ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)
IJDSIR : Dental Publication Service
Available Online at:www.ijdsir.com
Volume – 7, Issue – 4, August – 2024, Page No. : 239 - 247

Evaluation of the Effect of Various Dentin Bio-Modifications and Matrix Metalloproteinase (MMP) Inhibitors on Dentin Bonding to Adhesives- A Systematic Review

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Citation of this Article: Ms. Saaransh Handa, Ms. Mannat Kaur, "Evaluation of the Effect of Various Dentin Bio-Modifications and Matrix Metalloproteinase (MMP) Inhibitors on Dentin Bonding to Adhesives- A Systematic Review", IJDSIR- August – 2024, Volume –7, Issue - 4, P. No. 239 – 247.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Aim: To assess and evaluate the effect of various dentin bio-modifications and matrix metalloproteinase (MMP) inhibitors on dentin bonding to adhesives

Methods: Review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Electronic databases were searched from January 2000 to December 2023 for studies evaluating the effect of various dentin bio modifications and MMP inhibitors on dentin bonding. Quality assessment was evaluated using Cochrane risk of bias (ROB) -2 tool for randomized controlled trials (RCT) through its domains using Review manager (Rev Man) software version 5.3. The standardized mean difference (SMD) was used as summary statistic measure with random effect model ($p<0.05$).

Results: Sixteen studies fulfilled the eligibility criteria and were included in qualitative synthesis. Quality assessment revealed a moderate to low risk of bias. A variety of dentin modifiers and MMP inhibitors were included in review, of which 2% chlorhexidine and benzalkonium chloride being the most studied in twelve and five studies respectively. The pooled estimate through SMD suggested that 2% CHX 2.28 (-3.69 – 0.03) and BAC 2.50 (-7.80 – 2.79) had an overall greater detin bonding compared to other control measures used, however a statistical significance ($p<0.01$) was observed with CHX.

Conclusion: It was observed that PLGS showed continuous and better antibacterial property, greater

dentinal tubules penetration and showed a significant overall greater microbial load reduction.

Keywords: Shear Dentin Bonding, Systematic Review

Introduction

The complexity of dentin structure presents a significant obstacle to the endurance of composite resin restorations. Dentin is mostly composed of type I fibrillar collagen, which has qualities that provide tissue protection and improve adhesion by cross-linking, making the fibril resistant to degradation and keeping everything in place.[1] Other non-collagenous proteins include the majority of proteoglycans found in dentin tissue, as well as endogenous proteases such matrix metalloproteinases.[2,3] Current restoration approaches rely on the electrical components of the adhesive penetrating partially or completely into the demineralized collagen fibers that make up the dentin's organic matrix.[4] The hybrid layer is a mixture of four dentin polymers.[5] Too much monomer inclusion in the hydrophilic adhesive system, high water concentrations during bonding, insufficient monomer penetration for demineralized collagen, and so on. Many reasons might induce a decrease in dentin adhesion and degradation of the hybrid layer.[6] Water in the composite layer hydrolyses monomers and does not protect collagen fibres.[7-9] MMPs and other endogenous proteases target unfiltered and exposed collagen cells.[10] As a result, approaches such as dentin biomodification and the use of MMP inhibitors to improve the characteristics of composite materials have garnered increased attention as substrate materials have improved, and they are critical for extending the life of the dentin-resin bond.[11] Currently, significant expenditures are being employed in place of composites, which have a lifespan of 5 to 8 years.[12,13] This novel method to dental treatment employs synthetic bio-modifiers or natural products[8,14] to increase the ability to link collagen fibers, hence enhancing biomechanics and minimizing biodegradation.[8] Dentin biomodification is a relatively unknown method in dental care. As a result, it will provide a review of the most effective methods and solutions for increasing treatment stability while lowering cytotoxic effects. Studies have demonstrated that the adhesive-dentin bond degrades over time. Dentin adhesion decreases when the hybrid layer degrades.[11,12] The composite layer consists of joint regions created by dentin collagen matrix and resin adhesive. When exposed to acid (etch-and-rinse adhesives) or acidic monomers (self-etch adhesives), the demineralized dentin collagen matrix penetrates the adhesive.[13,14] Endogenous collagenolytic enzymes cause enzymatic destruction of the collagen matrix. Enzymes, matrix metalloproteinases (MMPs), and this enzyme all play critical roles in contraction.[12] MMP inhibitors can inhibit the action of these enzymes; the most researched are chlorhexidine (CHX), galatine, and benzalkonium chloride.15Recently, collagen cross-linkers have been found to block proteases. Looking through the evidence, no study has offered a complete, quantitative, and comparative review of the influence or effect of various dentin bio modifications and MMP inhibitors on dentin bonding. As a result, we updated our research for relevant articles and conducted a systematic review with the goal of providing an updated systematic assessment of the literature involving studies that assessed the effect of dentin bio modifications and MMP inhibitors on dentin bonding.

Methodology

Protocol development

This review was done and performed in according to the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) statement[16].

Study design

The research question "What is the efficacy of dentin modifications on dentin bonding and MMP activity? was put out in the Participants (P), Intervention (I), Comparison and Outcome(O) framework.

Eligibility Criteria

Inclusion Criteria:

1. Articles published in English language
2. Studies published between 2000 and 2023 in December with relevant data on the impact of dentin bio modifications on dentin bonding and MMP activity.
3. Studies report data as mean, standard deviation, and frequency.
4. The review comprised comparative, in vitro, and randomized controlled trials.
5. Articles in open access journals

Exclusion Criteria:

1. Studies undertaken before 2000.
2. Articles in non-English language.
3. We omitted reviews, abstracts, letters to the editor, editorials, and animal studies.
4. Articles not published in open access journals
5. Some articles fail to present study outcomes in terms of mean and standard deviation.

Screening Process

Two authors conducted the search and screening. The procedure of selecting articles was divided into two sections. Two reviewers examined the titles and abstracts of all articles in first round. Articles that did not fit the inclusion criteria were removed. Phase two entailed the independent screening and review of a few full manuscripts by the same reviewers. Discussions were undertaken to resolve any disagreements. When more information was requested, the study's corresponding authors were contacted by email.

Search Strategy

For research published within last 23 years (from 2000 to 2023), an electronic search was carried out till December 2023 utilizing the following databases: PubMed, google scholar and EBSCO host to retrieve English language articles.

The proper Boolean operators like AND/OR were used to combine the right key phrases and Medical Subject Heading (MeSH) terms. The keywords and their combinations: ''(Dentin AND bonding) OR (grape seed extract AND dentin AND bonding) OR chlorhexidine OR "benzalkonium chloride∗" OR "matrix metalloproteinase inhibitor∗" OR "MMP∗ inhibitor∗" OR "protease inhibitor") OR stability OR durability OR strength OR long-term) AND (dentin AND adhesive OR adhesive system" OR "hybrid layer" OR bond OR ("matrix metalloproteinase" AND OR stability OR durability OR strength OR long-term) AND (dentin AND adhesive∗ OR "adhesive system∗" OR "hybrid layer∗" OR bond OR ("matrix metalloproteinase" OR "MMP∗ inhibitor∗") AND dentin bonding OR (("Matrix Metalloproteinase Inhibitors") AND ("Dental Bonding") OR "Light-Curing of Dental Adhesives) OR "Self-Curing of Dental Resins").

Data extraction

Two independent reviewing authors extracted demographic research characteristics for all included studies using a Microsoft Excel spread sheet, and the following headings were used in the final analysis: Author(s), country of study, year of study, sample size, study methodology, bonding technique (E&R/SE), MMP inhibitor, dentin bonding reduction percentage, and conclusion.

Assessment of methodological quality

The methodological quality among included clinical trials or randomized controlled trials (RCT) was

executed by using Cochrane collaboration risk of bias (ROB) -2 tool17 through its various domains in Review Manager (Rev Man) 5.3 software.[18-20]

Result

After duplicates removal, reference list of included studies was screened. Of which 121 studies were excluded. After this full text articles were assessed for eligibility and articles that did not meet inclusion criteria were excluded. Sixteen studies fulfilled eligibility criteria and were included in qualitative synthesis as shown in Figure 1 below.

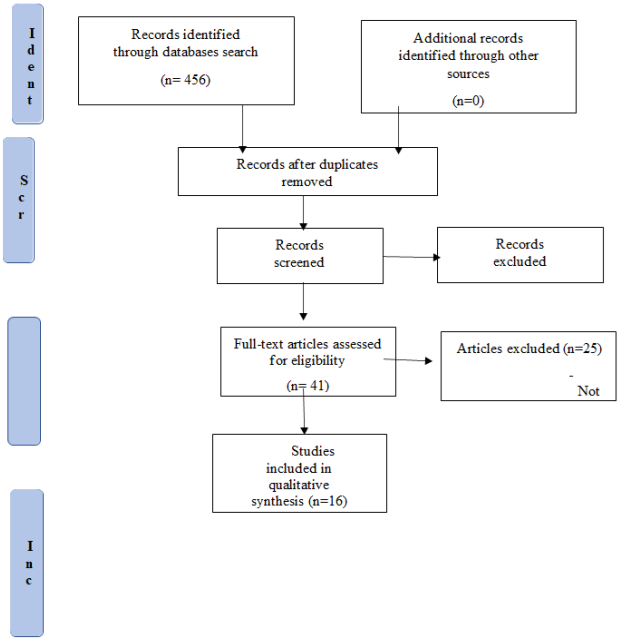

Figure 1: Prisma Flow Diagram

Study Characteristics

As shown in Table 1, data was evaluated from sixteen studies21-36 from an aggregate of total of 796 teeth subjected to dentin bio-modifiers and MMP inhibitors. All the included studies had in-vitro clinical trial study design. Among the included studies, four studies were conducted in Iran21,22,34,35., three studies in Turkey23,32,36, one in India24, two in Egypt26,28, two in Saudi Arabia27,33, one in Portugall28 and one in Sweden30. A variety of bio-modifiers and MMP inhibitors on increasing the dentin bonding or adhesion of various adhesive materials has been described with the type of bonding done, of which CHX 2% and BAC 1% were the most commonly used with controls.

Author, Years of Study	Country	Study Design	Sample Size	Bio Modifiers And MMP Inhibitors	Bonding Type (E&R/ SE)
Leitune et al.2011[21]	Iran	In-vitro clinical study	40	CHX 2% and control	E&R
Mobarak et al.2011[22]	Iran	In-vitro clinical study	120	CHX 2%, 5% and control	SE
Pomacóndor-Hernández et al.2013[23]	Turkey	In-vitro clinical study	8	CHX 2% and control	SE
Sabatini et al.2013[24]	Italy	In-vitro clinical study	25	CHX 2%, BAC 1%, control	E&R
Verma et al.2013[25]	India	In-vitro clinical study	20	CHX 2%, PAC 30% and control	E&R

Sabatini et al.2014[26]	Egypt	In-vitro clinical study	140	CHX 2%, BAC-PA, 0.25% BAC, 0.5%, 1%, 2% BAC and control	E&R
Montagner et al.2015[27]	Saudi Arabia	In-vitro clinical study	36	CHX 2%, NaOCL and control	E&R
Sabatini et al.2015[28]	Egypt	In-vitro clinical study	25	CHX 2%, BAC-PA 1%, BAC0.5%, BAC 1% and control	E&R
Carvalho et al.2016[29]	Portugal	In-vitro clinical study	30	Green tea 2%, CHX 2% and control	E&R
Loguercio et al.2016[30]	Sweden	In-vitro clinical study	30	MC 2%, CHX 2%, control	E&R
Nawareg et al.2016[31]	Italy	In-vitro clinical study	36	CHX 2%, CHX-MA 2% and control	E&R
Tekçe et al.2016[32]	Turkey	In-vitro clinical study	50	BAC 1%, CHX 2%, EDTA 0.5m	E&R and SE
Daood et al.2017[33]	Saudi Arabia	In-vitro clinical study	60	CHX 2%, QAS 2%, 5%,10% and control	E&R
Giacomini et al.2017[34]	Iran	In-vitro clinical study	90	CHX 2%, E-64 and control	E&R
El Gezawi et al.2018[35]	Iran	In-vitro clinical study	36	MDPB, BAC and control	SE
Malaquias et al.2018[36]	Turkey	In-vitro clinical study	50	CHX0 0.01%, 0.05%, 0.1%, 0.2% and control	E&R

Table 1: showing descriptive study details of included studies

bac: benzalkonium chloride; CHX: chlorhexidine; E&C: etch and rinse; EDTA: ethylene dioxide tri-aggregate; SE: self-etch; MDPB: methacrolxydodecylpyridium bromide; PAC: pro-anthocyanidines; QAS: quaternary ammonium silane

Assessment of methodological Quality

The highest ROB was seen for random sequence generation, blinding of participants and personnel, blinding of outcome assessment and selective reporting. All of the included studies reported moderate to lowest ROB. Domains of incomplete outcome data, blinding of outcome assessment and other bias were given the lowest ROB. ROB of various domains and of individual studies is depicted in Figure 2 and 3 as shown below

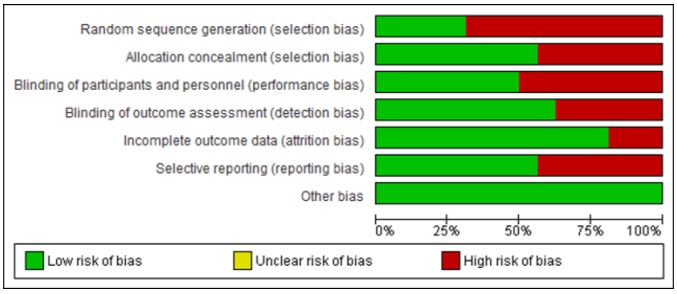

Figure 2: Showing ROB graph: presented as percentages across all included studies.

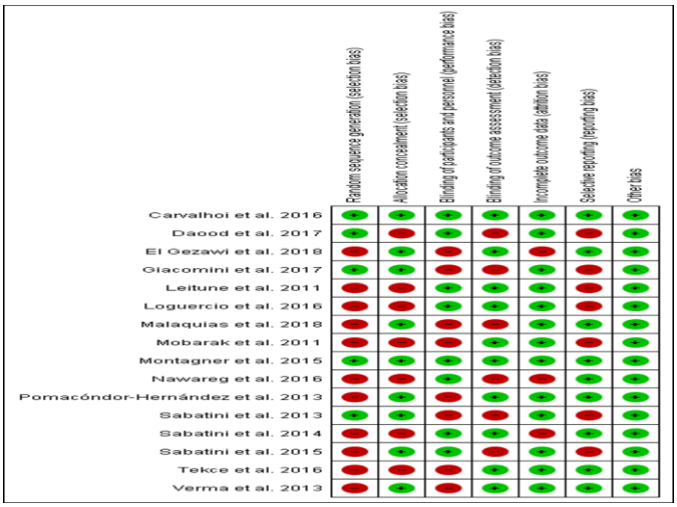

Figure 3: Showing ROB summary: for each included study

Discussion

Hardan et al.37 did a comprehensive study and meta-analysis to evaluate potential ways or tactics for increasing the bonding strength of commonly used adhesives. Databases for in vitro studies were searched until 2020. A total of 74 studies were reviewed, with 61 studies used for meta-analysis. It was discovered that the use of various MMP inhibitors, prolonged application time, scrubbing technique, selective dentin etching, non-atmospheric plasma, ethanol wet bonding, prolonged blowing time, multiple layer application, and prolonged curing time all improved dentin bonding. Meta-analysis revealed that MMP inhibitors had the highest statistical significance ($p<0.01$).

Kiuru et al.38 carried out a meta-analysis to determine the effect of several MMP inhibitors on total dentin bonding. Only the PubMed and Scopus databases were searched until July 2018.21 Studies were included in the review. It was discovered that among all MMP inhibitors, 0.2 - 2% chlorhexidine (CHX) and benzalkonium chloride (BAC) were the most regularly used when compared to a range of controls. The CHX group showed higher dentin bonding than the other controls. It was determined that the usage of CHX as an MMP inhibitor should be promoted more to improve dentin bonding.

Silva et al.39 conducted a systematic evaluation to determine the efficacy of collagen cross linking agents (CCLA) in dentin biomodifications for better adhesion. Databases were scanned until October 2020. Only three studies were considered in the review. Better outcomes were observed with CCLA.

Lewis et al.40 conducted a comprehensive review to determine the impact of MMP inhibitors on micro-tensile dentin bonding, bond durability, and mode of failure. Databases were searched from 2010 to 2022, yielding six in vitro studies that met the eligibility requirements. MMP inhibitors were observed to improve bond endurance and tensile dentin bonding in all tests, and it was concluded that they might be utilized as a pre-treatment for teeth with caries-affected dentin (CAD).The study was conducted to assess the influence or effect of various dentin biomodifications and MMP inhibitors on dentin bonding. Databases were searched till December 2023. 16 in- vitro studies fulfilled the eligibility criteria and were included in qualitative review and 15 studies for meta-analysis. All included studies had in-vitro study design. A variety of dentin modifiers and MMP inhibitors were included in review, of which 2% chlorhexidine (twelve studies22-34) and benzalkonium chloride (five studies26.28,32,35) being the most studied.

The systematic review is strengthened by adhering to the PRISMA guidelines, conducting a thorough unrestricted literature search, using reliable methodology for qualitative data synthesis, and assessing evidence quality using the Cochrane risk of bias tool for randomized controlled trials. The quality evaluation of the included studies was high overall, indicating a lack of potential and unavoidable sources of bias with little variability

and reporting issues. A systematic review is a transparent and repeatable technique for locating, selecting, and critically evaluating published or unpublished data to answer a specific research issue. Meta-analyses, which combine numerical data from linked studies, are usually partnered with systematic reviews. Systematic reviews and meta-analyses are widely considered the best sources of evidence. However, the quality of the included studies hasan impact on the strength of the evidence. The current evaluation includes a sufficient number of studies with a brief observation duration and a known risk of bias. As a result, the already available evidence is adequate for making therapeutic recommendations in response to the current systematic review's focus question.

Conclusion

The meta-analysis, which comprised research, significantly suggested the potential superiority and benefits of CHX in extending dentin bonding. However, because CHX and BAC have no possible deteriorating effect on immediate dentin bonding, their clinical use should be advised to increase or prolong resin-dentin bonding.

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