EFFECT OF ENAMEL DEPROTEINIZATION ON BONDING ORTHODONTIC BRACKETS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Sami Zohdi Saleem Alrai
BDS, University of Sharjah, 2017

Submitted to the Hamdan Bin Mohammed College of Dental Medicine
Mohammed Bin Rashid University of Medicine and Health Sciences
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Orthodontics
2022

ABSTRACT

Effect of enamel deproteinization on bonding orthodontic brackets: A systematic review and meta-analysis

Sami Zohdi Saleem Alrai

Supervisors: Dr. Samira Diar Bakirly and Prof. Ahmed Ghoneima

Background: Frequent deboning is common during orthodontic treatment. Enamel deproteinization with 5.25% NaOCl or papain has been proposed as one way to increase shear bond strength (SBS) of orthodontic brackets. Moreover, frequent appearance of white spot lesions is common yet unwanted consequence of orthodontic treatment. The use of fluoride releasing resin modified glass ionomer cements (RMGIC) as an adhesive for bonding has been proposed to help minimize white spot lesions. However, with their reduced SBS compared to resin composite, the use of RMGIC, clinically, is not highly recommended. Enamel deproteinization has been proposed as one way to increase SBS of RMGIC.

Aim: to systematically review studies assessing the effect of enamel deproteinization on SBS and adhesive remnant index (ARI) of orthodontic brackets by a systematic review of the published literature

Materials and Methods: Unrestricted electronic search of 5 databases and grey literature was performed. Following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement, randomized trials using extracted human premolar teeth with intact buccal surface, no cracks, no pretreatment with chemical agents, no caries and absence of congenital or developmental conditions with at least one group using deproteinization with 5.25%NaOCl or Papain as an additional measure while bonding were included to assess the effect of deproteinization on SBS as the main outcome and on ARI as a secondary outcome . The random effect method of combining treatment effects for different groups was used. Risk of bias assessment was performed using the Cochrane's collaboration tool risk of bias tool for randomized trials. Study selection, risk of bias assessment, and data-extraction were performed in duplicate.

Results: 19 studies met the inclusion criteria and were included in this systematic review; 14 studies were included the meta-analysis. Eleven studies were at high risk of bias and 4 were at unclear risk.

Very low evidence shows that 5.25%NaOCl improved the SBS 0.7(-1.86-0.47). $P=0.24$ and ARI 0.55 (-0.52 – 1.63) $P=0.3$ of brackets bonded with RMGIC to be comparable with resin composite only. However, with significantly high heterogeneity for SBS (I^2, 90%; $P<0.001$) and ARI (I^2, 86%; $P<0.001$) respectively. Moreover, for the other comparisons, when comparing 5.25%NaOCl with resin composite to resin composite only, no improvement in SBS 0.212 MPa (-0.16- 0.6), $P=0.27$ nor ARI 0.14(-0.3-0.56), $P=0.5$was shown. Similarly, when comparing 5.25%NaOCl RMGIC to RMGIC only, no improvement in SBS 0.36MPa (-0.19-0.89), $P=0.2$ nor ARI 0.54 (-0.5-0.1.62), $P=0.312$was shown. With regards to pretreatment with 10%Papain, a significant mean difference favoring the control group was shown for SBS 0.95MPa (0.63 – 1.26) $P<0.001$ and ARI 0.55 (0.23- 0.87), $P<0.05$.

Conclusion: There is no strong evidence that enamel deproteinization improves SBS and ARI of orthodontic brackets bonded with resin composite or RMGIC.

DEDICATION

At the beginning, all thanks goes to Allah (God) for giving me everything needed to complete this work. I also dedicate this work to my parents and the rest of my family for giving me their full support during these years, without them, none of this would be possible.

DECLARATION

I declare that all the content of this thesis is my own work. There is no conflict of interest with any other entity or organization

Name: Sami Alrai

Signature:

ACKNOWLEDGMENTS

I firstly acknowledge my main supervisor Dr. Samira Diar Bakirly for her valuable support and endless help during the process of writing the thesis. She encouraged me to finish this work to perfection and present it in reputable international orthodontic conferences.

I would also like to express my deep gratitude to Associate Professor Eleftherios G. Kaklamanos whom has generally given me his time and expertise during his unexpected events.

Lastly, my thanks goes to the program director Professor Ahmed Ghoneima for his valuable support and help during my residency and during the process of writing this paper. He always encouraged me and my colleagues to be the best in our field.

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1. INTRODUCTION

1.1 Bonding in orthodontics

Bonding of orthodontic brackets is one of the essential steps in orthodontic treatment. It is based on mechanical locking of an adhesive to the enamel surface. achieving sufficient bond strength requires fundamental requirements including cleaning the adhesive surface, providing good wetting, providing intimate adaptation, and adequate polymerization.[1–3]

In the early days of fixed appliance treatment, before enamel bonding became the routine practice, brackets were welded to gold or stainless steel bands. As the bands encompassed the teeth circumferentially, the orthodontist had to create spaces between the teeth in order to cement the bands and then these spaces had to be closed at the end of the treatment which was considered time consuming and uncomfortable for the patient. Moreover, banding teeth had caused gingival trauma and decalcification under the bands. [4]

The basis for adhesion of brackets to the enamel surface is enamel etching as proposed by Buonocore in 1955. He found that acrylic resin could be bonded to enamel that was conditioned with 85% phosphoric acid for 30 seconds. [5,6] The aim of enamel etching is to clean the surface, remove the smear layer and roughen the enamel surface to increase retention of the adhesive [7]. 30%-40%phosphoric acid (H3PO4) for 15 to 30 seconds has been used for years to bond resin based materials to enamel and has been reported that it provides the most retentive appearance[6,8]. the quality of enamel etching depends on the acid etchant's concentration, the etchant's composition and the time the etchant is in contact with the enamel surface [9]. The morphological changes produced by acid etching using scanning electron microscope were described by Gwinnett and Silverstone et al who divided the enamel etching patterns to 3 types. In type 1 etching pattern, the acid dissolves the head of the prism while the inter-prismatic enamel remains intact, forming a honeycomb appearance. Type 2 etching pattern, the peripheral zones of the prisms are diluted leaving the head of the prism intact. Type 3 etching pattern is characterized by superficial dissolution that does not alter the deeper strata where the enamel prisms are present [10,11]. clinically we can only observe the white chalky appearance reflecting the quantity but not the quality of the etched surface[12]. Types 1 and 2 are the most retentive etching patterns.[13]

1.1.1 Limitations of conventional acid etch treatment

It has been demonstrated that the topographic quality of enamel etching is not well distributed over the entire enamel surface when using phosphoric acid. Upon closer examination, more than 69% presented with no etching pattern, while 7% presented with tenacious etching and only 2% was ideally etched [8 14]. This is because Phosphoric acid etching mainly works on the inorganic matter, It doesn't eliminate the organic matter composed mainly enamel protein Amelogenin. It's believed that this outer layer of organic matter prevents the 37% phosphoric acid gel from properly etching the surface, resulting in inconsistent and unreliable surface for bonding. In order to enhance the bonding to enamel surface, it became necessary to remove this organic layer[14,15]. Therefore, various techniques were used to overcome this limitation including enamel abrasion [16], grinding air abrasion[17] and lasers[18], but without obtaining good results.

1.1.2 Enhancing the etching pattern by enamel deproteinization

A non-invasive technique frequently used in endodontics, utilizes Sodium Hypochlorite (NaOCl) as an irrigant solution to disinfect the canals, remove the debris and organic materials[19, 20]. The chemical reaction between sodium hypochlorite and organic matter has been reported by Estrela et al in 2002 with three main reactions, -1Sodium Hypochlorite reacts with grease acids (oil and lipids) present in the organic matter forming grease acid salts (soap) and glycerol (alcohol)-

reaction 1 (soaping of lipids), -2 Sodium hydroxide reacts with protein amino acids forming salt and water- reaction 2 (amino acid Neutralization reaction), -3 Hipochlorous acid reacts with amine group of amino acids forming chloramine and water- reaction 3 (chloramination reaction) [21]. Enamel deproteinization with sodium hypochlorite was proposed by Justus et al[22] in 2010, he concluded that enamel deproteinization eliminates the organic matter, which allowed to achieve more of type 1 and 2 etching patterns due to the ability of the acid etchant to penetrate more effectively into the enamel. Espinosa et al[12] in 2008 stated that enamel deproteinization with 5.25%Sodium Hypochlorite for 1 minute prior to etching with phosphoric acid doubles enamels retentive surface up to 94.47%.

Another material used as an enamel deproteinization agent is Papain gel. Papain is a proteolytic enzyme extracted from the latex of the leaves and fruits of the green adult papaya. It is characterized by having bactericidal, bacteriostatic and anti-inflammatory properties. [23]. Pinthon et al. reported that the usage of 10% papain gel before acid etching increased the bond strength[24]. He also concluded in another report that papain gel at concentrations of 8% and 10% significantly increased the shear bond strength of brackets bonded with RMGIC.[25]

1.2 Adhesives in Orthodontics

1.2.1 Resin Composite

Modern resin composite restorations was introduced by the work of Bowen in 1956, with the idea of development of the monomer 2,2-bis-4(2-hydroxy-3-methacryloyloxypropoxy) phenylpropane[26]. This substance is derived from the reaction of glycidyl methacrylate with bisphenol A to create the molecule bisphenol A-glycidyl methacrylate (Bis-GMA). The aim of his study was to combine the advantages of the acrylic system with the epoxy resin systems based on bisphenol A. The cured acrylic resins form linear polymers while new formulations may be polymerized by cross linking into a three dimensional network which contribute to better strength, less polymerization shrinkage and less water absorption. Polymerization of resin composite is either chemically or by light curing. [1,26].Another advantage of Bis-GMA is that it resembles the color of the tooth which proves to be excellent for restoring anterior teeth and bonding orthodontic attachments to enamel [26]. The technique of direct bonding was introduced by Newman in 1965, in a progress report in the *American Journal of Orthodontics* [27].

1.2.2 Glass Ionomer Cement (GIC)

Glass ionomer cement was introduced to dentistry by Wilson and Kent in 1972 [28]. It has been widely used in dentistry as restorative materials, fissure sealants, liners and bases and orthodontic cements. It bonds chemically to enamel, dentine, cementum, non-precious metals and plastic.[28,29]. The composition of glass ionomer cements is based on three main ingredients, which are polymeric water-soluble acid, basic glass and water. They are presented as glass powder and an aqueous solution of polymeric acid, which are mixed in order to form a viscous paste that sets rapidly. They can be mixed manually or it can be presented in a capsule separated by a membrane in which the membrane needs to be broken before mixing and the capsule is vibrated, the paste is extruded from the capsule to be used in intra-orally.[29]. The use of glass ionomer cements for bonding attachments should be limited only to patients who are at high risk for demineralization. This is due to their sustained fluoride release property following bonding in order to provide preventive actions and potentially remineralize early enamel demineralization[30]. Resin modified glass ionomer was introduced in 1988 by Antonucci et al [31]. It is composed of conventional GIC modified by water soluble resin. Composition of the liquid phase is polycarboxylic acid, 2-hydroxyethylmethacrylate (HEMA) and water. While the composition of the powder phase is the same as conventional GIC. [31]

1.2.3 Adhesion

As reported by Retief et al[32] in 1970, Adhesion is the molecular attraction between two surfaces of bodies or between molecules. These attractive forces are divided into physical forces including Van der Waals forces and hydrogen bonds and into chemical forces which arise from covalent and electrovalent bonds.

Retief et al[32] showed that surface contact is very critical to achieve optimal adhesion. Since proper adhesion can only be achieved if the forces between the two surfaces act at a very short distance. In the order of Ångström units, adhesion between two surfaces can't be achieved if the two surfaces are not flat at an atomic level. Clinically it's almost impossible to obtain such smooth surfaces. Since tooth surfaces are not smooth surfaces, an intermediate liquid adhesive between the bracket base and the enamel surface is needed. Wetting occurs if the attracting forces are strong. This adhesive forms a contact angle with the surface of the enamel. Smaller contact angle indicates better wetting and stronger adhesion.[32]

1.3 Shear bond strength

Bond strength is the force of debonding divided by the area of the bonded surface. Bond strength have been reported in units of Megapascals (MPa), kilograms per centimeter square (kg/cm^2) and pounds per square inch (Ib/in^2 or psi)[33]. Shear bond strength is usually tested in *vitro* using a universal testing machine. The bonded bracket is loaded until failure by a debonding apparatus, and this is usually done by a thin blade attached to a crosshead at set speeds that is slow enough to give standardized bond strength results.[34] Bond testing in *vitro* involves many variables that can influence the measured bond strength results. These variables include type of tooth, fluoride content of the tooth, storage media for the tooth before bonding, elapsed time of storage following bonding, configuration of specimen testing jig, crosshead speed of the universal testing machine and bonding area of the bracket. Currently, no standardized protocol exists for orthodontic bond strength measurements. [33]

The minimum clinically acceptable value for bond strength is a range from 6-8 MPa according to Reynolds[35], numerous amount of studies have been published since this time to test the shear bond strength of orthodontic brackets.[33]

1.3.1 Orthodontic bond failure

Treatment duration and efficiency are compromised by bond failures.[36–38] It has been reported that bracket failure is one of the most important predictors of treatment duration.[36,37] Every bracket failure can increase the treatment duration by 0.3 months, while three or more failures can increase the orthodontic treatment duration up to 1.5 months[38]. It is in the best interest of the patient and the orthodontist to keep the duration of orthodontic treatment as short as possible with maximum clinical efficiency.[39,40] Bond failures can result from many factors including faulty techniques during the bracket bonding procedure, resin manipulation during bonding and curing and bracket base design that can result in retention problems because of design defects or corrosion.[32,41]. In long term randomized and non-randomized studies[42–45], the overall bracket failure rate ranges from 6% to 8%. Half of the patients approximately experience at least one bracket failure[38,46]. Among the patients with at least one failure, about one third experienced only a single bracket failure, while the others exhibited multiple bracket failures.[38,46] Regarding gender, contradictory results exist between males and females in terms of bracket failure.[42–45] Some evidence show an association between patient's age at the onset of treatment and bracket failure, with younger patients demonstrating higher rate of bond failure[42]. however, those findings were refuted by the same research group in another study.[43] Difference in bracket failure between upper and lower teeth have been reported as well, with twice as much failure in the lower teeth than the upper teeth.

[44,45] Posterior teeth show significantly higher failure rates than anterior teeth.[42,44,45] Canines demonstrate the least failure rates of all teeth, while the lower second premolars demonstrate the highest failure rates. Possible explanations include poorer moisture control at posterior sites during bonding, higher masticatory loads in the posterior area and different microtopography of buccal enamel of the posterior teeth.[47] Several reports show that bond failure occurs mostly during the first six months[48,49], while House et al[50] in 2006 showed in their trial that bond failures increased at each time interval. No association was found between the type of malocclusion and the rate of bond failures.[49] Existing reports show mixed conclusions for the association between extraction and non-extraction treatment and bond failure.[37,49]

1.3.2 Adhesives and bond failure

Resin composite is the most frequently used adhesive in bonding orthodontic brackets. One of the main reasons is that they provide sufficient bond strength51. A 12 month prospective randomized clinical trial52 reported a failure rate of 2.8% for light cured and chemically cured resin composite, which is within the acceptable range for clinical use. Using glass ionomer cement for bonding orthodontic brackets was done with the aim of reducing the potential side effects that may occur with the acid etch technique and resin composite. These include demineralization, enamel fractures during debonding, removal of adhesive remnants and possible allergic reaction to these adhesives.53–55 However, it was found that glass ionomer cements demonstrate significantly higher bond failure rates compared to composite resin.56,57To overcome the low shear bond strength of glass ionomer cement, while still maintaining the fluoride releasing properties, bonding with resin modified glass ionomer (RMGIC) was attempted.58 However, still one of the major drawbacks is its weaker shear bond strength compared to resin composite.59,60

1.3.3 Adhesive remnant index (ARI)

Årtun and Bergland[61] in 1984 introduced the adhesive remnant index to evaluate the amount of adhesive remaining on the enamel surface after debonding. This index was developed in a pilot study of 20 extracted teeth. The scoring criteria ranging as follows. Score 0 = no adhesive left on the tooth, score 1 = less than half of the adhesive left on the tooth, score 2 = more than half of the adhesive left on the tooth and score 3 = all the adhesive is left on the tooth[61]. Many studies of bonding in orthodontics use this index referred as the 4-point scale[62–64].

Since this index is qualitative and subjective, some attempts have been made to modify the original scoring system. Many studies[62,65–68] expanded the ARI scores into 5-6 scales. A 5- point scale developed by Bishara et al[69] in 1990 is now commonly used. With the scores ranging as follows: 1= no adhesive remnant on the bracket base, 2= less than 10% of adhesive remnant on the bracket base, 3= more than 10% but less than 90% adhesive remnant on the bracket base, 4= more than 90% adhesive remnant on the bracket base and 5= all the adhesive remnant on the bracket base[69]. However, a direct comparison between the 4- and 5- point space is difficult since the range of scores are different[64]. This qualitative assessment is usually carried out by visual assessment with the naked eye or under magnification using a stereomicroscope. However, it was shown that the scores differ significantly under different magnifications[70]. When using the 4-point scale, under 20X magnification, score 0 decreased and score 2 increased compared to the naked eye. While score 1 decreased and score 3 increased compared with 10X magnification. However, there was no significant difference when the ARI was evaluated between 10X magnification and the naked eye.[70]

Several quantitative methods have been used to determine the ARI more precisely. These include scanning electron microscopy (SEM), 3-dimentional profilometry and finite element analysis.[64,70–]

[72] When comparing quantitative methods to qualitative methods, it was concluded that comparable results can be generated, in particular, the 5-point ARI scores when compared to SEM and elemental mapping.[64]

ARI score is an important factor to be considered in the selection of the appropriate adhesive for bonding orthodontic brackets. There is a debate whether different ARI scores reflect different shear bond strength values for different adhesive systems.[72–75] Moreover, adhesive systems with low adhesive remnant on the enamel surface has the advantage of faster and easier cleaning of the enamel surface after debonding with lesser chance of enamel damage. [76,77]

1.4 White spot lesions

Demineralization of smooth surfaces of enamel adjacent to orthodontic brackets is relatively a common finding[78]. Dental plaque is increased with marked decrease in resting pH due to marked shift in bacterial flora[79–82]. Enamel demineralization associated with orthodontic brackets is very rapid. Visible white spot lesions can be witnessed within 4 weeks of treatment.[83] Prevalence of WSLs has been reported in multiple studies, Gorelick et al[84] in 1982 reported that 50% of patients had at least one white spot lesion at the end of the treatment. Boeresma et al[85] in 2005 reported up to 97% of patients developed one or more lesions. Many orthodontic patients don’t comply with adequate oral hygiene measures which include regular tooth brushing and rinsing with fluoridated mouth rinses. Geiger et al[86] reported that less than 15% of orthodontic patients used fluoridated mouth rinses as instructed. Orthodontists are aware of the fluoride releasing properties of RMGIC, and that fluoride protects the enamel from developing white spot lesions[87,88].

2. AIMS AND OBJECTIVES

To our knowledge, no systematic review has been conducted reviewing the literature of the effects of enamel deproteinization on bonding orthodontic brackets. The aim of this project is to systematically review in *vitro* studies assessing the effects of enamel deproteinization on shear bond strength (SBS) and the adhesive remnant index (ARI) of orthodontic brackets bonded with different adhesives.

3. MATERIALS AND METHODS

3.1 Protocol and registration

Reporting of this systematic review was performed in accordance with the PRISMA statement for reporting systematic reviews of health and sciences.[89] , Our protocol was registered with the International Prospective Register of Systematic Review (PROSPERO). Registration number is CRD42022248012.

3.2 Eligibility criteria

The following selection criteria were applied for the review.

Type of studies: Randomized Controlled trials in *vitro.* Clinical trials in *vivo* were excluded.

Type of participants: Extracted human premolars with intact buccal surface, had no cracks, no pretreatment with chemical agents, no caries and absence of congenital or developmental conditions.

Studies with Extracted premolars with cracks, caries, restorations, history of previous orthodontic bonding, history of chemical pretreatment, signs of congenital or developments conditions and non-human teeth (e.g. Bovine teeth) were excluded.

Types of intervention: Enamel deproteinization with 5.25% NaOCl or Papain Gel prior to acid etching in the intervention group. The control group were not pretreated with an enamel deproteinization agent.

Type of outcome measure: Primary outcome is the shear bond strength of orthodontic brackets in Mega Pascal (MPa). Secondary outcome is the adhesive remnant index (ARI).

3.3 Information sources and search

The following electronic databases were systematically searched. PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus and Web of Science™ Core Collection. Grey literature source includes ProQuest Dissertations and Theses Global and the first ten pages from Google scholar If data from the study reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information. If we judged the missing data to render the result uninterpretable we excluded the data from the meta-analysis and clearly stated the reason.

The last search was run on 31st of May 2022th of March 2021. No restrictions were placed on the language, date or status of publication. After removal of all duplicates, articles were screened based on the title and abstract, full text articles were screened in case screening the title and abstract were insufficient to decide. The search was performed independently by two investigators (S.A and S.D.B) and then discussed to reach a common agreement.

The following search terms were used in our search: enamel deproteinization, deproteinization, sodium hypochlorite, NaOCl, papain, orthodontic bracket, bracket, orthodontic appliance, fixed appliance, bond strength, shear strength, shear bond strength, adhesive remnant index, ARI. (Table I)

3.4 Data collection process and data items

Data were extracted independently by two investigators (S.A and S.D.B). Data collection forms were used to record Publication details (authors and year), total teeth number, intervention in both groups, storage medium before bonding and before SBS testing, thermocycling, blade design, cross-head speed and outcome data of interest.

3.5 Risk of bias assessment of individual studies

Initially, our aim was to use a tool for assessing risk of bias in randomized trials specifically in *vitro.* We found a systematic review and meta-analysis[90] in *vitro* published in 2014 in the field of operative dentistry that developed a tool to evaluate the risk of bias according to the articles description of their parameters. Moreover, another systematic review and meta-analysis[91] in *vitro* published in 2016 in the field of pediatric dentistry "Adhesive systems for restoring primary teeth: a systematic review and meta-analysis of in vitro studies" assessed the risk of bias based on and adapted from the tool used in the previous study[90], the parameters assessed were randomization of teeth, materials used according to the manufacturer's instructions, adhesive procedures performed by the same operator, description of sample size calculation, and blinding of the operator of the testing machine. However, after further discussion between the authors, it was decided that this tool was not valid nor robust enough to assess the risk of bias.

Therefore, The Cochrane Collaboration's tool for assessing risk of bias in randomized trial was used to ascertain the validity of these trials. We selected this tool because it's considered both valid and robust to assess the risk of bias in randomized trials since its key domains can all be adequately scored when reading and assessing the included studies.

Two investigators independently determined the adequacy of random sequence generation, allocation concealment, blinding of operators, blinding of outcome assessors, incomplete outcome data, selective reporting of results and other potential sources of bias. The overall risk of bias was judged to be low, unclear or high. An overall low risk of bias is given if all key domains are judged to be at low risk of bias. An overall unclear risk of bias is given if one or more key domains were judged to be at unclear risk of bias. An overall high risk of bias is given if one or more key domains were judged to be at high risk of bias.[92].

3.6 Summary measure

Means difference and 95% confidence intervals (CI) of SBS and ARI were calculated to compare between the intervention group and control group. Meta-Analysis using the random-effect model was performed to estimate the pooled difference of the means and 95% CI. The measure of heterogeneity reported included the Cochran's Q statistics, I^2 index with the level of heterogeneity defined as low< 25, moderate >50, and high> 75, and the tau square (T^2) test. If more than 10 studies were included in the meta-analysis[93], Publication bias was assessed with a funnel plot and the Egger test.

3.7 Planned method of analysis

Statistical pooling of SBS and ARI with their respective 95%confidence interval (95%CI) was done considering different combination of deproteinization agents and adhesives.

For bonding with resin composite, groups bonded with light cured composite with total etch adhesive system were included in the meta-analysis. Bonding using self-etching primer (SEP) was excluded from the meta-analysis because we wanted to avoid inclusion of any trial twice in a single quantitative analysis.

With regards to the deproteinizing agent, Papain gel, groups pretreated with 10% papain were included in the meta-analysis. Groups using 8% papain were excluded due to limited number of studies.

For the etching agent, only 37% phosphoric acid treatment was included in the meta-analysis. Pretreatment with 10% polyacrylic acid, 10% maleic acid and 20% lactic acid were excluded from the meta-analysis due to the limited number of studies that use these agents in their methodology. Moreover, studies involving groups that were exposed to thermocycling with a control group that was not exposed to thermocycling were excluded from the meta-analysis since we considered thermocycling as a confounding variable.

For the ARI, only the 4-point and 5-point scales were included in the meta-analysis as they are the most commonly used scales in the literature. The scoring criteria for the 4-point scale was considered as the following, score 0: no adhesive left on the tooth, score 1: less than half of the adhesive left on the tooth, score 2: more than half of the adhesive left on the tooth and score 3: all the adhesive is left on the tooth. Moreover, for the 5-point scale, the scoring criteria was considered as the following, score 1: all adhesive remained on the tooth with the imprints of the bracket base, score 2: >90% of the adhesive remained on the tooth, score 3: 10% to 90% of the adhesive remained on the tooth, score 4: < 10% of the adhesive remained on the tooth and score 5: no adhesive remained on the tooth.

For the 5- point scale, the scores were reversed to ensure that both the 4-point scale and the 5-point scale are aligned (e.g., low scores that represented little or no adhesive remnant on the tooth surface on a 5-point scale were adjusted so that the scores matched those of the 4-point scale). If the mean and SD of the ARI scale values were not reported in each study for all the included teeth in the groups, it was then calculated and reported for each study.

We investigated potential source of heterogeneity through subgroup analysis: thermocycling (without thermocycling (group A) versus with thermocycling (group B)).

Quality of Evidence assessment: Grade assessment of certainty was determined through considerations of five domains, risk of bias, inconsistency, indirectness, imprecision and publication bias[94].

4. RESULTS

4.1 Study selection

The search provided a total of 167 citations (Fig1). After elimination of the duplicates, 91 articles remained. Of those 91 articles, 64 studies were excluded from the title, 8 studies were excluded after careful reading of the abstract and full texts because of pretreatment done on flourotic enamel,[95,96] bovine teeth[24,25,97,98] and demineralized enamel[99] and one study was done in *vivo.*[100] 19 studies[7,14,22,101–116] met the inclusion criteria and were included in this systematic review. Five trials were excluded from the quantitative synthesis because of reporting of data with the median[116] the author was contacted via an email to check if they had any data available recorded using the mean and the standard deviation, however, there was no response. One study[114] only used GIC as an adhesive, one study[108] only used nano-silver modified resin adhesive, one study[107] bonded the intervention group using SEP only and one study[106] etched the enamel surface of the intervention group with 10% maleic acid and 20% lactic acid only.. Therefore, 14 trials were included in the meta-analysis.

Duplicate information was detected and excluded in the trials published by Trindade et al[113] and Pereira et al[114]. Only non-duplicate information extracted from both trials were included.

4.2 Study characteristics:

4.2.1 Methods

All nineteen studies selected were randomized controlled trials in *vitro* published in English. (Tables II and III)

4.2.2 Participants

Included studies involved 1399 extracted human premolar teeth all fitting the inclusion criteria

4.2.3 Intervention

Description of the different variables used in the study methodology is the following

In regards to *storage medium* before bonding, six studies stored their samples in distilled water[22,101,103,113,115,116], six studies[105,107–110,112] used thymol solution, four studies[7,14,102,104] used saline solution, one study used sodium chloride[111], one study used artificial saliva[114] and one study didn't report it.[106] For storage medium before SBS testing, ten studies[14,22,103,106–108,113–116] used distilled water, four studies[7,102,109,111] used artificial saliva, one study[105] used thymol solution, one study in an incubator[112] and three studies[101,104,110] didn't report it.

For *thermocycling*, only six studies[14,22,101,106,108,112] have done this step for all the specimens, Moreover, one study[110] had a separate intervention group where thermocycling was done, however, the rest of the sample groups didn't undergo thermocycling. In regards to the blade design used to debond the brackets, eight studies[7,106,107,109,110,112,114,115] used a knife blade, two studies[103,113] used a chisel tip, two studies[22,108] used a wire looped around the bracket, two studies[14,104] used a shear probe and five studies[101,102,105,111,116] didn't report it. For the crosshead speed, seven studies[14,22,101,104,106,107,110] had a crosshead speed at 1mm/min, ten studies[7,102,105,108,109,111–115] at 0.5mm/min, one study[103]nat 0.1mm/min and one study[116] and 2.25mm/min.

For the *intervention*, several groups were selected according to the combined deproteinization agent and adhesive protocol used in the studies.

For studies using 5.25%NaOCl with light resin composite compared to light cured resin composite only (using total etch and self-etch adhesive systems); ten studies[7,22,102,105–107,111,112,115,116] with a total of 628 premolars were included. Three of those ten studies[105,111,112] had additional groups were they used self-etch adhesive system using self-etching primer (SEP) and one study[107] used

SEP for all of the intervention groups. One study[107] had three separate groups pretreated with 5.25%NaOCl for 60, 30 and 15 seconds respectively. Nine studies[7,22,102,105,107,111,112,115,116] used 37%phosphoric acid to etch the enamel surface for both the intervention and the control group and only one study[106] used 10%maleic acid and 20%lactic acid for the intervention group, etching with 37%phosphoric acid was done in one of the control groups only.

For studies using 5.25%NaOCl with chemically cured composite compared to chemically cured composite only, one study[102] with a total of 26 premolars was included, 37% phosphoric acid was used to etch the enamel surface.

For studies using 5.25%NaOCl and RMGIC compared to RMGIC only, Five studies[22,101,103,110,113] with a total of 340 premolars were included, all groups used 37% phosphoric acid to etch the enamel surface, however, one study[113] had an additional group etched with 10% polyacrylic acid for both the intervention and the control groups.

For studies using 5.25% NaOCl with RMGIC compared to resin composite only, four studies[22,101,110,113] with a total of 248 premolars were included, all groups used 37% phosphoric acid to etch the enamel surface.

For studies using 5.25% NaOCl with GIC compared to GIC only and resin composite only, one study[114] with a total of 60 premolars was included in this group, 10% polyacrylic acid was used to etch the enamel surface bonded with GIC in both the intervention and the control group, however, 37% phosphoric acid was used to etch the enamel surface bonded with resin composite. For studies comparing 5.25% NaOCl with cyanoacrylate adhesive compared to cyanoacrylate adhesive only, one study[112] with a total of 20 premolars was included, 37% phosphoric acid was used to etch the enamel surface.

For studies using 5.25% NaOCl with nano-silver resin modified adhesive compared to nano-silver resin modified adhesive only, one study[108] with a total of 20 premolars was included, 37% phosphoric acid was used to etch the enamel surface.

For studies using papain with light cured resin composite compared to light cured resin composite only, five studies[7,14,104,109,115] with a total of 235 premolars were included, All the studies used 10% papain gel. However, two studies[104,109] had an additional group pretreated with 8% papain gel. 37%phosphoric acid was used to etch the enamel surface.

Finally, for studies using papain and RMGIC to RMGIC only, one study104 with a total of 45 premolars was included, 10% papain was used and 37% phosphoric acid was used to etch the enamel surface.

4.2.4 Outcomes

4.2.4.1 Primary outcome,

In 18 studies[7,14,22,101–115], the primary outcome was the mean shear bond strength in MPa. The trial by Rivera-Prado et al[116] recorded SBS with the Median in Kg/cm^2, The measurement unit was converted to MPa.

4.2.4.2 Secondary outcomes

In 16 studies7,14,22,102,103,105–113,115 the secondary outcome, ARI, was recorded. Eleven studies used the 4-point scale for assessment7,14,102,110–115. Four studies22,105 used the 5-point scale . One study103 assessed the ARI by the formula: Area of residual resin/ area of the bracket base X 100, the average of two readings was recorded for each specimen.

For magnification, one study assessed the ARI under 20X magnification113, four studies22,103,110,112 under 10X magnification, three studies7,14,115 under 16X magnification, two studies102,111 under 2X magnification, one study114 under 200X using a USB digital microscope, one study106 under 40x magnification and one study107 under 25x magnification and three studies105,108,109 Didn't report the degree of magnification.

4.3 Risk of bias within studies

13 studies were graded with a high risk of bias and 6 studies as Unclear. (Table IV)

Generation of the random sequence was considered adequate in four studies[105,107,108,110]. Allocation concealment was thought to be reliable in three study[107,108,110]. Blinding of operators performing the bonding procedure is highly unlikely, moreover, lack of blinding is unlikely to introduce a risk of bias in the trial. Blinding of assessors was mentioned only in one study[110]. Complete outcome data was reported in all trials. One study scored a high risk of bias in selective reporting, where higher SBS in any control group wasn't adequately reported[105]. Other potential source of bias is when the specimens didn't undergo thermocycling after bonding the brackets. Six studies had all their specimens undergo thermocycling after bonding [14,22,101,106,108,112]

4.4 Risk of bias across the studies

Test for publication bias was not undertaken as no more than 7 studies were included in an individual meta-analysis.

4.5 Results of individual studies

Results of the groups (Tables V, VI, VII, VIII, IX, X, XI and XII) included in the quantitative synthesis are the following.

4.5.1 SBS

A of total 757 premolars were included in the quantitative synthesis (Fig 2). 391 premolars were pretreated with enamel deproteinization (261 with 5.25%NaOCl and 105 with 8% and 10% papain) and 391 without deproteinization. Subgroup analysis involves groups without thermocycling (group A) versus with thermocycling (group B).

For 5.25% NaOCl with light cured resin composite compared to light cured resin composite only using total etch adhesive system (groups 1A and 1B), the overall effects demonstrate no significant difference between both interventions with a mean difference of 0.212 MPa (-0.16- 0.6), *P*=0.27. Low heterogeneity was detected (I^2, 45.9%; *P*=0.086). The test for subgroup differences indicates no statistically significant subgroup effect *P*=0.7.

For 5.25% NaOCl with RMGIC compared to RMGIC only, the overall effects demonstrate no significant difference between both interventions with a mean difference of 0.36MPa (-0.19-0.89), *P*=0.2. Statistically significant high heterogeneity was detected (I^2, 73%; $P<0.05$).

The test for subgroup differences indicates no statistically significant subgroup effect *P*=0.09.

For 5.25% NaOCl with RMGIC compared to light cured resin composite only. The overall effects demonstrates no significant difference between both interventions with a mean difference of -0.7(-1.86-0.47). *P*=0.24. Statistically significant high heterogeneity was detected (I^2, 90%; $P<0.001$). The test for subgroup differences indicates no statistically significant subgroup effect *P*=0.0541.

For 10% Papain gel- light cured composite Vs light cured composite only (4B). A significant mean difference favoring the control group was shown 0.95MPa (0.63 – 1.26) P<0.001. The test for homogeneity confirmed low heterogeneity (I2, 0.00%; P=0.47).

4.5.2 ARI

A of total 655 premolars were included in the quantitative synthesis (Fig 2). 315 premolars were pretreated with enamel deproteinization (225 with 5.25%NaOCl and 90 with 10%Papain) and 340 without deproteinization. Subgroup analysis involves groups without thermocycling (group A) versus with thermocycling (group B).

For 5.25% NaOCl with light cured resin composite compared to light cured resin composite only, the overall effects show no significant difference between both interventions with a mean difference of 0.14(-0.3-0.56), P=0.5, High heterogeneity was detected (I^2, 75%; P=0.4). The test for subgroup differences indicates no statistically significant subgroup effect P=0.9.

For 5.25% NaOCl with RMGIC compared to RMGIC only, the overall effects demonstrate no significant difference between both interventions with a mean difference 0.54 (-0.5-0.1.62), P=0.312. Statistically significant high heterogeneity was detected (I^2, 86%; P<0.001). The test for subgroup differences indicates a statistically significant subgroup effect P=0.004.

For 5.25% NaOCl with RMGIC compared to light cured composite only (3A and 3B groups), the overall effects demonstrate no significant difference between both interventions with a mean difference 0.55 (-0.52 – 1.63) P=0.3. Statistically significant high heterogeneity was detected (I^2, 86%; P<0.001). The test for subgroup differences indicates a statistically significant subgroup effect P=0.0038.

For the 10% Papain gel- light cured composite Vs light cured composite only (4B). The overall effect shows a statistically significant difference favoring the control group with a mean difference of 0.55 (0.23- 0.87), P<0.05. The test for homogeneity confirmed moderate heterogeneity (I^2, 66%; P=0.051).

5. DISCUSSION

5.1 Summary of evidence

19 studies were included in the systematic review. 14 studies were included in the quantitative synthesis.

When reviewing the trials, there were some differences in several variables that may affect the measured bond strength. Generally, these variables are type of tooth, thermocycling, fluoride content of the tooth, disinfection and storage medium of the tooth and crosshead speed of mechanical testing. Unfortunately, this highlights a lack of a standardized testing protocol for orthodontic bond strength measurements. We tried to standardize these variables as we could to minimize any bias in our results. For type of teeth, only extracted human premolar teeth were included. For the fluoride content, extracted teeth with fluorosis were excluded in our search. For other variables, it was generally difficult to avoid inclusion of studies without some differences in these variables, in which most of them have mixed conclusions in the literature regarding their effect on bond strength testing results. For storage medium, a meta-analysis by Finnema et al[117] in 2010 showed that water storage decreased bond strength values by 10.7 MPa on average, however, they reported that this finding was influenced by one large study sample in which artificial saliva was the storage medium[118]. One report showed that artificial saliva decreases the bond strength values similar to the effect of water degredation.[119] Muhlemann et al[120] in 1964 showed that saline solution tend to soften the enamel more than distilled water and that sodium chloride solutions (5-20%) didn’t show any hardness reducing effect. other reports concluded that isotonic saline solution and distilled water can be safely recommended as storage medium and that dry, formalin and ethanol storage should be avoided.[121,122] For cross head speed, the meta-analysis by Finnema et al[117] showed that an increase in cross head speed of 1mm/min resulted in an increase in the average bond strength by 1.3MPa. other reports showed an opposite effect.[123,124] while one report showed that cross head speed variation between 0.1 and 5 had no effect on the bond strength[125]. There is no clear explanation for the discrepancy of these results, several unknown confounding factors might be responsible. However, only thermocycling had a solid conclusion in the literature. It was shown that thermocycling reduces the bond strength of orthodontic brackets because it simulates the temperature dynamics in the oral environment.[126–129]. Bishara et al[129] recommended that thermocycling should be part in any methodology testing shear bond strength of any adhesive.

The trials were divided according to the deproteinization agents used (5.25% NaOCl and 10% Papain) and adhesives used to accurately assess the effect of deproteinization on resin composite and RMGIC respectively. A subgroup analysis was done to assess the magnitude of effect of thermocycling on SBS and ARI

For SBS, the quantitative synthesis showed that enamel deproteinization with 5.25% NaOCl generally doesn't improve SBS of orthodontic brackets bonded with either resin composite or RMGIC, Interestingly, it was found that for group 2 (5.25%NaOCl RMGIC VS RMGIC only), mean SBS for both intervention and control groups were similar, While for group 3 (5.25% NaOCl RMGIC Vs resin composite only), SBS values were comparable showing that 5.25%NaOCl increases SBS values for RMGIC to the level of resin composite. These results can be explained by the high heterogeneity within these groups. Therefore, the validity of treatment effect for 5.25%NaOCl on SBS is uncertain due to inconsistency. These results show that there is no clear advantage of enamel deproteinization to improve SBS when bonding. There was no clear subgroup effect reported, meaning that thermocycling doesn't modify the intervention with deproteinization compared to the control. However, the small number of trials and samples in one or both of the groups (A and B) may not show a true subgroup effect. Moreover, significantly high heterogeneity within several groups may render their results to be meaningless. Therefore, this subgroup analysis is unable to show the true effect of thermocycling on SBS values.

For ARI, the quantitative synthesis shows no clear advantage of enamel deproteinization with 5.25%NaOCl or 10% Papain compared to the control. The only positive result was found in group 3 (5%NaOCl RMGIC Vs resin composite only) were the ARI were comparable showing that 5.25%NaOCl increases SBS values for RMGIC to the level of resin composite, however, significantly high heterogeneity makes their validity uncertain due to inconsistency. For the subgroup analysis, the same conclusion as with SBS results was shown. Clinically, the choice of bonding modality is using total etch or self-etch adhesive system with resin composite as an adhesive. Studies assessing the effect of Enamel deproteinization were done with the aim to assess whether a higher SBS and ARI with bonding can be obtained. Our result show that for SBS, there is no clear advantage of enamel deproteinization with 5.25%NaOCl or Papain and that debonding rate will not be affected. Moreover, our results don't encourage clinicians to bond with RMGIC with enamel deproteinization to reduce white spot lesions due to low SBS of RMGIC compared to resin composite, adequate oral hygiene measures is still considered the most appropriate way to reduce incidence of white spot lesions. In regards to ARI, our results show that there is no clear advantage of enamel deproteinization to increase the ARI scores, meaning that enamel deproteinization doesn't increase the amount of adhesive remaining on the tooth surface after debonding, indicating that adhesion strength is not significantly affected with enamel deproteinization.

For the grade assessment of certainty, the level of evidence is very low indicating caution regarding the strength of the evidence presented.

5.2 Limitations

The impact of bias on the outcome of systematic reviews is well documented[130]. Unfortunately, most of the studies were scored with a high risk of bias with only 6 studies[14,22,101,106,108,112] with unclear risk of bias. Most of the studies scored a high risk of bias due to absence of thermocycling in their testing protocol. We considered thermocycling an essential step in SBS testing protocol due to the solid evidence shown on its effect on reducing SBS[126–129], and its absence renders the study to be at high risk of bias.

The lack of a standardized testing protocol for orthodontic bond strength measurements in our included articles may make it difficult to draw conclusions from such studies. Moreover, significantly high heterogeneity within each group may render drawing valid conclusions.

6. CONCLUSION

1. There is no strong evidence that enamel deproteinization improves SBS and ARI of orthodontic brackets bonded with resin composite or RMGIC

2. A standardized testing protocol for orthodontic bond strength measurements is urgently needed to draw valid and confident conclusions

3. High quality randomized controlled trials in *vitro* Investigating the effects of enamel deproteinization on bonding orthodontic brackets are needed to assess the true effect of this technique

4. In absence of clear evidence favoring deproteinization, the choice of bonding modality remains either total etch or self-etch adhesive system and bonding with resin composite.

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Table I. search strategy

Database [2022 05 31]	Search strategy	Hits
General Sources		
PubMed http://www.ncbi.nlm.nih.gov/pubmed	("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR "bracket*" OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI)	**18**
Cochrane Central Register of Controlled Trials http://onlinelibrary.wiley.com/cochranelibrary/search	("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR bracket* OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI) in Record Title OR ("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR bracket* OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI) in Abstract - (Word variations have been searched)	**1**
Cochrane Database of Systematic Reviews http://onlinelibrary.wiley.com/cochranelibrary/search	("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR bracket* OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI) in Record Title OR ("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR bracket* OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI) in Abstract - (Word variations have been searched)	**0**
Scopus https://www.scopus.com/search/form.url?zone=TopNavBar&origin=searchbasic	TITLE-ABS-KEY (("enamel deproteinization" OR deproteinization OR "sodium hypochlorite" OR naocl OR papain) AND ("orthodontic bracket" OR bracket OR "orthodontic appliance" OR "fixed appliance") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ari))	**25**
Web of Science™ Core Collection http://apps.webofknowledge.com/	TOPIC: (("enamel deproteinization" OR "deproteinization" OR "sodium hypochlorite" OR NaOCl OR "papain") AND ("orthodontic bracket*" OR bracket* OR "orthodontic appliance*" OR "fixed appliance*") AND ("bond strength" OR "shear strength" OR "shear bond strength" OR "adhesive remnant index" OR ARI)) Timespan: All years. Databases: WOS, KJD, RSCI, SCIELO, ZOOREC. Search language=Auto	**21**

Table II. Summary of study characteristics

Study	Total teeth number	Intervention Vs. Control		Storage medium before bonding	Storage medium before SBS testing	Thermocycling	Blade design	Cross head speed	Outcome
		Intervention group Deproteinization agent Adhesive Etching agent Sample size	Control group Adhesive Etching agent Sample size						
Justus et al 2010	76	1- 5.25% NaOCl light cured resin composite (37%PA) n=19 2- 5.25% NaOCl RMGIC (37%PA) n=19	1- light cured resin composite only (37%PA) n=19 2- light cured resin composite only (37%PA) n=19	Distilled water	Distilled water	500 cycles between 5°C and 55°C	wire looped around the bracket	1mm/min	SBS and ARI
Ghoubril et al 2020	90	1- 5.25% NaOCl RMGIC (37%PA) n=30	1- light cured resin composite only (37%PA) n=30	1%thymol water	Not reported	None	Knife blade	1mm/min	SBS and ARI

		2- 5.25% NaOCl RMGIC (37%PA) n=30	2- RMGIC only (37%PA) n=30							
Trindade et al 2013	100	1- 5.25% NaOCl RMGIC (37%PA) n=20 2- 5.25% NaOCl RMGIC (37%PA) n=20 3- 5.25% NaOCl RMGIC (10%PAA) n=20 4- 5.25% NaOCl RMGIC (10%PAA) n=20	1- light cured resin composite only (37%PA) n=20 2- RMGIC only (37%PA) n=20 3- light cured resin composite only (37%PA) n=20 4- RMGIC only (10%PAA) n=20	Distilled water	Distilled water	None		Chisel tip	0.5mm/min	SBS and ARI

Elnafar et al 2014	72	1- 5.25% NaOCl RMGIC (37%PA) n=36	1- RMGIC only (37%PA) n=36	Distilled water	Distilled water	None	Chisel tip	0.1mm/min	SBS
Hamdane et al 2017	90	1- 5.25% NaOCl RMGIC (37%PA) n=30 2- 5.25% NaOCl RMGIC (37%PA) n=30	1- light cured resin composite only (37%PA) n=30 2- RMGIC only (37%PA) n=30	Distilled water	Not reported	500 cycles between 5°C and 55°C	Not reporte d	1mm/min	SBS and ARI
Mahmoud et al 2019	60	1- 5.25% NaOCl light cured resin composite (37%PA) n=10 2- 5.25% NaOCl light cured resin composite (SEP) n=10	1- light cured resin composite only (37%PA) n=10 2- light cured resin composite only (SEP) n=10	1% thymol solution	incubator	500 cycles between 5°C and 55°C	Knife blade	0.5mm/min	SBS and ARI

		3- 5.25% NaOCl cyanoacrylate adhesive (37%PA) n=10	3- cyanoacrylate adhesive only (37%PA) n=10						
Panchal et al 2019	90	1- 5.25% NaOCl light cured resin composite (37%PA) n=30 2- 10%Papain light cured resin composite (37%PA) n=30	1- light cured resin composite only (37%PA) n=30 2- light cured resin composite only (37%PA) n=30	saline solution	artificial saliva	None	Knife blade	0.5mm/min	SBS and ARI
Sharma et al 2020	75	1- 5.25% NaOCl light cured resin composite (37%PA) n=25 2- 10%Papain light cured	1- light cured resin composite only (37%PA) n=25 2- light cured resin composite	Distilled water	Distilled water	None	Knife blade	0.5mm/min	SBS and ARI

		resin composite (37%PA) n=25	only (37%PA) n=25						
Salim et al 2017	52	1- 5.25% NaOCl light cured resin composite (37%PA) n=13 2- 5.25% NaOCl chemically cured resin composite (37%PA) n=13	1- light cured resin composite only (37%PA) n=13 2- chemically cured resin composite only (37%PA) n=13	saline solution	artificial saliva	None	Not reporte d	0.5mm/min	SBS and ARI
Ongkowidj aja et al 2017	48	1- 5.25% NaOCl light cured resin composite (37%PA) n=12 2- 5.25% NaOCl light cured resin composite (SEP) n=12	1- light cured resin composite only (37%PA) n=12 2- light cured resin composite only (SEP) n=12	sodium chloride	artificial saliva	None	Not reporte d	0.5mm/min	SBS and ARI

Grabouski, J 2016	66	1- 5.25% NaOCl light cured resin composite (37%PA) n=17 2- 5.25% NaOCl light cured resin composite (SEP) n=15	1- light cured resin composite only (37%PA) n=17 2- light cured resin composite only (SEP) n=17	0.2%thymol and distilled water	thymol solution	None	Not reported	0.5mm/min	SBS and ARI
Rivera-Prado et al 2015	50	1- 5.25% NaOCl light cured resin composite (37%PA) n=25	1- light cured resin composite only (37%PA) n=25	Bidistilled water	Bidistilled water	None	Not reported	2.25mm/min	SBS
Agarwal et al 2015	50	1- 10%Papain light cured resin composite (37%PA) n=25	1- light cured resin composite only (37%PA) n=25	Saline with thymol crystals	Distilled water	500 cycles between 5°C and 55°C	Shear probe	1 mm/min	SBS and ARI
Rajkumar, R 2015	90	1- 10%Papain light cured resin composite (37%PA)	1- light cured resin composite only (37%PA) n=15	isotonic saline	Not reported	none	Shear blade	1mm/min	SBS

		n=15							
		2- 8%Papain light cured resin composite (37%PA) n=15	2- light cured resin composite only (37%PA) n=15						
		3- 10%Papain RMGIC (37%PA) n=15	3- RMGIC only (37%PA) n=15						
		4- 8%Papain RMGIC (37%PA) n=15	4- RMGIC only (37%PA) n=15						
		5- 10%Papain RMGIC (37%PA) n=15	5- light cured resin composite only (37%PA) n=15						
		6- 8%Papain RMGIC (37%PA) n=15	6- light cured resin composite						

			only (37%PA) n=15						
Pereira et al 2013	60	1- 5.25% NaOCl GIC (10%PAA) n=20 2- 5.25% NaOCl GIC (10%PAA) n=20	1- GIC only (10%PAA) n=20 2- light cured resin composite only (37%PA) n=20	Artificial saliva	Distilled water	None	Knife blade	0.5mm/min	SBS and ARI
Daou et al 2021	125	1- 5.25% NaOCl (60 sec) light cured resin composite (SEP) n=25 2- 5.25% NaOCl (30 sec) light cured resin composite (SEP) n=25	1- light cured resin composite only (37%PA) n=25 2- light cured resin composite only (37%PA) n=25	0.1% thymol solution	Distilled water		Knife blade	1mm/min	SBS and ARI

		3- 5.25% NaOCl (15 sec) light cured resin composite (SEP) n=25 4- 5.25% NaOCl (60 sec) light cured resin composite (SEP) n=25 5- 5.25% NaOCl (30 sec) light cured resin composite (SEP) n=25 6- 5.25% NaOCl (15 sec) light cured resin composite (SEP) n=25	3- light cured resin composite only (37%PA) n=25 4- light cured resin composite only (SEP) n=25 5- light cured resin composite only (SEP) n=25 6- light cured resin composite only (SEP) n=25						

Qadri, 2017	30	1- 8% Papain light cured resin composite (37%PA) n=10 2- 10% Papain light cured resin composite (37%PA) n=10	1- light cured resin composite only(37%PA) n=10 2- light cured resin composite only(37%PA) n=10	0.1%thymol solution	Artificial saliva	None	Knife blade	0.5mmlmin	SBS and ARI
Sharma et al 2020	125	1- 5.25% NaOCl light cured resin composite (10%MA) n=25 2- 5.25% NaOCl light cured resin composite (20%LA) n=25 3- 5.25% NaOCl light cured resin composite (10%MA)	1- light cured resin composite only(37%PA) n=25 2- light cured resin composite only(37%PA) n=25 3- light cured resin composite only (10%MA)	Not reported	Distilled water with 0.1% thymol solution.	500 cycles between 5°C and 55°C	Knife blade	1mm/min	SBS and ARI

		n=25 4- 5.25% NaOCl light cured resin composite (10%MA) n=25 5- 5.25% NaOCl light cured resin composite (20%LA) n=25 6- 5.25% NaOCl light cured resin composite (20%LA) n=25	n=25 4- light cured resin composite only (20%LA) n=25 5- light cured resin composite only(10% MA) n=25 6- light cured resin composite only(20%L A) n=25						
Elhiny & El-Refai 2021	20	1- 5.25% NaOCl Nano-silver modified resin adhesive (37%PA) n=10	1- Nano-silver modified resin adhesive (37%PA) n=10	0.025%thymol solution	Distilled water	6000 cycles between 5°C and 55°C	A 020” stainless steel wire	0.5mm/min	SBS and ARI

NaOCl: Sodium hypochlorite

PA: Phosphoric acid

PAA: Polyacrylic acid

MA: Maleic acid

LA: Lactic acid

SEP: Self-etch primer

Sec: seconds

°C: Celsius

*: only these specimens were exposed to thermocycling, the other specimens were not exposed

°C: Celsius

Table III. Summary of study characteristics (degree of magnification) and ARI scoring system used

Study	magnification	ARI scoring system
Ghoubril et al 2020	10x under optical microscope	0-3*
Ongkowidjaja et al 2017	2x under stereomicroscope	0-3
Mahmoud et al 2019	10x under stereomicroscope	0-3
Justus et al 2010	10x under stereomicroscope	1-5**
Trindade et al 2013	20x under digital Microscope	0-3
Elnafar et al., 2014	10x under stereomicroscope	Area of residual resin/ area of the bracket base X 100% (average of 2 readings)
Panchal et al 2019	16x under stereomicroscope	0-3
Agarwal et al 2015	16x under stereomicroscope	0-3
Pereira et al 2013	Microscopically photographed at 200x using a USB Digital Microscope	0-3
Sharma et al 2020	16x under stereomicroscope	0-3
Salim et al 2017	2x under stereomicroscope	0-3
Grabouski, J 2016	Stereomicroscopy (magnification not reported)	1-5
Daou et al 2021	25x under a dental microscope	0-3*
Qadri, 2017	Not reported	0-3*
Sharma et al 2020	40x under stereomicroscope	1-5**
Elhiny & El-Refai 2021	Not reported	1-5**

*: Adhesive remnant index scoring criteria:

0: no adhesive left on the enamel

1: less than half of the adhesive left on the enamel
2: more than half of the adhesive left on the enamel
3: all of the adhesive remained on the enamel surface

**: Modified adhesive remnant index (5-point scale) scoring criteria: (after the scores were reversed)
1: no adhesive remained on the tooth
2: < 10% of the adhesive remained on the tooth
3: 10% to 90% of the adhesive remained on the tooth
4: >90% of the adhesive remained on the tooth
5: all adhesive remained on the tooth with the imprints of the bracket base

Table IV. Risk of bias within studies

Study	random sequence	Allocation concealment	blinding of the operator performing the bonding	blinding of outcome assessment	incomplete outcome data	selective reporting	Other bias	Final Grade
Ghoubril et al 2020	Low	Low	Low	Low	Low	Low	High	High
Ongkowidjaja et al 2017	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Mahmoud et al 2019	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Trindade et al 2013	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Panchal et al 2019	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Pereira et al 2013	Unclear	Unclear	Low	Unclear	Low	Low	High	High

Sharma et al 2020	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Rivera-Prado et al 2015	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Agarwal et al 2015	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Hamdane et al 2017	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Justus et al 2010	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Salim et al 2017	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Elnafar et al 2014	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Rajkumar, R 2015	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Grabouski, J 2016	Low	Unclear	Low	Unclear	Low	High	High	High
Daou et al 2021	Low	Low	Low	Unclear	Low	Low	High	High
Qadri, 2017	Unclear	Unclear	Low	Unclear	Low	Low	High	High
Sharma et al 2020	Unclear	Unclear	Low	Unclear	Low	Low	Low	Unclear
Elhiny & El-Refai 2021	Low	Low	Low	Unclear	Low	Low	Low	Unclear

Table V. Mean and SD SBS for Group 1 (5.25%NaOCl- light cured composite Vs light cured composite only)

Group 1	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 1A 5.25%NaOCl with light cured composite Vs light cured composite only (without thermocycling)	Panchal et al 2019	60	21.98	6.68	17.47	5.98
	Sharma et al 2020	50	16.33	5.79	13.23	4.73
	Salim et al 2017	26	13.05	2.35	14.36	2.9
	Ongkowidjaja et al 2017	24	13.06	3.66	12.91	3.99
	Grabouski, J 2016	34	16.75	4.36	18.44	5.81
Group 1B 5.25%NaOCl with light cured composite Vs light cured composite only (with thermocycling)	Justus et al 2010	38	9.41	4.46	8.12	3.1
	Mahmoud et al 2019	20	14.54	2.76	13.48	2.79

Table VI. Mean and SD SBS for Group 2 (5.25%NaOCl- RMGIC Vs RMGIC only)

Group 2	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 2A 5.25%NaOCl with RMGIC Vs RMGIC only (without thermocycling)	Ghoubril et al 2020	60	8.25	4.63	6.88	3.59
	Trindade et al 2013	40	5	2.49	6.72	2.31
	Elnafar et al 2014	72	17	5.37	13.86	4.41
Group 2B 5.25%NaOCl with RMGIC Vs RMGIC only (with thermocycling)	Justus et al 2010	38	9.64	5.01	5.71	3.87
	Hamdane et al 2017	60	9.57	3.26	8.14	2.1

Table VII. Mean and SD SBS for Group 3 (5.25%NaOCl- RMGIC Vs light cured composite only only)

Group 3	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 3A 5.25%NaOCl with RMGIC Vs light cured composite only (without thermocycling)	Ghoubril et al 2020	60	8.25	4.63	8.93	3.82
	Trindade et al 2013	40	5	2.49	17.08	6.39
Group 3B 5.25%NaOCl with RMGIC Vs light cured composite only (with thermocycling)	Justus et al 2010	38	9.64	5.01	8.12	3.1
	Hamdane et al 2017	60	9.57	3.26	11.33	2.6

Table VIII. Mean and SD SBS for Group 4 (10% papain gel- light cured composite Vs light cured composite only)

Group 4	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 4B 10% papain gel with light cured composite Vs light cured composite only	Panchal et al 2019	60	25.73	8.87	17.47	5.98
	Sharma et al 2020	50	18.58	6.25	13.23	4.73
	Rajkumar, R 2015	30	18.35	2.35	16.04	1.34
	Agarwal et al 2015	50	36.88	7.96	29.77	6.51

Table IX. Mean and SD ARI for Group 1 (5.25%NaOCl- light cured composite Vs light cured composite only)

Group 1	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 1A 5.25%NaOCl- with light cured composite Vs light cured composite only (without thermocycling)	Panchal et al 2019	60	2.53	0.79	2.17	0.73
	Sharma et al 2020	50	1.8	1	1.6	0.957
	Salim et al 2017	26	1.846	0.8	1.6	0.65
	Ongkowidjaja et al 2017	24	1.3	0.778	0.916	0.67
	Grabouski, J 2016	34	3.06	0.66	3.06	0.43
Group 1B 5.25%NaOCl with light cured composite Vs light cured composite only (with thermocycling)	Justus et al 2010	38	3.17	1.54	3.74	1.1
	Mahmoud et al 2019	20	2.4	0.7	2.1	0.74

Table X. Mean and SD ARI for Group 2 (5.25%NaOCl- RMGIC Vs RMGIC only)

Group 2	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 2A 5.25%NaOCl with RMGIC Vs RMGIC only (without thermocycling)	Ghoubril et al 2020	60	1.3	0.53	1.4	0.67
	Trindade et al 2013	40	2.5	0.76	2.35	0.745
Group 2B 5.25%NaOCl with RMGIC Vs RMGIC only (with thermocycling)	Justus et al 2010	38	3.05	0.78	1.68	0.58
	Hamdane et al 2017	60	3.5	1.2	3.1	1.155

Table XI. Mean and SD ARI for Group 3 (5.25%NaOCl- RMGIC Vs light cured composite only only)

Group 3	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 3A 5.25%NaOCl with RMGIC Vs light cured composite only (without thermocycling)	Ghoubril et al 2020	60	1.3	0.5	1.93	0.78
	Trindade et al 2013	40	2.5	0.76	2.35	0.81
Group 3B 5.25%NaOCl with RMGIC Vs light cured composite only (with thermocycling)	Justus et al 2010	38	3.05	0.78	3.7	1.1
	Hamdane et al 2017	60	3.5	1.2	3.9	1.1

Table XII. Mean and SD ARI for Group 4 (10% papain gel- light cured composite Vs light cured composite only)

Group 4	Study	Sample size	SBS Mean intervention	SD intervention	SBS Mean control	SD control
Group 4B 10% papain gel with light cured composite Vs light cured composite only	Panchal et al 2019	60	2.73	0.58	2.17	0.73
	Sharma et al 2020	50	1.96	0.9	1.6	0.96
	Agarwal et al 2015	50	2.28	0.737	2.16	0.8

Figure 1. Flow of records through the reviewing process.

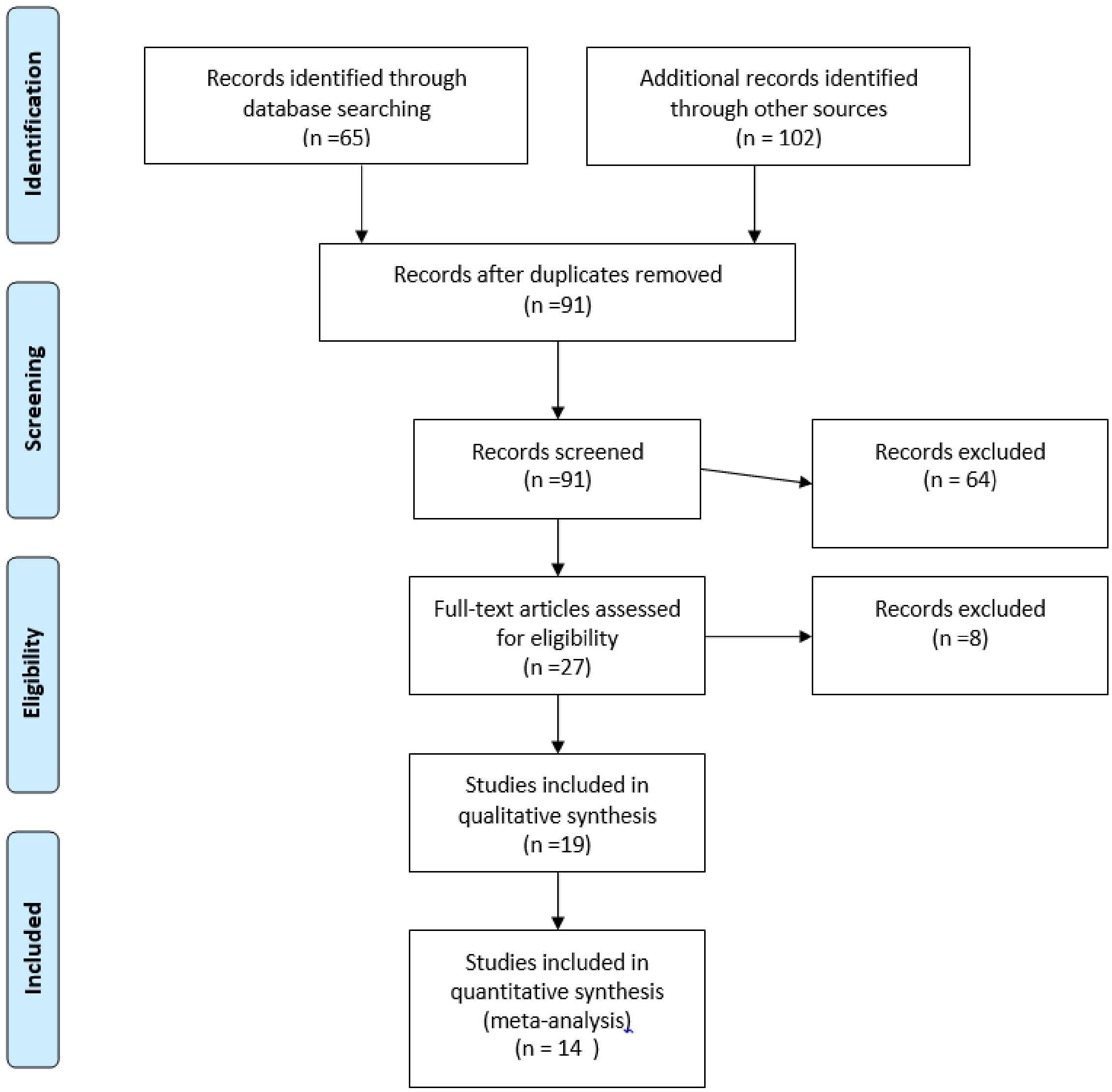
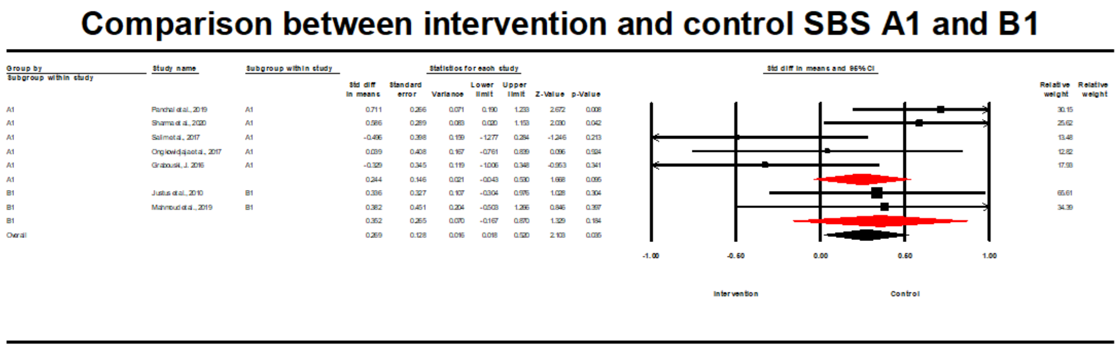
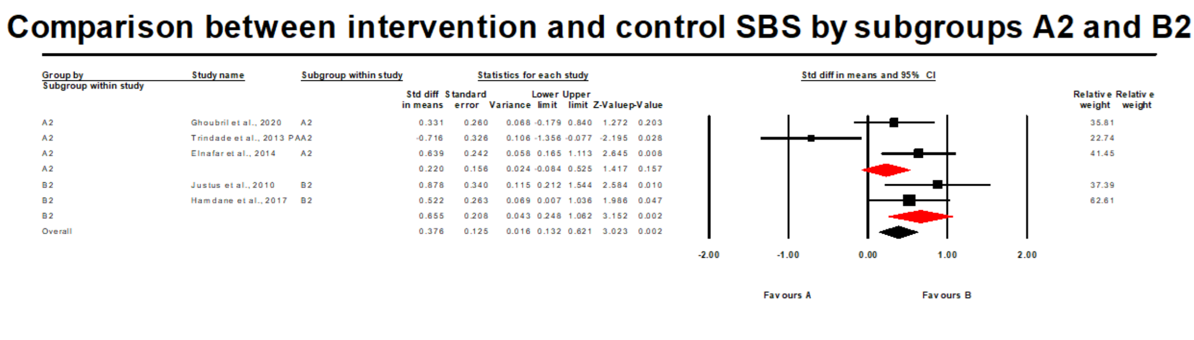


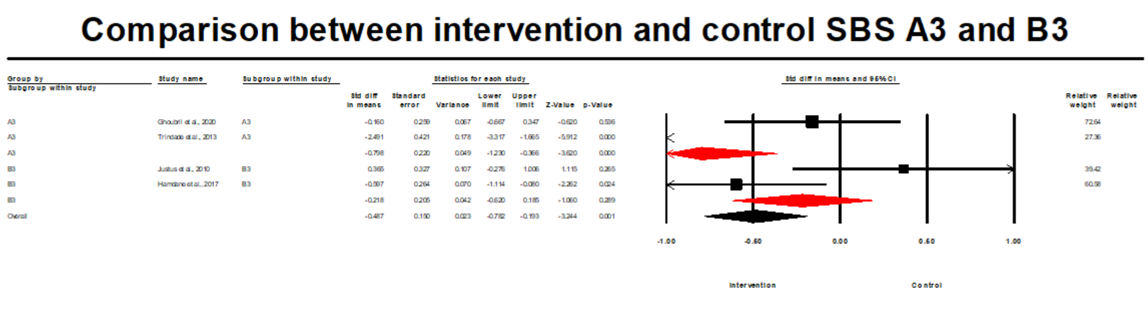
Figure 2. Forest Plot for each individual meta-analysis



A1 & B1 SBS



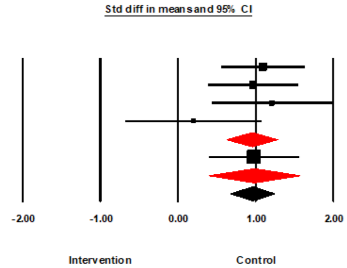
SBS A2 & B2



A3 & B3 SBS

Comparison between intervention and control SBS by subgroups A4 and B4

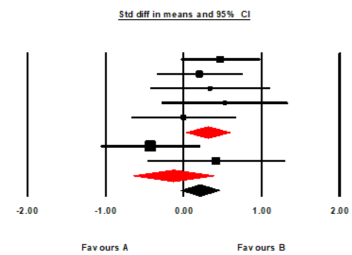
Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
A4	Panchal et al., 2019	A4	1.092	0.277	0.077	0.550	1.634	3.945	0.000	36.70	
A4	Sharma et al., 2020	A4	0.965	0.299	0.089	0.380	1.551	3.230	0.001	31.48	
A4	Rajkumar.R., 2019	A4	1.208	0.397	0.158	0.429	1.986	3.042	0.002	17.83	
A4	Qadri, 2017	A4	0.196	0.448	0.201	-0.683	1.075	0.437	0.662	13.99	
A4			0.947	0.168	0.028	0.619	1.276	5.650	0.000		
B4	Agarwal et al., 2015	B4	0.978	0.299	0.090	0.391	1.564	3.267	0.001	100.00	
B4			0.978	0.299	0.090	0.391	1.564	3.267	0.001		
Overall			0.955	0.146	0.021	0.668	1.241	6.526	0.000		



SBS A4 & B4

Comparison between intervention and control ARI by subgroups A1 and B1

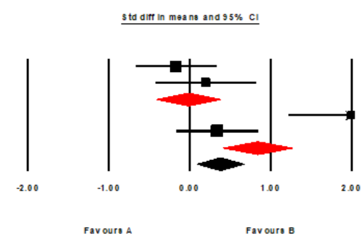
Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
A1	Panchal et al., 2019	A1	0.473	0.262	0.069	-0.040	0.986	1.808	0.071	30.57	
A1	Sharma et al., 2020	A1	0.204	0.284	0.080	-0.351	0.760	0.721	0.471	26.05	
A1	Salim et al., 2017	A1	0.338	0.395	0.156	-0.437	1.112	0.854	0.393	13.43	
A1	Ongkowidjaja et al., 2017	A1	0.529	0.415	0.172	-0.285	1.343	1.274	0.203	12.15	
A1	Grabouski, J. 2016	A1	0.000	0.343	0.118	-0.672	0.672	0.000	1.000	17.81	
A1			0.307	0.145	0.021	0.024	0.591	2.124	0.034		
B1	Justus et al., 2010	B1	-0.426	0.328	0.108	-1.069	0.217	-1.298	0.194	65.50	
B1	Mahmoud et al., 2019	B1	0.417	0.452	0.204	-0.469	1.302	0.921	0.357	34.50	
B1			-0.135	0.266	0.071	-0.656	0.385	-0.509	0.610		
Overall			0.206	0.127	0.016	-0.043	0.455	1.621	0.105		



ARI A1 & B1

Comparison between intervention and control ARI by subgroups A2 and B2

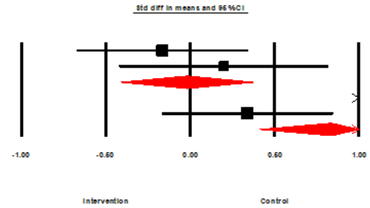
Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
A2	Ghoubril et al., 2020	A2	-0.166	0.259	0.067	-0.672	0.341	-0.640	0.522	60.04	
A2	Trindade et al., 2013	A2	0.199	0.317	0.100	-0.422	0.821	0.629	0.530	39.96	
A2			-0.020	0.200	0.040	-0.413	0.373	-0.098	0.922		
B2	Justus et al., 2010	B2	1.993	0.397	0.158	1.215	2.771	5.022	0.000	30.03	
B2	Hamdane et al., 2017	B2	0.340	0.260	0.068	-0.170	0.849	1.306	0.192	69.97	
B2			0.836	0.218	0.047	0.410	1.263	3.845	0.000		
Overall			0.373	0.147	0.022	0.084	0.662	2.533	0.011		



ARI A2 & B2

Comparison between intervention and control ARI A3 and B3

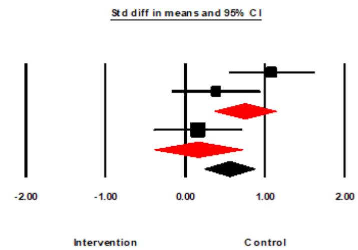
Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
A3	Ghoubril et al., 2020	A3	-0.166	0.259	0.067	-0.672	0.341	-0.640	0.522	60.04	
A3	Trindade et al., 2013	A3	0.199	0.317	0.100	-0.422	0.821	0.629	0.530	39.96	
A3			-0.020	0.200	0.040	-0.413	0.373	-0.098	0.922		
B3	Justus et al., 2010	B3	1.993	0.397	0.158	1.215	2.771	5.022	0.000	30.03	
B3	Hamdane et al., 2017	B3	0.340	0.260	0.068	-0.170	0.849	1.306	0.192	69.97	
B3			0.836	0.218	0.047	0.410	1.263	3.845	0.000		



A3 & B3 ARI

Comparison between intervention and control ARI by subgroups A4 and B4

Group by Subgroup within study	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
A4	Panchal et al., 2019	A4	1.081	0.276	0.076	0.540	1.623	3.912	0.000	51.61	
A4	Sharma et al., 2020	A4	0.387	0.285	0.081	-0.173	0.946	1.355	0.175	48.39	
A4			0.745	0.199	0.039	0.356	1.135	3.753	0.000		
B4	Agarwal et al., 2015	B4	0.156	0.283	0.080	-0.399	0.711	0.551	0.582	100.00	
B4			0.156	0.283	0.080	-0.399	0.711	0.551	0.582		
Overall			0.551	0.163	0.026	0.232	0.870	3.390	0.001		



ARI A4 & B4