutralizing substance is important to reverse the negative effects of the irrigating solution used in endodontic treatment and increase the bond strength between dentine and resin cement. More studies should be conducted to describe the best clinical protocol for using sodium hypochlorite neutralizing agents.

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