J Oral Res
research in oral sciences

Review

EFFECTIVENESS OF CHLORHEXIDINE ORAL RINSE IN PREVENTING PLAQUE ACCUMULATION AND GINGIVITIS IN PATIENTS UNDERGOING ORTHODONTIC TREATMENT- A SYSTEMATIC REVIEW AND META ANALYSIS.

Eficacia del enjuague oral de clorhexidina en la prevención de la acumulación de placa y la gingivitis en pacientes en tratamiento de ortodoncia: Una Revisión Sistemática y metaanálisis.

Selvaraj Abirami.[1]
Ramasamy Navaneethan.[1]
Ravindra Kumar Jain.[1]

AFFILIATIONS:
[1]Department of Orthodontics and Dentofacial Orthopaedics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, India.

CORRESPONDING AUTHOR:
Selvaraj Abirami. Saveetha Nagar, Thandalam, Kanchipuram - Chennai Rd, Chennai, Tamil Nadu 602105, India.
E-mail: varshaabi77@gmail.com

CITE AS:
Abirami S, Navaneethan R, & Jain RK. Effectiveness Of Chlorhexidine Oral Rinse In Preventing Plaque Accumulation And Gingivitis In Patients Undergoing Orthodontic Treatment- A Systematic Review And Meta Analysis.
J Oral Res.2022;11(4):1-16
doi:10.17126/joralres.2022.049

ABSTRACT:

Aim: The aim of this review was to systematically assess and report the effectiveness of chlorhexidine (CHX) mouthwash in preventing plaque accumulation and gingivitis in patients undergoing orthodontic treatment.

Material and Methods: The review was prepared according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines and registered under PROSPERO database (CRD42020170776). Four electronic databases were systematically searched along with a complimentary manual search of orthodontic journals until June 2022. Only Randomized Control Trials (RCTs) reporting on antiplaque and antigingivitis efficacy of Chlorhexidine mouthwash compared with placebo or control in orthodontic patients were included. Risk of bias assessment was done using Cochrane ROB-2. Quantitative analysis (Random-Effects Model and Standard Mean Difference (SMD)) with 95 % confidence interval was used.

Results: Six RCTs were included for qualitative analysis and four were included for quantitative analysis with a total of 211 participants. Out of six studies, 3 were judged to have a low risk of bias, two had some concerns and one of them had high risk of bias. Random effects meta-analysis performed for anti-plaque effect reported a significant reduction of -1.2 SMD for CHX at 4 to 6 weeks with low heterogeneity (I2-35%). The anti-gingivitis effect at 4 to 6 weeks was significant for CHX with a SMD of -1.03 and a moderate heterogeneity (I^2-65%).

Conclusion: On analyzing the available evidence a moderate level of certainty supports a short-term reduction in plaque accumulation and gingivitis in orthodontic patients subjected to rinsing with chlorhexidine oral rinse.

KEYWORDS:

Chlorhexidine; effectiveness; dental plaque; gingivitis; orthodontic appliances, fixed; systematic review.

Received: November 22, 2021 | **Accepted:** March 16, 2022 | **Published online:** August 30, 2022.

RESUMEN:

Objetivo: El objetivo de esta revisión fue evaluar e informar sistemáticamente la efectividad del enjuague bucal con clorhexidina (CHX) para prevenir la acumulación de placa y la gingivitis en pacientes que reciben tratamiento de ortodoncia.

Material y Métodos: La revisión se preparó de acuerdo con las pautas de Preferred Reporting Items for Systematic Reviews (PRISMA) y se registró en la base de datos PROSPERO (CRD42020170776). Se realizaron búsquedas sistemáticas en cuatro bases de datos electrónicas junto con una búsqueda manual gratuita de revistas de ortodoncia hasta junio de 2022. Solo se incluyeron ensayos controlados aleatorios (ECA) que informaron sobre la eficacia antiplaca y antigingivitis del enjuague bucal con clorhexidina en comparación con placebo o control en pacientes de ortodoncia. La evaluación del riesgo de sesgo se realizó mediante Cochrane ROB-2. Se utilizó un análisis cuantitativo (modelo de efectos aleatorios y diferencia de medias estándar (SMD)) con un intervalo de confianza del 95 %.

Resultados: Se incluyeron seis ECA para el análisis cualitativo y cuatro para el análisis cuantitativo con un total de 211 participantes. De los seis estudios, se consideró que tres tenían un bajo riesgo de sesgo, dos tenían algunas preocupaciones y uno de ellos tenía un alto riesgo de sesgo. El metanálisis de efectos aleatorios realizado para el efecto antiplaca informó una reducción significativa de -1,2 SMD para CHX a las 4 a 6 semanas con baja heterogeneidad (I2-35%). El efecto antigingivitis a las 4 a 6 semanas fue significativo para CHX con una SMD de -1,03 y una heterogeneidad moderada (I^2-65%).

Conclusión: Al analizar la evidencia disponible, un nivel de certeza moderado apoya una reducción a corto plazo en la acumulación de placa y gingivitis en pacientes ortodóncicos sometidos a enjuague con enjuague bucal con clorhexidina.

PALABRAS CLAVE:

Clorhexidina; efectividad; placa dental; gingivitis; aparatos ortodóncicos fijos; revisión sistemática.

INTRODUCTION.

Fixed orthodontic appliances serve as areas for retention and accumulation of plaque resulting in poor oral hygiene thus leading to gingival inflammation and periodontal breakdown characterized by edema, redness, and bleeding upon probing.[1] Hyperplastic gingivitis appears within 1 to 2 months[2] of appliance placement and attachment loss has been reported even after two years after the removal of appliances.[3,4]

Maintenance of adequate oral hygiene is difficult in patients undergoing orthodontic treatment[5] owing to the presence of multiple attachments compromising the dexterity of the patient during prophylaxis. This factor subsequently leads to an increase in the microbial flora predisposing the risk of White Spot Lesions (WSLs).[6,7] Although mechanical oral hygiene is the most preferred and effective way for plaque control, patients do not demonstrate sufficient proficiency when multiple attachments are placed intraorally. Hence, chemical agents are used as adjuvants to brushing and flossing methods for reduction of plaque and gingivitis.[8]

During orthodontic space closure, the oral environment is susceptible to invasion by microbial flora due to the presence of multiple attachments such as power chains, soldered power arms and NiTi coil springs. These attachments make manual brushing difficult and render multiple sites inaccessible for appropriate cleansing. Subsequently, patients may benefit from additional mouthwashes that can exhibit good antibacterial activity.

Antimicrobial mouth rinses have been introduced as an effective method for reducing dental plaque accumulation.[9] Rinsing with Chlorhexidine mouthwash can be considered as one of the

most popular methods for plaque control for management of gingivitis and has been proved to be very effective[10] and has been regarded as Gold standard' for plaque control.[11] Chlorhexidine (CHX) is a cationic chemical agent which exhibits its antibacterial activity by disrupting bacterial cell walls.[12,13]

The superiority of this agent over other chemical agents is its substantivity that prolongs its antibacterial action.[14] Chlorhexidine has a long history of effective use as an anti-gingivitis and antiplaque agent.[15-17] Although there are clinical trials on effectiveness of chlorhexidine in orthodontic patients, there are no reported systematic reviews specifically comparing chlorhexidine to placebo or control. Hence the present review aims to systematically search and analyze the available literature on the effectiveness of chlorhexidine (CHX) mouthwash in preventing dental plaque formation and gingivitis among patients undergoing orthodontic treatment.

MATERIALS AND METHODS.

Protocol registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered under the PROSPERO database with protocol number CRD42020170776.

Search strategy and Eligibility criteria

Electronic databases including *PUBMED*, *The Cochrane Library*, *Google Scholar* and *LILACS* up to June 2022 were performed. Key words were customized for each database and have been mentioned in Table 1.

Initially, titles and abstracts of all studies identified through search strategies were screened by two independent authors and irrelevant studies were excluded based on eligibility criteria. Full texts were then procured for the articles which fulfilled the inclusion criteria mentioned below. The reference lists of the identified articles were also hand searched for additional relevant studies.

Furthermore, a complimentary search was also done in the following journals- World journal of orthodontics, American Journal of Orthodontics and Dentofacial Orthopedics, European Journal of Orthodontics, Journal of Clinical Orthodontics, Seminars in Orthodontics and Angle Orthodontics. Bibliographies of the included full text articles were scanned for relevant studies. No restrictions were done on the language or date of publication when searching the electronic databases.

PICO analysis for this review is mentioned in Table 2.

ELIGIBILITY CRITERIA:

Eligibility criteria for this review are mentioned in Table 2.

Study selection

Two authors (AS and NR) performed the search independently employing the search strategy mentioned (Table 1). Eligibility criteria mentioned (Table 2) was used to screen the studies and any disagreements regarding study selection were resolved by mutual discussion by the two authors.

Data collection process

All studies meeting the selection criteria were included in the review. The selection process of included studies is depicted in the PRISMA flow chart (Figure 1).

Data required for analysis were extracted by both reviewers (AS and NR) independently. A table (Table 3) for describing the 'Study characteristics' of the included articles was made that included the following information: first author, year of publication, type and study design, sample size, age, gender, intervention, frequency, variables, adjunctive oral measures and evaluation periods. Any (AS and NR) disagreements between the reviewers regarding data collection was handled by mutual discussion until a consensus was achieved. Any disagreements that remained were resolved by conversation with a third reviewer (RKJ).

Review outcomes

The primary outcomes assessed in this review were anti plaque and antigingivitis efficacy as assessed with plaque index and gingival index. Secondary outcomes assessed were the probing

ISSN Print 0719-2460 - ISSN Online 0719-2479.

depth and changes in oral microbial flora. All of the review outcomes (Table 2).

Risk of Bias

The Cochrane risk of bias 2 (RoB2) tool was used for assessment of the risk of bias across the studies[18]. The tool assesses risk of the included studies based on five domains: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. Two authors (AS and NR) performed the risk of bias independently and a third author (RKJ) was consulted for resolving any disagreements. The Cohen k test was used to assess the level of agreement between the reviewers. Any publication bias in the included studies was assessed with a funnel plot.

META ANALYSIS

Statistical heterogeneity was evaluated from obtained forest plots of Plaque Index and Gingival Index from the included studies. A chi-square test was used to determine heterogeneity where a P value below 0.1 meant significant heterogeneity. I2 tests were done to quantify the extent of heterogeneity with values of 25 per cent, 50 per cent, and 75 per cent, corresponding to low, moderate, and high heterogeneity, respectively. A random effects model was chosen to determine the pooled estimates because of the high heterogeneity. A Tau^2 test was also used to assess heterogeneity in the random-effects model. Meta-analyses were undertaken using the Review Manager (RevMan) program (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Level of Evidence

The certainty of the scientific evidence was assessed using the GRADEpro (Grading of Recommendations Assessment, Development, and Evaluation) guidelines. The quality of the evidence for the primary outcome (Plaque index and gingival index) was rated by two reviewers (AS and NR) based on the following factors: risk of bias, consistency of results, directness of evidence, precision, publication bias, and magnitude of the effect. Any disagreements between the reviewers (AS and NR) were resolved by the third author (RKJ).

RESULTS.

The electronic search identified a total of 325 studies. After removal of duplicates there were a total of 322 articles; which were then subjected to further screening. After screening through titles, a total of 305 were irrelevant and were excluded. Full text of 17 studies were retrieved and screened for eligibility criteria.

Out of the 17 studies a total of 11 articles were excluded with reasons and the remaining 6 were included for qualitative analysis. 4 out of the 6 included RCTs were included for the quantitative analysis. The results of the search are illustrated in the PRISMA flow chart (Figure 1). A total of 211 participants were involved and all of them were treated with either chlorhexidine or placebo mouthwash (Table 3).

RISK OF BIAS OF THE INCLUDED STUDIES

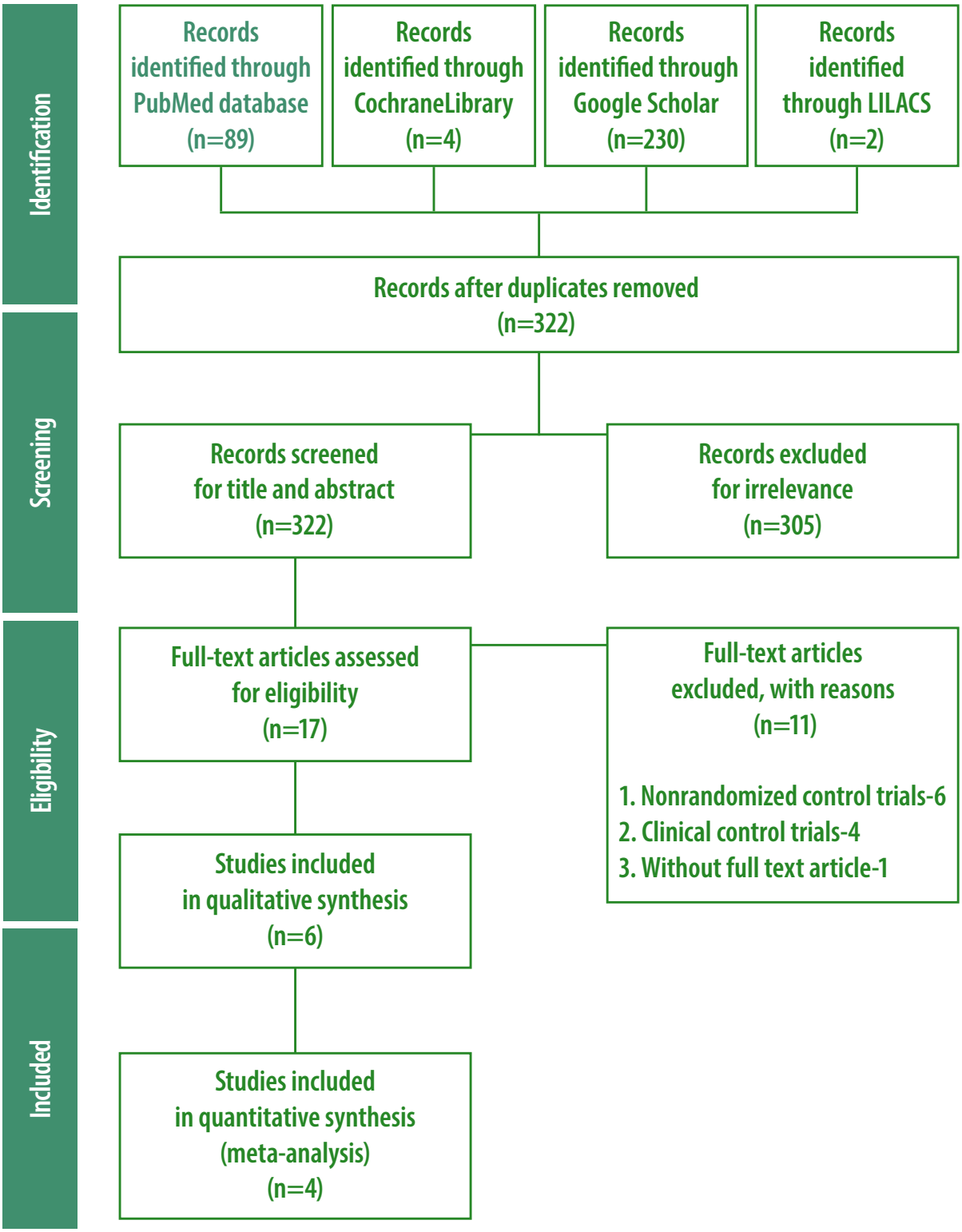
Results of risk of bias for included RCTs are presented in figure 2. Out of six RCTs, three were judged to have a low risk of bias, two reported some concerns, one reported high risk (Figure 2).

ANTIPLAQUE EFFECT

5 Out of 6 RCTs, reported CHX is more effective in reducing plaque accumulation than placebo oral rinse or no intervention with a statistically significant difference (p<0.05) at 4 to 6 weeks.[19–23] One study reported that CHX is more effective at the end of 3 months[24] (Table 4).

Figure 3 is a graphical representation of a random effects model done to compare the plaque index between the two groups. 4 of the included studies were assessed for plaque index. The overall effect p-value<0.00001 [SMD=-1.20 (95% CI=-1.70 to -0.70)] indicates statistically significant reduction in plaque accumulation when CHX mouthwash is used. The heterogeneity (I^2=35%) is low and indicates good reliability.

Figure 1. PRISMA flow chart of the study.



ISSN Print 0719-2460 - ISSN Online 0719-2479.

Figure 2. Risk of bias summary of studies included in the review.

Figure 3. Random-effects meta-analyses for anti plaque efficacy

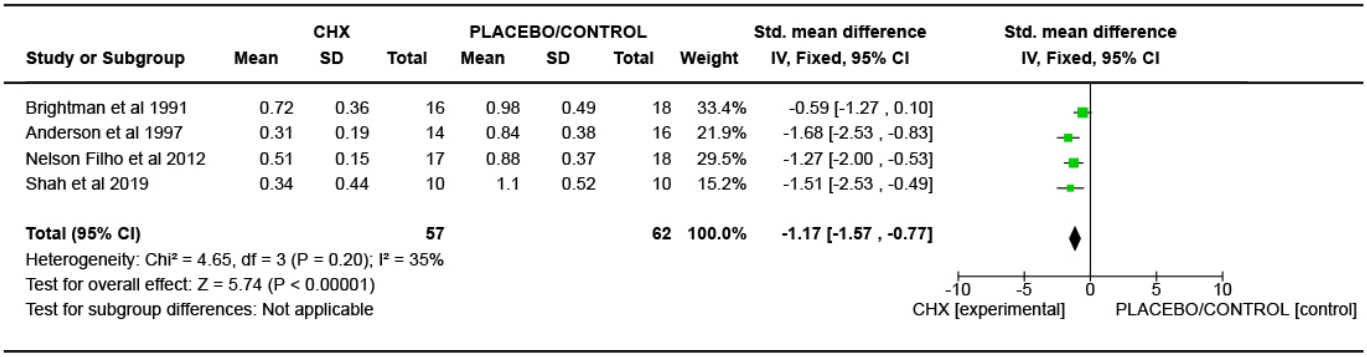


Figure 4. Random-effects meta-analyses for anti -gingivitis effect

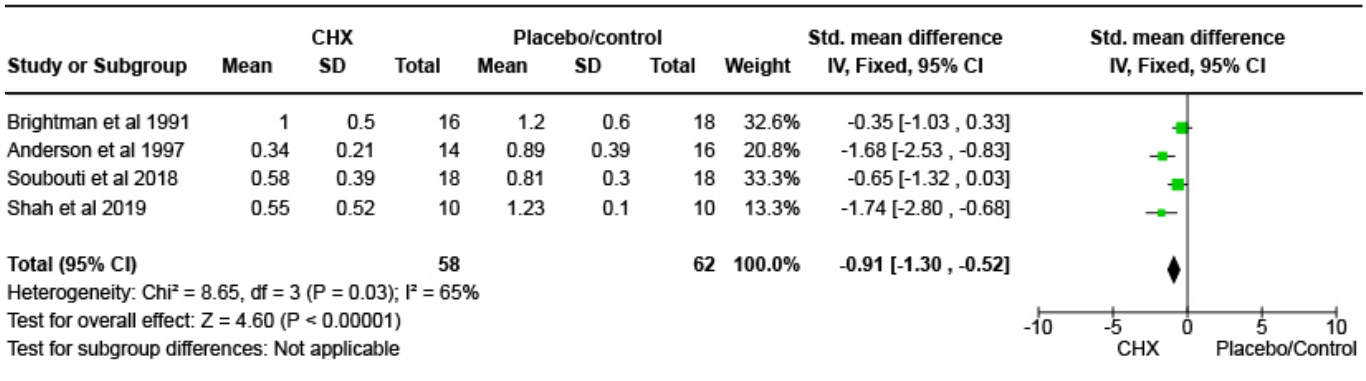
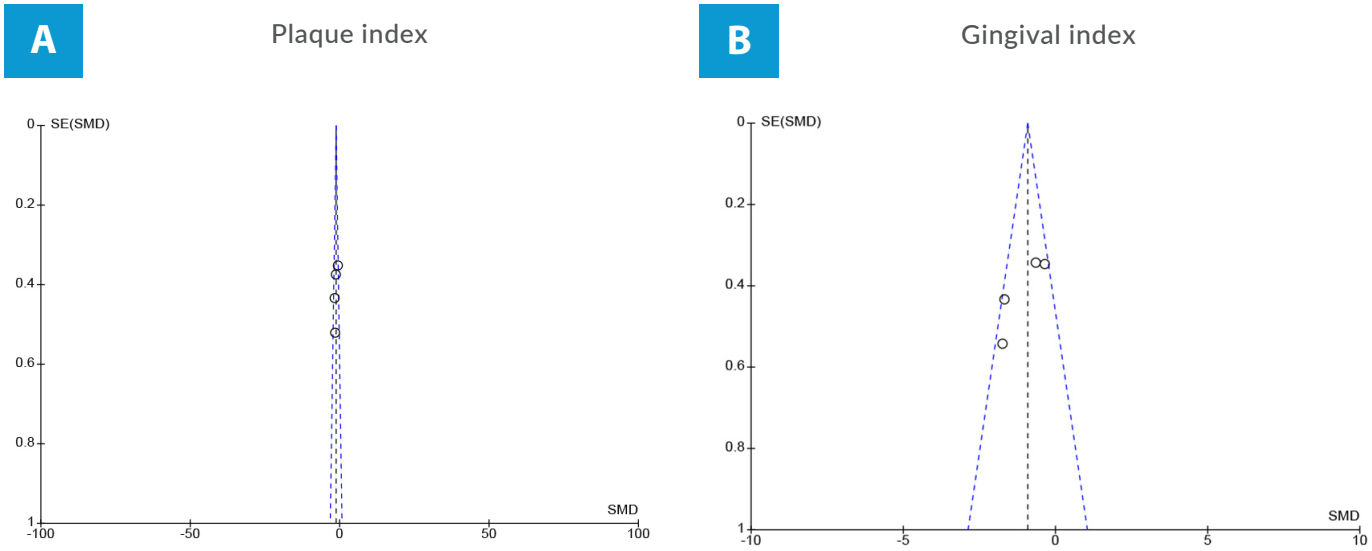


Figure 5. Funnel plots of (A) plaque and (B) gingival index.



ANTI GINGIVITIS EFFECT

Out of six RCTs, four studies reported on gingival index[19–21,24] and among them one study reported CHX is more effective in reducing gingival inflammation than placebo oral rinse or no intervention with statistically significant difference (p<0.05)[19] at 4 weeks.

Studies by Brightman *et al.*,[21] and Anderson *et al.*,[24] reported that there was a statistically significant difference (p<0.001) in gingival index between the two groups after 12 weeks and chlorhexidine was more effective in reducing gingival inflammation (Table 4).

Figure 4 is a graphical representation of a random effect model done to compare the gingival index between the two groups. A random effects model including 4 studies was performed. The overall effect p-value=0.003 [SMD=-1.03 (95% CI=-1.71 to -0.35)] which indicates statistically significant reduction in gingival inflammation when CHX mouthwash is used. The heterogeneity (I^2=65%) is moderate and indicates fair reliability.

GINGIVAL BLEEDING INDEX

Out of six RCTs, three studies[20,21,23] reported on gingival bleeding index, among them only two studies such as Soubouti *et al.*,[20] and Goes *et al.*,[23] reported that CHX is more effective in reducing gingival bleeding than placebo oral rinse or no intervention with statistically significant difference at 4 weeks (p=0.02) and 15 days (p=0.003) respectively. Another study[21] reported that a statistically significant difference (p<0.001) was observed between the two groups only at the end of 12 weeks (Table 4).

PROBING DEPTH

Out of six RCTs, only studies by Anderson *et al.*,[20] and Soubouti *et al.*,[24] reported probing depth and found that CHX is more effective in reducing probing depth than placebo oral rinse or no intervention with statistically significant difference at 3 months (p<0.05) and 1 month (p=0.04) respectively (Table 4).

ORAL MICROBIAL FLORA

Out of 6 studies, two studies reported on oral

ISSN Print 0719-2460 - ISSN Online 0719-2479.

Table 1. Search keywords and databases used in this study.

DATABASES	KEYWORDS / MESH TERMS	NUMBER OF ARTICLES
PUBMED	((((((orthodontics) OR (orthodontic patients)) OR (fixed appliances)) OR (fixed orthodontic appliances) AND (randomizedcontrolledtrial[Filter])) AND (((chlorhexidine) OR ([("Chlorhexidine"[Mesh]) OR chlorhexidine OR (chlorhexidine di-gluconate) OR (chlorhexidine gluconate) OR (zinc-chlorhexidine) OR (chlorhexidine glucona te lidocaine hydrochloride) OR CHX OR (CHX formulations) OR (chlorhexidine phosphanilate) OR phosphanilate) OR (chlorhexidine di-acetate)])) OR (mouthwash>] ["Mouthwashes"[Mesh]) OR (Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse]) AND (randomizedcontrolledtrial [Filter]))) AND ((placebo) OR (control) AND (randomizedcontrolledtria[Filter]))) AND (((((((((plaque) OR (plaque control)) OR (anti plaque efficacy)) OR (plaque formation)) AND (gingivitis)) OR (anti-gingivitis efficacy)) OR (plaque induced gingivitis)) OR (antimicrobial efficacy)) OR (antimicrobial activity) AND (randomizedcontrolledtrial [Filter])) AND (randomizedcontrolledtrial [Filter]) Filters: Randomized Controlled Trial	89
COCHRANE	""orthodontic appliance AND "chlorhexidine"AND "placebo" AND "dental plaque" AND "gingivitis"	4
GOOGLE SCHOLAR	chlorhexidine and placebo and plaque and gingivitis, CHX, "plaque and gingivitis" -HERBAL -MOUTHWASH	230
LILACS	chlorhexidine or chx [abstract} AND placebo or control [abstract] AND antiplaque or anti-gingivitis efficiency [Abstract words]	2

Table 2. PICO analysis used for study selection.

Category	Inclusion Criteria	Exclusion Criteria
Participants	Patients undergoing fixed orthodontic treatment	studies on patients undergoing treatment with removable appliances or who underwent ortho-gnathic surgery or cleft lip and palate surgeries.
Intervention	Use of Chlorhexidine mouthwash	Use of other oral hygiene aids
Comparator	Use of placebo or control	
Outcomes	primary outcome - anti plaque and antigingivitis efficacy as assessed with indices. secondary outcome - pocket probing depth, changes in oral microbial flora.	

Table 3. General characteristics of included articles.

YEAR OF PUBLICATION	Study 1 *et al.*,[24] 1997	Study 2 *et al.*,[28] 2019	Study 3 *et al.*,[29] 2018	Study 4 *et al.*,[23] 2016	Study 5 *et al.*,[21] 1991	Study 6 *et al.*,[22] 2012
TYPE AND DESIGN OF STUDY	Randomized control Trial	Randomized control Trial	Single Blind-Randomized control Trial	Double blind-Randomized control Trial	Double blind-Randomized control Trial	Randomized control Trial
SAMPLE AND AGE/ GENDER	n=30 11-15 Years	n=30 Any age	n=54 12-21 years 31 females 23 males	n=30 10-40 Years 4 males 26 females	n=34 11-17 Years 21 girls 15 boys	n=33 11-33 Years
INTERVENTION	Group 1: 0.12%CHX Group 2: Control / Placebo	Group1: 0.2% CHX Group 2: Control	Group 1: Orthokin (Diluted CHX) Group 2: Placebo	Group 1: 0.12% CHX Group 2: Placebo	Group 1: 0.12% CHX Group 2: Placebo	Group 1: 0.12%CHX Group 2: Placebo
FREQUENCY	Twice a day for 3 months 15 ml/30 sec.	Twice a day 10 ml in 10 ml distilled water.	Twice a day for 1 month 15 ml/30 sec	Twice a day for 15 days. 15 ml/1 min	Twice a day for 3 months. ½ ounce /30 sec	Twice a week for 30 days. 10 ml/30sec
VARIABLES	Plaque Index Gingival Index Gingival Bleeding Index Plaque Index	Plaque Index Gingival Index *Streptococcus mutans*	Gingival Index Gingival Bleeding Index Probing Depth Plaque Index	Gingival Bleeding Index Plaque Index	Gingival Index Plaque Index	A. actinomyce-temcomitans
ADJUNCTIVE ORAL HYGIENE MEASURES	Brushing Twice daily	--- --- ---	--- --- ---	Brushing Flossing	Brushing with fluoride toothpaste	Brushing with fluoride toothpaste
EVALUATION PERIODS	Baseline - (8-10 days) At 1,2,3 month	1st,2nd,3rd,4th week	1 month	Day 1 Day 15	Baseline 6 weeks, 3 months	Baseline and 30 days
STATISTICAL ANALYSIS	Paired t test	Paired t-test Wilcoxon signed-rank	One-way ANOVA, Paired & independent sample t-test	One-way ANOVA, t-test	independent sample t-test	Mann-whitney, kruskal-wallis, Dunn tests
CONCLUSION	CHX is effective in reducing plaque, gingivitis and probing depth compared to placebo. compared to placebo.	CHX is effective in reducing plaque and gingivitis as well as in levels of Streptococcus mutans count compared to placebo.	CHX is effective in reducing plaque and probing depth compared	CHX is effective in reducing plaque and gingivitis compared to placebo.	CHX is effective in reducing plaque and gingivitis compared to placebo.	CHX is effective in reducing plaque accumulation and in levels of *Actinomyces actinomyce-temcomitans.*

ISSN Print 0719-2460 - ISSN Online 0719-2479.

Table 4. Results and conclusion of the included studies.

Study	AUTHOR AND YEAR OF STUDY	RESULTS	CONCLUSION
1.	Anderson *et al.*,[24] (1997)	A significant difference ($p<0.05$) was noted between the two groups for both plaque and gingival indices as well as for probing depth only at an increased period of 90 days.	CHX is effective in reducing plaque and gingivitis and probing depth compared to placebo.
2.	Shah *et al.*,[19] (2019)	A significant difference ($p<0.05$) was noted between the two groups for both plaque and gingival indices. There was a significant reduction ($p<0.05$) in *Streptococcus mutans* count with CHX as compared with placebo.	CHX is effective in reducing plaque and gingivitis as well as in levels of *Streptococcus mutans* count compared to placebo.
3.	Sobouti *et al.*,[20] (2018)	A significant difference ($p<0.05$) was noted between the two groups for Plaque Index, Gingival Bleeding Index and also for pocket probing depth, but there was no significant difference was observed in relation to Gingival Index ($p=0.1112$).	CHX is effective in reducing plaque and probing depth compared to placebo.
4.	Goes *et al.*,[23] (2016)	A significant difference ($p<0.05$) was noted between the two groups for both Plaque and Gingival Bleeding Indices.	CHX is effective in reducing plaque and gingivitis compared to placebo.
5.	Brightman *et al.*,[21] (1991)	Plaque Index showed a statistically significant difference between the two groups at 6 ($p<0.01$) and 12 weeks ($p<0.001$). Gingival and Gingival Bleeding Index showed that there was a statistically significant difference ($p<0.001$) between the two groups only at the end of 12 weeks.	CHX is effective in reducing plaque and gingivitis compared to placebo.
6.	Nelson-Filho *et al.*,[25] (2012)	A significant difference ($p= 0.0006$) was noted between the two groups for the Plaque Index. There was a significant reduction in Actinomyces actinomycetemcomitans count with CHX as compared with placebo ($p=0.0003$).	CHX is effective in reducing plaque accumulation and in levels of Actinomyces actinomycetemcomitans compared to placebo.

Table 5. Search keywords and databases used in this study.

No.	AUTHOR	YEAR	STUDY DESIGN	LEVEL OF EVIDENCE
1.	Anderson *et al.*,[24]	1997	Randomised Control Trial	Level 2
2.	Shah *et al.*,[19]	2019	Randomised Control Trial	Level 2
3.	Sobouti *et al.*,[20]	2018	Randomised Control Trial	Level 2
4.	Goes *et al.*,[23]	2016	Randomised Control Trial	Level 2
5.	Brightman *et al.*,[22]	1991	Randomised Control Trial	Level 2
6.	Nelson-Filho *et al.*,[25]	2011	Randomised Control Trial	Level 2

microbial flora changes. Studies by Shah *et al.*,[19] and Nelson-filho *et al.*,[25] had shown statistically significant reduction ($p<0.05$) of oral microbial flora with Chlorhexidine mouthwash than placebo oral rinse or no intervention.

But these two studies had assessed different microbial flora, Nelson-filho *et al.*,[25] evaluated the colony forming units of Actinomyces actinomycetemcomitans between the two groups and reported a significant reduction in Actinomyces actinomycetemcomitans count in CHX group as compared to placebo ($p=0.0003$).

Shah *et al.*,[19] evaluated Streptococcus mutans counts by comparing chlorhexidine with control, where CHX showed significant reduction in *Streptococcus mutans* counts compared to the control group ($p<0.05$) (Table 4).

Publication Bias of Included Studies

Visual assessment of funnel plots revealed presence of mild publication bias due to increased standard error of the outcome (Figure 5).

Assessment of certainty of evidence

Regarding the antiplaque and antigingivitis effect of CHX/placebo mouthwash, the quality of the available evidence was assessed by the Grading of Recommendations.

Assessment, Development and Evaluation (GRADE) approach using the GRADEpro guideline development tool.[26]

The certainty of evidence for antiplaque and antigingivitis effect of CHX / placebo mouthwash at 4 to 6 weeks was found to be moderate owing to high risk of bias assessment for one of the included studies.

The risk of publication bias was also a contributing factor in the certainty of the results obtained being moderate evidence. (Figure 6).

DISCUSSION.

This systematic review was carried out to evaluate the available evidence and report on the effectiveness of using Chlorhexidine mouthrinse in managing gingivitis and prevention of plaque accumulation among subjects undergoing orthodontic treatment. The primary outcomes assessed in this review were antiplaque effect and antigingivitis effect and secondary outcomes assessed were the probing depth and changes in oral microbial flora (Table 2).

All included studies had a second level of evidence according to OCEBM levels of evidence[27] (Table 5). The findings of this systematic review report that Chlorhexidine is effective in short term reduction of plaque accumulation and gingival inflammation in subjects undergoing orthodontic treatment and it also reduces pocket probing depth and acts as an antimicrobial agent ($p<0.05$).

Risk of bias was assessed for all included studies using the Cochrane Collaboration tool for RCTs. Out of six included RCTs, three had low risk of bias, two had high risk of bias, and one had an unclear risk of bias (Table 4 and Figure 2).

ISSN Print 0719-2460 - ISSN Online 0719-2479.

Hence the available evidence is of moderate quality. Quantitative analysis involving four studies was done for plaque index and gingival index at 4 to 6 weeks and a significant reduction with chlorhexidine than placebo or no mouthrinse was reported. In the present review, different protocols for chlorhexidine usage were noted.

Four studies[21,23–25] have compared 0.12% chlorhexidine with placebo, one study[20] compared diluted CHX with placebo and one study[19] compared 0.2 % CHX with control. For plaque index assessment, four studies[21, 24, 25,28] used Silness and Loe's index, Soubouti *et al.*,[29] used O'Leary plaque index and Goes *et al.*,[23] used Ainamo and Bay visible plaque index, five out of six studies reported chlorhexidine to be more efficient in reducing plaque accumulation around orthodontic brackets (p<0.05) at 4 to 6 weeks.[19–23] Anderson *et al.*,[24] reported CHX to be effective in reducing plaque accumulation only after an interval of 3 months. For gingival index assessment, two studies re-ported CHX to be effective only after an interval of 3 months.[21,24]

This finding may be influenced by the baseline study groups included in both the studies. Anderson et al included younger patients (11-15 years) who may not have adequate motivation towards maintaining oral hygiene.[24]

Brightman *et al.*,[21] included participants with moderate gingivitis and CHX may take a longer period to exhibit its action. Only one study reported both groups to have equal therapeutic effects in reducing inflammation,[20] this might be due to the use of diluted CHX compared to placebo mouthwash as placebo itself has some hygienic effects.

Three studies[20,21,23] assessed gingival bleeding index out of which Soubouti *et al.*,[20] and Goes *et al.*,[23] reported CHX to be clinically effective with statistically significant difference noted at 4 weeks (p=0.02) and 15 days (p=0.003) intervals respectively. Another study[21] reported CHX to be more effective in reducing gingival bleeding by 77% with statistically significant difference (p<0.001) noted after 3 months.

This may be due to the inclusion of participants with different baseline levels affecting response of gingival tissues to CHX. Secondary outcomes assessed were periodontal probing depth and changes in oral microbial flora. For assessment of Pocket probing depth, Soubouti *et al.*,[20] reported decreased probing depth at 1 month time interval with CHX. Anderson *et al.*,[24] reported decreased probing depth only at the end of 3 months (p<0.05). CHX is more effective in reducing probing depth than placebo or no intervention at different periods.

This may be due to the age groups and gingival health of participants involved in these studies. For assessment of changes in oral microbial flora two studies[19,22] have reported CHX to be more effective in reducing oral microbial flora than placebo or no intervention on a short-term evaluation.

Nelson Filho *et al.*,[22] reported significant reduction in Actinomyces actinomycetemcomitans count with CHX compared to placebo (p=0.0003), although CHX was not used frequently.

Shah *et al.*,[19] reported significant reduction in *Streptococcus mutans* count with CHX compared to placebo at four weeks. Most of the studies reported on using CHX only for a short term because of the disadvantages of using it in the long term which includes staining, burning sensation and altered taste.[30] Chlorhexidine usage on a long term of more than 4 weeks has been associated with extrinsic tooth staining.[31]

In the current review, the included trials reported using different concentrations of CHX mouthrinse[32,33] in orthodontic patients. There is no existing systematic review on CHX oral rinse in patients undergoing orthodontic treatment. A few previous systematic reviews have shown similar results with CHX mouthwash reporting gre-ater antiplaque efficacy and antigingivitis efficacy compared to other mouthwashes or placebo mouthwash, but these comparisons have been done in non-orthodontic patients.[34–36]

STRENGTHS AND LIMITATIONS

Limited number of studies included in this review limits the validity of the results and could reduce the generalizability of the outcomes observed.

One important aspect in evaluating the efficacy of any mouthwash is the duration of evaluation. According to the American Dental Association (ADA), a 6-month period is the optimum period to evaluate the efficacy and safety of a mouthrinse.[8] But in the present systematic review the studies included had evaluated effectiveness of CHX was only for 15 days to 3 months.

IMPLICATIONS FOR RESEARCH

Future high-quality studies evaluating the long-term effects, adverse effects, oral microbiota changes following the use of CHX oral rinse and comparison with other novel herbal mouthrinses in patients undergoing orthodontic treatment should be performed.

CONCLUSION.

Within the limitations of the review, we can conclude that there is a moderate level of certainty in the available evidence to suggest a short-term reduction in dental plaque accumulation and incidence of gingivitis with chlorhexidine mouthrinse.

Hence CHX mouthrinse can be recommended as an adjunct to regular oral hygiene aids in patients undergoing orthodontic treatment.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

Conflict of interests:

None of the authors has conflicts of interest to declare.

Ethics approval:

Does not apply.

Funding:

Selfunding.

Authors' contributions:

The three authors have equal contribution in the compilation, revision and analysis of the articles for this research work.

Acknowledgements:

None.

REFERENCES.

1. Mariotti A. Dental plaque-induced gingival diseases. Ann Periodontol. 1999;4(1):7-19. doi: 10.1902/annals.1999.4.1.7. PMID: 10863371.
2. Zachrisson BU, Zachrisson S. Gingival condition associated with partial orthodontic treatment. Acta Odontol Scand. 1972;30(1):127-36. doi: 10.3109/00016357209004597. PMID: 4504433.
3. Zachrisson BU. Periodontal condition in orthodontically treated and untreated individuals. American Journal of Orthodontics 1974; 65(4): 435. doi.org/10.1016/0002-9416(74)90282-6
4. Zachrisson BU, Alnaes L. Periodontal condition in orthodontically treated and untreated individuals. II. Alveolar bone loss: radiographic findings. Angle Orthod. 1974;44(1):48-55. doi: 10.1043/0003-3219(1974)044<0048:PCIOTA>2.0.CO;2. PMID: 4520950.
5. Ristic M, Vlahovic Svabic M, Sasic M, Zelic O. Clinical and microbiological effects of fixed orthodontic appliances on periodontal tissues in adolescents. Orthod Craniofac Res. 2007;10(4):187-95. doi: 10.1111/j.1601-6343.2007.00396.x. PMID: 17973685.
6. Paolantonio M, Festa F, di Placido G, D'Attilio M, Catamo G, Piccolomini R. Site-specific subgingival colonization by Actinobacillus actinomycetemcomitans in orthodontic patients. Am J Orthod Dentofacial Orthop. 1999;115(4):423-8. doi: 10.1016/s0889-5406(99)70263-5. PMID: 10194288.
7. Sinclair PM, Berry CW, Bennett CL, Israelson H. Changes in gingiva and gingival flora with bonding and banding. Angle Orthod. 1987;57(4):271-8. doi: 10.1043/0003-3219(1987)057<0271:CIGAGF>2.0.CO;2. PMID: 3479031.
8. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. J Am Dent Assoc. 2006;137(12):1649-57. doi: 10.14219/jada.archive.2006.0110. PMID: 17138709.
9. Paraskevas S. Randomized controlled clinical trials on agents used for chemical plaque control. Int J Dent Hyg. 2005;3(4):162-78. doi: 10.1111/j.1601-5037.2005.00145.x. PMID: 16451305.
10. James P, Worthington HV, Parnell C, Harding M, Lamont T, Cheung A, Whelton H, Riley P. Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database Syst Rev. 2017 31;3(3):CD008676. doi: 10.1002/14651858.CD008676.pub2. PMID: 28362061; PMCID: PMC6464488.
11. Jones CG. Chlorhexidine: is it still the gold standard? Periodontol 2000. 199715:55-62. doi: 10.1111/j.1600-0757.1997.tb00105.x. PMID: 9643233.
12. Davies A. The mode of action of chlorhexidine. J Periodontal Res Suppl. 1973;12:68-75. doi: 10.1111/j.1600-0765.1973.tb02167.x. PMID: 4269603.
13. Brecx M, Theilade J. Effect of chlorhexidine rinses on the morphology of early dental plaque formed on plastic film. J Clin Periodontol. 1984;11(9):553-64. doi: 10.1111/j.1600-051x.1984.tb00908.x. PMID: 6593327.
14. García-Caballero L, Quintas V, Prada-López I, Seoane J, Donos N, Tomás I. Chlorhexidine substantivity on salivary flora and plaque-like biofilm: an in situ model. PLoS One. 2013;8(12):e83522. doi: 10.1371/journal.pone.0083522. PMID: 24386220; PMCID: PMC3873939.
15. Puig Silla M, Montiel Company JM, Almerich Silla JM. Use of chlorhexidine varnishes in preventing and treating periodontal disease. A review of the literature. Med Oral Patol Oral Cir Bucal. 2008;13(4):E257-60.
16. Emilson CG. Susceptibility of various microorganisms to chlorhexidine. Scand J Dent Res. 1977;85(4):255-65. doi: 10.1111/j.1600-0722.1977.tb00561.x.
17. Matthijs S, Adriaens PA. Chlorhexidine varnishes: a review. J Clin Periodontol. 2002;29(1):1-8. doi: 10.1034/j.1600-051x.2002.290101.x. PMID: 11846842.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.
19. Shah SS, Nambiar S, Kamath D, Suman E, Unnikrishnan B, Desai A, Mahajan S, Dhawan KK. Comparative Evaluation of Plaque Inhibitory and Antimicrobial Efficacy of Probiotic and Chlorhexidine Oral Rinses in Orthodontic Patients: A Randomized Clinical Trial. Int J Dent. 2019;2019:1964158. doi: 10.1155/2019/1964158.
20. Sobouti F, Rakhshan V, Heydari M, Keikavusi S, Dadgar S, Shariati M. Effects of fixed orthodontic treatment and two new mouth rinses on gingival health: A prospective cohort followed by a single-blind placebo-controlled randomized clinical trial. Int Orthod. 2018;16(1):12-30. doi: 10.1016/j.ortho.2018.01.027.
21. Brightman LJ, Terezhalmy GT, Greenwell H, Jacobs M, Enlow DH. The effects of a 0.12% chlorhexidine gluconate mouthrinse on orthodontic patients aged 11 through 17 with established gingivitis. Am J Orthod Dentofacial Orthop. 1991;100(4):324-9. doi: 10.1016/0889-5406(91)70069-9. PMID: 1927982.
22. Nelson-Filho P, Valdez RM, Andrucioli MC, Saraiva MC, Feres M, Sorgi CA, Faccioli LH. Gram-negative periodontal pathogens and bacterial endotoxin in metallic orthodontic brackets with or without an antimicrobial agent: an in-vivo study. Am J Orthod Dentofacial Orthop. 2011;140(6):e281-7. doi: 10.1016/j.ajodo.2011.06.026.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

23. Goes P, Dutra CS, Lisboa MR, Gondim DV, Leitão R, Brito GA, Rego RO. Clinical efficacy of a 1% Matricaria chamomile L. mouthwash and 0.12% chlorhexidine for gingivitis control in patients undergoing orthodontic treatment with fixed appliances. J Oral Sci. 2016;58(4):569-574. doi: 10.2334/josnusd.16-0280. PMID: 28025442.

24. Anderson GB, Bowden J, Morrison EC, Caffesse RG. Clinical effects of chlorhexidine mouthwashes on patients undergoing orthodontic treatment. Am J Orthod Dentofacial Orthop. 1997;111(6):606-12. doi: 10.1016/s0889-5406(97)70312-3. PMID: 9199591.

25. Nelson-Filho P, Carpio-Horta KO, Andrucioli MC, Feres M, Bezerra da Silva RA, Garcia Paula-Silva FW, Romano FL. Molecular detection of Aggregatibacter actinomycetemcomitans on metallic brackets by the checkerboard DNA-DNA hybridization technique. Am J Orthod Dentofacial Orthop. 2012;142(4):481-6. doi: 10.1016/j.ajodo.2012.04.021. PMID: 22999671.

26. Schünemann H, Brożek J, Guyatt G, Oxman A. The GRADE handbook. Available at: https://gdt.gradepro.org/app/handbook/handbook.html

27. OCEBM Levels of Evidence. Available at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.

28. Shah SS, Nambiar S, Kamath D, Suman E, Unnikrishnan B, Desai A, Mahajan S, Dhawan KK. Comparative Evaluation of Plaque Inhibitory and Antimicrobial Efficacy of Probiotic and Chlorhexidine Oral Rinses in Orthodontic Patients: A Randomized Clinical Trial. Int J Dent. 2019;2019:1964158. doi: 10.1155/2019/1964158. PMID: 30930947; PMCID: PMC6410424.

29. Sobouti F, Rakhshan V, Heydari M, Keikavusi S, Dadgar S, Shariati M. Effects of fixed orthodontic treatment and two new mouth rinses on gingival health: A prospective cohort followed by a single-blind placebo-controlled randomized clinical trial. Int Orthod. 2018;16(1):12-30. doi: 10.1016/j.ortho.2018.01.027. Epub 2018 Feb 23. PMID: 29478929.

30. Solís C, Santos A, Nart J, Violant D. 0.2% chlorhexidine mouthwash with an antidiscoloration system versus 0.2% chlorhexidine mouthwash: a prospective clinical comparative study. J Periodontol. 2011;82(1):80-5. doi: 10.1902/jop.2010.100289. Epub 2010 Jul 27. PMID: 20653433.

31. James P, Worthington HV, Parnell C, Harding M, Lamont T, Cheung A, Whelton H, Riley P. Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database Syst Rev. 2017;3(3):CD008676. doi: 10.1002/14651858.CD008676.pub2. PMID: 28362061; PMCID: PMC6464488.

32. Jacob B, Nivedhitha MS. Comparative Assessment of the Antibacterial Efficacy of Natural Products and Chlorhexidine Mouthwash against Streptococcus Mutans: A Systematic Review. J Clin Diag Res. 2018; 12(12): ZE01-ZE07

33. Kapoor D, Kaur N, Nanda T. Efficacy of two different concentrations of chlorhexidine mouth-rinse on plaque re-growth. Indian J Dent. 2011; 2: 11–15.

34. Afennich F, Slot DE, Hossainian N, Van der Weijden GA. The effect of hexetidine mouthwash on the prevention of plaque and gingival inflammation: a systematic review. Int J Dent Hyg. 2011;9(3):182-90. doi: 10.1111/j.1601-5037.2010.00478.x. Epub 2010 Sep 6. PMID: 21356020.

35. Jassoma E, Baeesa L, Sabbagh H. The antiplaque/anticariogenic efficacy of Salvadora persica (Miswak) mouthrinse in comparison to that of chlorhexidine: a systematic review and meta-analysis. BMC Oral Health. 2019;19(1):64. doi: 10.1186/s12903-019-0741-5. PMID: 31029127; PMCID: PMC6486980.

36. Al-Maweri SA, Nassani MZ, Alaizari N, Kalakonda B, Al-Shamiri HM, Alhajj MN, Al-Soneidar WA, Alahmary AW. Efficacy of aloe vera mouthwash versus chlorhexidine on plaque and gingivitis: A systematic review. Int J Dent Hyg. 2020;18(1):44-51. doi: 10.1111/idh.12393. Epub 2019 Mar 25. PMID: 30829440.