

An In Vitro Evaluation of The Effect of Titanium Dioxide Nanoparticle on The Shear Bond Strength and Antimicrobial Property of Orthodontic Adhesive: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The objective of this review was to systematically analyse available literature on the effects of titanium dioxide nanoparticles (TiO₂ NPs) in improving the antimicrobial activity and shear bond strength when incorporated in orthodontic adhesives.

Methods: All invitro studies that have evaluated the shear bond strength and the antimicrobial activity of TiO₂ NPs infiltrated orthodontic adhesive were included in this review. A comprehensive search in 5 electronic databases namely, Google scholar, PUBMED, EMBASE, Cochrane and Web of science were done up to January 2023. Using the reference method for invitro studies, the Risk of bias ROB was evaluated. Meta-analysis using Random Effects Model was performed for assessing the antimicrobial activity against *S. mutans*, *C. albicans* and *L. Acidophilus*.

Results: All the included studies had a moderate risk of bias. On qualitative analysis, a significant antimicrobial effect against *Streptococcus mutans* and *Lactobacillus acidophilus* and a non-significant shear bond strength of TiO₂ infiltrated orthodontic adhesive was reported. The meta-analysis revealed a significant overall antimicrobial effect and non-significant shear bond strength values with a high heterogeneity.

Conclusion: An overall significant antimicrobial effect of TiO₂ infiltrated orthodontic adhesive against *S. mutans* and *L. Acidophilus* was noted but with a high heterogeneity and a moderate risk of bias. An overall non-significant shear bond strength of TiO₂ infiltrated orthodontic adhesive was noted but with a high heterogeneity and a moderate risk of bias.

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How to cite this article: : Harsha L, Subramanian K A, An In vitro evaluation of the effect of Titanium dioxide nanoparticle on the shear bond strength and antimicrobial property of orthodontic adhesive: A Systematic review and meta-analysis. Journal of Complementary Medicine Research, Vol. 13, No. 5, 2022 (pp. 105-114)

INTRODUCTION

It is known in orthodontic literature that enamel demineralisation, white spot lesions and incipient dental caries around the bonded brackets are the potential adverse effects of fixed orthodontic therapy (1). White spot lesions develop rapidly around the brackets with the 1st month of treatment with a frequency of 2-96% (2,3). This could be associated with compromised oral hygiene due to bonded brackets, leading to biofilm and plaque formation consisting of multispecies cariogenic bacteria (4,5). The primary preventive measures as enumerated over the years include good oral hygiene maintenance and sugar-controlled diet. While the secondary preventive measure includes fluoridation by means of toothpastes, mouthwashes etc. But these methods are not reliable as they are subjective in nature

KEYWORDS:

Bacterial growth, smokers, non-smokers

ARTICLE HISTORY:

Received June 18, 2022

Accepted Oct 17, 2022

Published Dec 15, 2022

DOI:

10.5455/jcmr.2022.13.05.20

This void has led to the development of materials that incorporate antimicrobial agents like chlorhexidine into orthodontic adhesives (6,7). However, it provided short term antimicrobial effects and also altered the mechanical properties invariably, questioning its further use in orthodontics (8).

With the development of nanobiotechnology and nanomedicine, a number of novel antimicrobial nanomaterials have been formulated for effective use in dentistry. Studies conducted previously have also evaluated the antimicrobial and mechanical properties of these nano infiltrated orthodontic adhesives (9,10). Titanium dioxide is one such nanoparticle that has proven to be an effective antimicrobial agent that does not affect the mechanical property of the adhesive.

To substantiate the same, a high-quality meta-analysis and pooled data from a systematic review with statistical significance would provide scientific evidence. To the best of our knowledge a previous systematic review was conducted evaluating the effect of antimicrobial agent infiltrated orthodontic adhesives on its mechanical properties (11,12). But there is lack of evidence on the antimicrobial effect of broad spectrum nanoparticles that have been incorporated into orthodontic adhesives to improve its efficiency in preventing enamel demineralisation and White spot lesions. Hence, the present systematic review and meta-analysis aimed to evaluate systematically all available published literature qualitatively and quantitatively on the shear bond strength and antimicrobial effect of titanium dioxide (TiO₂) nanoparticle infiltrated orthodontic adhesive.

MATERIALS AND METHODS

Focused Question

With reference to the preferred reporting items for systematic review and meta-analysis the following 2 questions were constructed, A) Does TiO₂ NP s incorporation in orthodontic adhesive influence the shear bond strength? B) Does the TiO₂ NPs infiltrated orthodontic adhesive have good antimicrobial activity against oral microbes?

Protocol registration

The systematic review was prepared adhering to the reporting guidelines for Systematic reviews and Meta-Analysis in the PRISMA 2020 statement. The Systematic review Is not registered in PROSPERO.

Literature Search Protocol

A comprehensive search in 5 databases namely, Google scholar, PUBMED, EMBASE, Cochrane and Web of science were done up to January 2023. Using, open access sources, open grey and grey net, Grey literature were also searched. The detailed search strategy on PubMed is mentioned in Table 1. The same search strategy was applied for all other databases. The article references lists were also screened. The search was restricted to only invitro English literature published before January 2023. Using the Endnote application (version X9; Clavirate Analytics, Philadelphia, PA, USA) all duplicates were removed.

Table 1: Search Strategies

PUB MED SEARCH	Results
Search Details	
((((((TITANIUM dioxide nanoparticle[Title/Abstract]) OR (TiO ₂ Nanoparticle[Title/Abstract])) OR (noninfiltrated[Title/Abstract])) OR (Titanium dioxide nanoparticle)) OR (TiO ₂) AND (fha[Filter])) AND (((((((Shear bond strength) OR (mechanical property)) OR (bond strength)) OR (debonding strength)) OR (antimicrobial activity)) OR (antibacterial activity)) OR (s. mutans)) OR (oral microbes) AND (fha[Filter])) AND (((Orthodontic adhesive) OR (orthodontic cement)) OR (orthodontic composite) AND (fha[Filter])) AND (fha[Filter]))	67
((((((((Shear bond strength) OR (mechanical property)) OR (bond strength)) OR (debonding strength)) OR (antimicrobial activity)) OR (antibacterial activity)) OR (s. mutants)) OR (oral microbes) AND (fha[Filter])) AND (((((TITANIUM dioxide nanoparticle[Title/Abstract]) OR (TiO ₂ Nanoparticle[Title/Abstract])) OR (noninfiltrated[Title/Abstract])) OR (Titanium dioxide nanoparticle)) OR (TiO ₂) AND (fha[Filter]))	3.065
((((((TITANIUM dioxide nanoparticle[Title/Abstract]) OR (TiO ₂ Nanoparticle[Title/Abstract])) OR (noninfiltrated[Title/Abstract])) OR (Titanium dioxide nanoparticle)) OR (TiO ₂) AND (fha[Filter])) AND (((((((Shear bond strength) OR (mechanical property)) OR (bond strength)) OR (debonding strength)) OR (antimicrobial activity)) OR (antibacterial activity)) OR (s. mutans)) OR (oral microbes) AND (fha[Filter])) AND (((Orthodontic adhesive) OR (bonding)) OR (orthodontic cement)) OR (orthodontic composite)	244
(((Orthodontic adhesive) OR (bonding)) OR (orthodontic cement)) OR (orthodontic composite)	2,90,084

(((((((Shear bond strength) OR (mechanical property)) OR (bond strength)) OR (debonding strength)) OR (antimicrobial activity)) OR (antibacterial activity)) OR (s. mutants)) OR (oral microbes)	8,79,219
(((((((Shear bond strength) OR (mechanical property)) OR (bond strength)) OR (debonding strength)) OR (antimicrobial activity)) OR (antibacterial activity)) OR (s. mutans)) OR (oral microbes)	7,63,692
(((TITANIUM dioxide nanoparticle [Title/Abstract]) OR (TiO2 Nanoparticle[Title/Abstract])) OR (noninfiltrated[Title/Abstract])) OR (Titanium dioxide nanoparticle)) OR (TiO2)	34.575

Eligibility Criteria

The PICO for this systematic review is, Population (P): Orthodontic adhesive Intervention (I) TiO2 NPs

Comparison (C): Control with no nano infiltration Outcomes (O): Shear bond strength, antimicrobial activity Study (S): Invitro studies The inclusion and exclusion criteria for including studies in this systematic review are mentioned in Table 2.

Table 2: PICO Analysis and eligibility criteria

PICO	Inclusion criteria	Exclusion criteria
Population (P): Orthodontic adhesive	Only orthodontic adhesive	Restorative composites, glass ionomer cement, varnish
Intervention (I): Titanium dioxide nanoparticle	Only Titanium dioxide nanoparticle	Other nanoparticles like Ag, or silica, etc.
Comparison (C): no nanoparticle	=	=
Outcomes (O): Primary: shear bond strength, antimicrobial activity	Shear bond strength and Anti- microbial activity	Any other properties
Study Design	Only in-vitro studies	Randomized and non-randomized Control trials.

Data Extraction And Assessment

All studies that fit as per the inclusion criteria after full text reading by the three authors (HL, AKS, PA) were included in this review. The selection process is represented in the PRISMA flowchart 2020 Figure 1. The intra-examiner agreement based on kappa statistics was 95%. Any disagreements were resolved by discussion. The data extracted by the 3 authors from the included studies were the name of the author, year of publication, concentration of TiO2 NPs infiltrated in the orthodontic adhesive, the shear bond strength and the antimicrobial activity specifying the organism against which the sample was tested. Table 3 represents the study characteristics of the review which comprises all of the general information of the included studies. Table 4 represents the data of the outcomes evaluated in this systematic review.

Quality assessment

The risk of bias assessment tool was adapted from previously published systematic reviews (22,23). (Table 5) Studies with one to three “Yes” responses were deemed to have a low risk of bias. Studies scoring four to six “Yes” were considered to have a medium risk of bias, while those scoring seven to nine

“Yes” were considered to have a high risk of bias.

Quantitative Assessment of the included studies

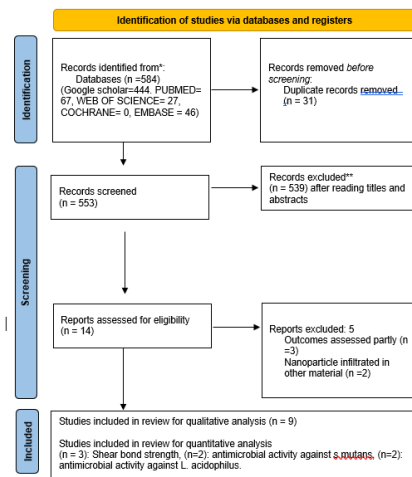
Meta-analysis of the primary outcomes was performed using Cochrane review manager software (Revman version 5.4). The overall effects were calculated using a random effects model (DerSimonian-Laird random effects pooling method). The antimicrobial effect was expressed in the form of mean CFU/ml.

RESULTS

Study Selection

The electronic search identified a total of 584 articles. After removing the duplicates, 553 studies were further screened. After screening of the titles and abstracts, only 14 studies were selected. On further screening of the studies for eligibility criteria 5 studies were excluded. Finally, 9 studies were relevant and were included for qualitative analysis. 3 studies were selected for quantitative analysis of the outcome shear bond strength, 2 studies each were included for quantitative analysis of antimicrobial activity against *S. mutans* and *L. Acidophilus* (Figure 1).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372: n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Figure 1: PRISMA Flowchart for study selection.

Study characteristics

Table 3 provides a summary of the characteristics of the eleven studies that were included. Shear bond strength and antimicrobial activity was the primary outcome evaluated by

all of the included studies (Table 4). The antimicrobial effect of the coated brackets against *Streptococcus mutans*; *Lactobacillus Acidophilus*; and *S. sanguinis* was assessed as the number of Colony Forming Units (CFU/ ml × 10⁵).

Table 3: Characteristics table

AUTHOR	YEAR	GROUPS	N	NP %	PARAMETERS EVALUATED	METHODS	REF
PUTRI et al	2021	G1 - Teeth bonded with TiO2 infiltrated orthodontic adhesive. G2 - Teeth bonded with chitosin infiltrated adhesive G3 - teeth bonded using orthodontic adhesive resin only	G1 - 10 G2 - 10 G3 - 10	Not mentioned	AMA	s. mutans colony count after incubation at 37 deg C for 24 hrs.	13
Assery et al	2019	G1 - 1% TiO2 infiltrated adhesive G2 - 3% TiO2 infiltrated adhesive G3- control	G1- 30 G2 - 30 G3- 30	1% and 3%	SBS, AMA	SBS - UTM AMA - S. mutans CFU in BHI agar.	14
Poosti et al	2013	G1 - 1% TiO2 infiltrated adhesive G2 - Control	G1 - 15 G2 - 15	1%	SBS, AMA	SBS - UTM AMA - CFU in blood agar	15
Yassaei et al	2020	10 groups	66 samples totally.	1%	AMA	AMA - CFU & Zone of inhibition	16

		One among them is 1% TiO2 infiltrated composite	6 per group				
Behnaz et al	2018	G1 - Control G2 - infiltrated composite TiO2		0.1%	SBS	SBS - UTM	17
Sodagar et al	2017	G1 - 1% TiO2 infiltrated adhesive G2- 5% TiO2 infiltrated adhesive G3- 10% TiO2 infiltrated adhesive G4 - control	G1 - 12 G2 - 12 G3 - 12 G4 - 12	1%, 5%, 10%	SBS, AMA	SBS - UTM AMA - Disc diffusion assay	18
Mahendra et al	2020	G1 - 1% TiO2 infiltrated adhesive G2 - Control	G1 - 20 G2 - 20	1%	SBS, AMA	SBS - UTM AMA - disc diffusion assay	19
Reddy et al	2016	G1 - 1% TiO2 infiltrated adhesive G2 - control	G1 - 30 G2 - 30	1%	AMA	SBS - UTM	20
Felemban et al	2017	G1 - 1% TiO2 infiltrated adhesive G2 - 0.5% TiO2 infiltrated adhesive G3 - control	G1 - 20 G2 - 20 G3 - 20	0.5%, 1%	SBS	SBS - UTM	21

Table 4: Results of primary outcome

Author	Shear bond strength	Antimicrobial activity: (Cfu/ml) ×10 ⁵	P value	Conclusion
PUTRI et al, 2021. Incubation period: 24 h	-	<i>S. Mutans</i> Groups G 1: 2.36 +/- 1.94 G 2: 2.09 +/- 1.92 G 3: 1.5 +/- 1.24	(p > 0.05)	No significant difference in the number of Streptococcus mutans colonies around the bracket which was bonded using orthodontic adhesive resin incorporated with titanium dioxide nanoparticles
Assery et al, 2019 Incubation period: 48 h	G1 - 13.2 +/- 1.8 G2 - 12.9 +/- 2.7 G3 - 12.3 +/- 0.9	<i>S. mutans</i> G1 - 5.2 G2 - 5.8 G3 - 44.2	SBS: (p > 0.05) AMA: (p > 0.05)	1% TiO ₂ infiltrated orthodontic adhesive had bactericidal effect against <i>S. mutans</i> . No statistically significant difference between SBS between the 3 groups.

Poosti et al, 2013 Incubation period: 24 h	G1 - 14.3 +/- 1.26 G2 - 14.4 +/- 1.2	<i>S. Mutans</i> G1 - 8.2 +/- 3.9 G2 - 69.1 +/-14.59			SBS: (p>0.05) AMA: (p<0.05)	Adding TiO2 nanoparticle to orthodontic composite enhances its antibacterial effect without compromising the shear bond strength.
Yassaei et al, 2020 Incubation period: 24 h	-	<i>S. mutans</i> 1% TiO2 orthodontic composite: 241.67 +/- 66.45 Control: 300 +/- 0			(p>0.05)	1% titanium oxide reduced the number of colonies but presented no significant difference with control group,
Behnaz et al, 2018	G1 - 145 +/- 3.87 G2 - 123.92 +/- 3.17	-			(p < 0.05)	The addition of TiO2 nanoparticles might reduce SBS, but the adhesion might still be at an acceptable level.
Sodagar et al, 2017	G1 - 18.1 +/- 4.6 G2 - 13.9 +/- 6.00 G3 - 3.5 +/- 3.28 G4 - 34.47 +/- 6.7	<i>S. Mutans</i> G1 - 435.33 +/- 41.04 G2 - 133 +/- 23.25 G3 - 14 +/- 3.606 G4 - 889.6 +/- 115.1	<i>S. sanguinis</i> G1 - 181.6 +/- 17.2 G2 - 47 +/- 5.5 G3 - 173 +/- 4.5 G4 - 630.6 +/- 94.69	<i>L. acidophilus</i> G1 - 54 +/- 13.74 G2 - 28 +/- 1 G3 - 7 +/- 2 G4 - 89 +/- 19.31	SBS: (p < 0.05)	Incorporating TiO2 nanoparticles into composite resins confer antibacterial properties to adhesives, while the mean shear bond of composite containing 1% and 5% nanoparticles still in an acceptable range.
Mahendra et al, 2020	G1 - 17.17 +/- 8.3 G2 - 24.67 +/- 6.4	<i>S. Mutans</i> G1 - 1.908 +/- 0.202 G2 - 2.405 +/- 0.102	<i>L. acidophilus</i> G1 - 1.611 +/- 0.22 G2 - 2.20 +/- 0.13	SBS: (p < 0.05) AMA: (P<0.05)	there is a significant difference in the antibacterial activity and shear bond strength of nanocomposites.	
Reddy et al, 2016	G1 - 6.33 +/- 1.51 G2 - 9.43 +/- 3.03	-			(p < 0.05)	A significant difference was observed between the 2 groups.
Felemban et al, 2017	G1 - 25.05 +/- 0.2 G2 - 20.32 +/- 0.47 G3 - 14.75 +/- 0.25	-			(p < 0.001)	The addition of ZrO2-TiO2 nanoparticles on resin-based adhesives increase the shear bond strengths of the adhesive in vitro.

Risk of bias within included studies

Out of the included studies, all studies had moderate risk of bias. The overall risk of bias of the review was reported as

moderate risk of bias (Table 5). In all of the included studies, sample randomization and blinding were not reported. In studies showing moderate risk of bias, in addition to the above parameters sample size calculation was not done.

Table 5: Assessment of the risk of bias in the included studies.

Author		P U T R I e t a l , 2 0 2 1.	Ass e r y e t a l, 20 19	P o o s t i e t a l , 2 0 1 3	Yassa e i e t a l, 2020	Behn az e t a l, 2018	Sodaga r e t a l, 2017	Mahe ndra e t a l, 2020	R e d d y e t a l , 2 0 1 6	Felemba n e t a l , 2017
Reporti ng Bias	Quantitat ive analysis	+	+	+	+	+	+	+	+	+
	Definitive values	+	+	+	+	+	+	+	+	+
Assess ment Bias	Presence of control group	+	+	+	+	+	+	+	+	+
	Blinding	-	-	-	-	-	-	-	-	-
	Assessme nt methods	+	+	+	+	+	+	+	+	+
Sampli ng Bias	Sample randomiz ation	-	-	-	-	-	-	-	-	-
	Sample preparati on	+	+	+	+	+	+	+	+	+
	Sample size calculatio n	-	-	-	-	-	-	-	+	-
Method of Preparation of composite		+	+	+	+	+	+	+	+	+
Risk of bias		M	M	M	M	M	M	M	M	M

2/ less: Low (L), 3-6: Moderate (M), > 6: High (H)

Summary of findings

Table 4 gives the results of the primary outcomes. 6 studies evaluated the antimicrobial effect of titanium dioxide nanoparticle infiltrated orthodontic adhesive against *S. mutans*, 2 studies reported the activity against *L. Acidophilus* and 1 study evaluated the activity against *S. sanguinis* all reported lesser CFUs /ml of *S. mutans* when compared to conventional orthodontic adhesive indicating a good antimicrobial effect (13-16, 18,19).

7 studies (14,15, 17-21) summarized the outcome, shear bond strength of the TiO2 infiltrated orthodontic adhesive. 1% TiO2 when infiltrated into orthodontic adhesive showed no significant difference in the SBS when compared to

conventional orthodontic adhesive.

Results of quantitative analysis

The meta-analysis of the 3 included studies (15,18,19) reported the shear bond strength of 1%TiO2 infiltrated orthodontic adhesive. The overall heterogeneity across the studies was found to be high (I2= 86%). Thus, a random effects model was used to quantitatively assess the shear bond strength. Figure 2 shows no significant pooled mean difference between 1% TiO2 infiltrated orthodontic adhesive and conventional orthodontic adhesive (SMD = -1.19; p value = 0.07; 95 % CI = -2.47 to 0.09).

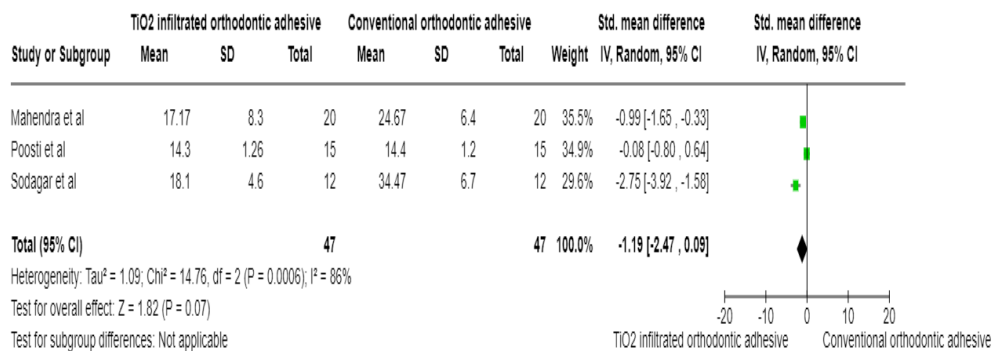


Figure 2: Metanalysis for the outcome shear bond strength of 1% TiO2 infiltrated orthodontic adhesive when compared to conventional orthodontic adhesive.

The meta-analysis of the 2 included studies reported the antimicrobial effect of 1%TiO2 infiltrated orthodontic adhesive against *S. mutans*. The overall heterogeneity across the studies was found to be low (I²= 0%). Thus, a random effects model

was used to quantitatively assess the antimicrobial effect. Figure 3 shows significant pooled mean difference between 1% TiO2 infiltrated orthodontic adhesive and conventional orthodontic adhesive (SMD = -5.33; p value = 0.00001; 95 % CI = -6.54 to -4.11) for number of CFUs against *S. mutans*.

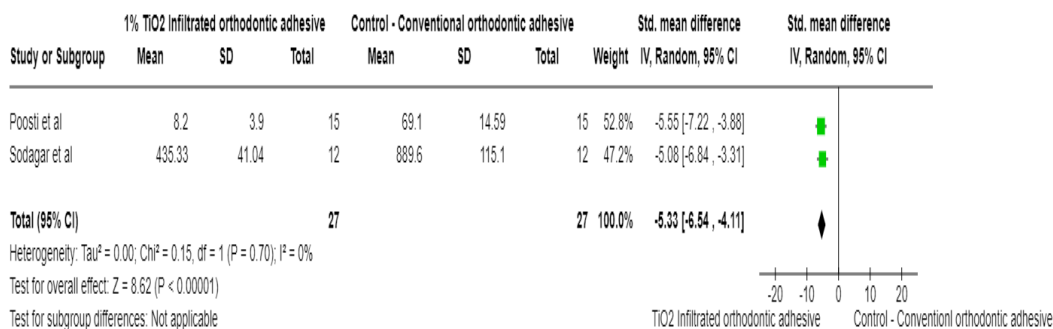


Figure 3: Metanalysis for the outcome antimicrobial activity against *S. mutans* of 1% TiO2 infiltrated orthodontic adhesive when compared to conventional orthodontic adhesive.

The meta-analysis of the 2 included studies reported the antimicrobial effect of 1%TiO2 infiltrated orthodontic adhesive against *L. Acidophilus*. The overall heterogeneity across the studies was found to be moderate (I²= 63%). Thus, a random effects model was used to quantitatively assess the antimicrobial effect. Figure 4 shows significant pooled mean

difference between 1% TiO2 infiltrated orthodontic adhesive and conventional orthodontic adhesive (SMD = -2.62; p value = 0.00001; 95 % CI = -3.78 to -1.46) for number of CFUs against *L. acidophilus*. There is a substantial unexplained heterogeneity between the included studies within each of the subgroups. Therefore, the validity of the total effect estimate for each subgroup is uncertain.

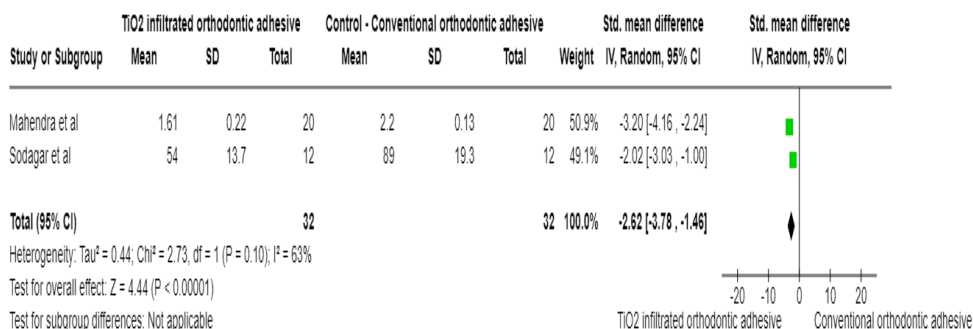


Figure 3: Metanalysis for the outcome antimicrobial activity against *L. acidophilus* of 1% TiO2 infiltrated orthodontic adhesive when compared to conventional orthodontic adhesive

DISCUSSION

Previously, many attempts were made to develop orthodontic adhesives with good antimicrobial properties in order to prevent enamel demineralisation around bonded orthodontic brackets, but how successful the same would be was not evaluated (24-27). Studies do agree that orthodontic adhesives infiltrated with TiO₂ nanoparticles have improved antimicrobial activity when tested in vitro. But in vivo evaluation of the antimicrobial activity and its effect on the shear bond strength needs to be evaluated.

The present systematic review and meta-analysis confirmed the collected effect of the data from in vitro experimental studies that revealed associated between antimicrobial activity and shear bond strength of TiO₂ infiltrated orthodontic adhesive. According to the results of the meta-analysis, no significant difference in the shear bond strength was observed between 1%TiO₂ infiltrated orthodontic adhesive and conventional orthodontic adhesive. This indicates that incorporating TiO₂ nanoparticle does not influence the shear bond strength which is similar to a recent meta-analysis (12).

In addition to evaluation of shear bond strength, the antimicrobial activity of the TiO₂ infiltrated orthodontic adhesive against *S. mutans* and *L. acidophilus* was evaluated. Since white spot lesions are usually detected around orthodontic brackets, it is critical that the adhesive possess antimicrobial properties. In the present study, quantitative analysis showed that there was a significant improvement in the antimicrobial activity of TiO₂ infiltrated orthodontic adhesive against *S. mutans* and *L. acidophilus*.

The antimicrobial effect of TiO₂ coatings was due to release of hydroxyl ions. TiO₂ exhibited this property either by UV light illumination or by N-doping in visible light spectrum (28-33). Therefore, visible regions have more clinical acceptability. Most studies claim the annealing temperature of 450 degrees at 2 h results in the formation of anatase phase of TiO₂ which has better antimicrobial activity than the other phases. F. Özyildiz et al (30) and S. Cao et al. (34) showed strong antimicrobial potential at 500 degrees Celsius and 700 degrees Celsius respectively.

The role of adding 1%TiO₂ nanoparticles to orthodontic adhesives in controlling WSLs and tooth decay around bonded orthodontic brackets is still poorly explained; the data available are sparse and, to the best of our knowledge, there is no systematic review and meta-analysis relating the characteristics of such modification and outcome. This highlights the necessity of programs to produce orthodontic adhesives containing antimicrobial nanoparticles in standardized commercial-scale due to the WSLs, particularly in cases with poor oral hygiene, to reduce the caries rate and maintain oral health and the low potential for post-treatment complications.

LIMITATIONS

Different concentrations of TiO₂ used in 3 studies.

The diameter and thickness of the test discs were not clearly mentioned in all included studies.

In vivo studies to correlate the obtained outcomes is essential.

CONCLUSIONS

The results were well described in all included studies and none of them had a high risk of bias due to missing data.

1%TiO₂ nanoparticle infiltrated orthodontic adhesive had significant improvement in antimicrobial activity against *S. mutans* and *L. Acidophilus*.

1%TiO₂ nanoparticle infiltrated orthodontic adhesive had no significant difference in the shear bond strength when compared with conventional orthodontic adhesive.

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