Review

A systematic review on the use of chlorhexidine mouth rinse for the prevention of alveolar osteitis: dose, regime and risk analysis

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Abstract

Background
Alveolar osteitis (AO) is a complication following dental extractions. There is evidence for the use of chlorhexidine (CHX) in the prevention of AO. Recent systematic reviews have several limitations and do not include recent trials. Our aim was to assess the efficacy of CHX rinse in the prevention of AO and describe which dose and regime is optimal and potential adverse reactions.

Methods
MEDLINE, EMBASE, SCOPUS, Web of Science and Cochrane databases were searched for randomised controlled trials (RCTs) comparing the use of CHX rinse with no treatment, placebo rinse or saline to reduce the incidence of AO in patients undergoing an extraction. The Critical Appraisal Skills Programme checklist and risk of bias 2 tool was utilised for quality assessment. Treatment effect was assessed using absolute risk reduction, relative risk reduction and the number needed to treat to benefit (NNTB). Meta-analysis was performed using risk ratio. Fixed effects meta-analysis was used for sensitivity analysis.

Results
Of 230 RCTs identified, nine were included. 0.12% CHX rinse is more effective at reducing the incidence of AO compared to a placebo rinse yet offered no benefit over saline. There is no evidence to suggest 0.2% is more effective. Rinsing twice daily for seven days postoperatively may be optimal, however this cannot be confirmed by the data currently available. 4.3% of participants experienced minor adverse reactions; bad taste, dysgeusia and staining were common. The evidence is limited by a high risk of performance bias and failure to comprehensively account for risk factors.

Conclusion
0.12% CHX rinse is an effective and safe treatment to prevent AO. CHX is no more effective than saline, however, this evidence is significantly weaker. The most efficacious dose and regime may be 0.12% twice daily for seven days postoperatively. Further trials are needed to confirm these results.

Keywords

Chlorhexidine, rinse, alveolar osteitis.

Abbreviations

AO – alveolar osteitis
ARR – absolute risk reduction
CASP – Critical Appraisal Skills Programme
CHX – chlorhexidine
CI – confidence interval
LTF – loss to follow-up
M3M – mandibular third molar
NHS – National Health Service
NNTB – number needed to treat
PICO – patient-intervention-comparison-outcome
RCTs – randomised controlled trials
RoB2 – risk of bias 2
RRR – relative risk reduction

Introduction

Alveolar osteitis (AO) is a complication following permanent tooth extraction. Reported incidence is between 1% and 38% in mandibular third molar (M3M) extractions.[1] AO is characterised by halitosis and intense pain unrelieved by analgesics. Other symptoms include lymphadenopathy, insomnia and dizziness.[2] Blum[3] defines AO as 'postoperative pain inside and around the extraction site, which increases in severity at any time between the first and third day post-extraction, accompanied by a partial or total disintegrated blood clot within the socket'. The pathophysiology of AO is poorly understood. Birns[4] hypothesised that AO is the result of increased local fibrinolysis leading to the disintegration of the blood clot and alveolar bone exposure. Risk factors for AO include surgical trauma, surgeon inexperience, oral contraceptives, smoking and poor oral hygiene.[5]

In 45% of patients with AO, multiple post-extraction visits are needed for symptomatic relief, placing a burden on the National Health Service (NHS) and dental professionals. Societal costs due to time off work and the effect this has on patients must also be highlighted.[6] Therefore, an effective prophylactic treatment would be beneficial. Various interventions have been suggested, notably chlorhexidine (CHX), which has been widely reported in the literature to reduce the incidence of AO. CHX is a broad-spectrum antimicrobial agent and is used extensively in dentistry to prevent biofilm formation.[7]

Current evidence for the use of CHX is conflicting. Several studies have shown CHX, in rinse or gel formulation, reduces the incidence of AO.[6,8,9,10] However, Yengopal et al[11] did not identify sufficient evidence to support the use of CHX. There are several limitations of these studies. Wang et al,[10] Rodriguez-Sanchez et al[9] and Yengopal et al[11] failed to exclude studies that combine CHX with antibiotics, confounding the contribution of CHX. Taberner-Vallverdú et al[8] presented conflicting grades of recommendation and included only one non-randomised trial which assessed a CHX rinse against a control. Regarding dosage and regime, a review by Mínguez-Serra et al[12] found the optimum regime to be twice daily for seven days postoperatively using 0.2%. However, this study is outdated and included non-randomised trials which failed to report on the methodological quality of the evidence. Although the most recent review was published in 2021,[10] it failed to include the most recent randomised controlled trials (RCTs). Additionally, none of the reviews to date were focused on CHX rinse. CHX rinse requires little patient education to be implemented effectively and therefore we felt a focused review on this topic would be advantageous. As a result, we identified a need in the literature to provide an up-to-date summary of the current evidence accounting for the limitations discussed.

The primary aim of this review was to assess the efficacy of CHX rinse in the prevention of AO. Our secondary aims were to describe what doses and regimes were used and any adverse reactions that occurred, providing insight into which dose or regime may be optimal and if the benefits of CHX outweighed its adverse reactions. By doing this, clinicians will better be able to educate patients on how to prevent post operative complications such as AO.

Methods

Search methods

A search of Ovid MEDLINE, EMBASE, SCOPUS, Web of Science and Cochrane databases was conducted on 12 July 2022 and reported in line with PRISMA guidelines for relevant trials up to July 2022. **Appendix A** displays the search strategy, including the search terms used and Boolean operators applied. In addition to database searches, the reference lists were consulted to supplement the literature search.

Selection criteria

Inclusion criteria

We only considered completed RCTs up to July 2021. Articles needed to have satisfied the patient-intervention-comparison-outcome (PICO) criteria: 'In patients undergoing an extraction, does the use of a CHX rinse reduce the incidence of AO to a greater extent when compared to no treatment, a placebo rinse or saline?' A depiction of this criteria can be seen in **Figure 1**. We did not require a specific concentration or dose of CHX to be used. We did not limit our review to M3M extractions and considered articles that extracted one or more permanent tooth from any site. The required primary outcome was the incidence of AO. Studies needed to have clearly defined their criteria for a diagnosis of AO. No date or language restrictions were applied.

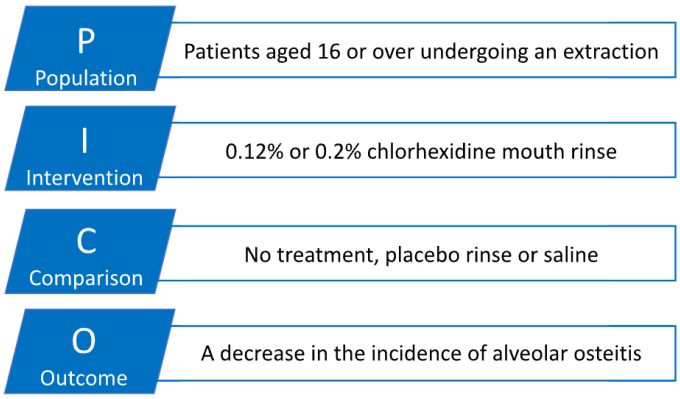

Figure 1. PICO question to be explored in this review.

Exclusion criteria

We excluded review articles, replies and expert opinion pieces. Any trials that compared CHX rinse to an active intervention, combined CHX with another form of treatment, or focused on CHX in other formulations, such as gel, were excluded.

Selection of studies

Articles sourced from our literature search were recorded and duplicates removed using EndNote Online. All remaining articles were screened and evaluated independently by two reviewers (LF and FL) to eliminate bias or errors in methodology. Firstly, articles were screened based on their title and abstract and excluded if the above criteria were not fulfilled. Full text articles of the remaining publications were retrieved and assessed for inclusion eligibility. The results obtained from each author were compared and any differences were discussed and resolved. This process produced a set of publications that satisfied all aspects of the PICO criteria.

Outcome variables and analysis

Our primary outcome was the incidence of AO. Secondary outcomes included the dose and regime of CHX administration and reported adverse effects. To analyse and compare treatment effects both within and across studies, absolute risk reduction (ARR), relative risk reduction (RRR) and the number needed to treat to benefit (NNTB) was calculated by the reviewers where this was not provided by the trial authors. Meta-analysis was performed using the Review Manager software provided by the Cochrane Collaboration. This permitted subgroup analysis which was required due to the variation in CHX concentration and controls used, allowing us to determine if differing results could be attributed to varying methodology. Risk ratios (RR), 95% confidence intervals (CI) and p-values were used to assess and compare the treatment effect. Statistical heterogeneity was assessed using the I2 test and a null hypothesis test where $p<1$ was considered to represent significant statistical heterogeneity. The Mantel-Haenszel statistical method and random effects

analysis, owing to heterogeneity in participants, interventions, and intervention delivery, was used to perform the meta-analysis. A narrative summary was provided for secondary outcomes that were not meta-analysed.

Sensitivity analysis

We pre-specified two sensitivity analyses: i) Including only trials classified as 'low risk' for random sequence generation and allocation concealment; ii) Fixed effects meta-analyses. The latter allowed us to identify the presence of small-study effects.

Quality assessment

To assess the methodological quality of the publications, both authors independently utilised the 'Critical Appraisal Skills Programme' (CASP) checklist for RCTs.[13] We reported our bias analysis summary using the CASP checklist assessment in line with the Cochrane Collaboration's recommendations.[14] Additionally, the risk of bias 2 (RoB2) excel tool for RCTs provided by the Cochrane Review Group was used to allow a more robust bias analysis.[15] The GRADEPro software online was used to grade the certainty of evidence for each outcome.

Results

Study selection

Our literature search yielded 230 articles once duplicates were removed. After title and abstract screening, 203 articles were excluded. The full content of the remaining 27 articles were retrieved for evaluation. Of these, 18 were excluded in line with our exclusion criteria. Consequently, nine articles were included in this review. **Figure 2** illustrates the selection process and **Appendix B** lists the full text articles excluded including our justification.

Study characteristics

Study design and participants

All included studies were published between 1990 and 2021 and were parallel group RCTs, except one that used a split mouth design.[16] In all studies, participants were healthy individuals aged 16 or over requiring at least one M3M extraction, excepting one study where participants required any tooth extracting[17] and one that only included heavy smokers.[16] Mean age varied from 21.4[18] to 43.4.[17] Sample size ranged from 53[16] to 744.[17]All follow ups were between days three and seven. A summary of the trials can be seen in **Table 1**.

Interventions and controls

All studies compared a CHX rinse to either saline solution,[18,19,20] a placebo solution,[21,22,23] or water.[16,17,24] Most studies used a concentration of 0.12%, except two that used 0.2%[19,20] and one that failed to specify.[24] Rinsing regimes varied: two studies prescribed a single preoperative rinse[18,24]; two studies asked participants to rinse twice daily for seven days postoperatively.[17,19] Three studies used preoperative rinsing followed by twice daily for seven days[16,20,23]; and two studies prescribed twice daily rinsing for seven days preoperatively, followed by seven days postoperatively[21,22]

Outcomes

All studies report the incidence of alveolar osteitis (AO) and all, except one,[24] state the dose and regime used. Five studies report the presence or absence of adverse events.[17,20,21,22,23]

Quality assessment

Risk of Bias (RoB2) analysis

Most studies within this review show concerns regarding the randomisation process, with only three studies reporting sound methodology.[16,18,23] Two studies were at high risk of bias due to deviations from the intended interventions and missing outcome data.[18,22] This is due to their high LTF without supporting evidence suggesting that this had a minimal effect on their ability to conduct an intention-to-treat analysis. All studies are at low risk of bias due to inappropriate methodology regarding the measurement of the intended outcome. Two studies show either some concern or a high risk of bias regarding the selection of the reported results owing to missing data.[22,23] Overall, only one study presents a low risk of bias across all domains.[16] These results can be seen in **Figure 3**.

Treatment effect analysis

Incidence of alveolar osteitis

Of the seven studies that reported the incidence of AO by subject, four reported strong evidence for the use of the intervention over the control (ARR: 4.6-25%, RRR: 37.8-63%, NNTB: 4-21.88, p <0.04).[17,21,23,24] Two reported no evidence for the use of the intervention over the control (ARR: 2.8-4.4%, RRR: 11.8-21.2%, NNTB: 22.7-35.7, p >0.05).[19,20] The remaining study did not report p-values, however the incidence of AO across all treatment groups was between 17.9% and 23.7% (ARR: 1.2-4.8%, RRR: 5.1-24.5%, NNTB: 17.2-83.3).[18] A summary of the treatment effect can be found in **Table 2**.

Four studies reported the incidence of AO by extraction site and all presented strong evidence for the use of the intervention over the control (ARR: 10.3- 37.8%, RRR: 44.2-61.9%, NNTB: 2.6-9.7, p <0.041).[16,21,22,23]

Regarding our meta-analysis, risk ratio was lowest when comparing 0.12% CHX rinse to a water rinse (RR: 0.39, 95% CI [0.25, 0.59]) and highest when comparing 0.12% CHX rinse to saline (RR: 0.86, 95% CI [0.42, 1.76]). No statistical heterogeneity was present within subgroups (I^2 = 0%). Heterogeneity was greater for subgroup differences, however, this was insignificant (I^2 = 46.2%, P=0.11). Overall, these results favour the use of a CHX rinse compared to the control (RR: 0.55, 95% CI [0.44, 0.68]). These results can be seen in **Figure 4**.

Adverse reactions to CHX

Out of a total of 1043 participants exposed to CHX, there were 15 reports of a bad taste, 18 cases of dysgeusia, 10 reports of staining to the oral tissues, one case of stomatitis and one case of brief stomach upset.

Sensitivity analysis

Owing to insufficient low risk of bias studies, a sensitivity analysis using the pooled treatment effect from low-risk studies alone was unable to be completed. Fixed effects meta-analysis showed little difference in the estimated treatment effect compared to our random effects meta-analyses, showing that the small sample size in some studies did not overestimate the treatment effect. This meta-analysis can be seen in **Appendix C**.

Certainty of evidence and level of recommendation

The results pertaining to the primary outcome of this review were graded to have very low certainty. This is due to the high risk of bias across the included studies and imprecision of the results. Despite this, the cost-effectiveness, ease of implementation, and minimal adverse events associated with CHX rinse, as shown by the moderate certainty level for this outcome, outweigh the uncertainty of these results. This allows the authors to make a conditional recommendation for the use of 0.12% CHX rinse to prevent AO. As discussed, a recommendation cannot be made regarding the dose

and regime. These recommendations can be seen in **Figure 5**.

Discussion

Summary of evidence

Our primary aim was to assess if the use of a CHX mouth rinse was effective at reducing the incidence of AO following tooth extraction. Our meta-analysis has shown six RCTs to favour the use of a CHX rinse to reduce the incidence of AO[16,17,21,22,23] whilst three showed little to no additional protection over saline.[18,19,20] Methodological heterogeneity regarding the controls used could explain the differing results. Studies that supported the use of CHX rinse used water or a placebo solution as the control, whereas those that did not used saline. Saline solution provides protection against post-operative complications such as AO,[25] yet water offers no antimicrobial properties, and it is unknown if the placebo solutions afforded any protection. This is most notable for the study conducted by Ragno and Szkutnik[23] as they failed to define the content of their placebo solution. Participants who used saline would have had a lower incidence of AO compared to those that used a control with no antimicrobial properties. Naturally, the results show that CHX is effective at reducing the incidence of AO when compared to placebo rinses, however, may offer no additional protection against AO over saline.

We also sought to describe what doses and treatment regimens were used to gain an insight into which regime may be optimal. Due to a variation in population selection criteria, controls used, methodological quality and the use of intraoperative irrigation in some studies, we were unable to identify a preferred rinsing regime. The optimum regime would be one producing the desired effect with minimal exposure to CHX, thus reducing side effects. It would be reasonable to conclude that a two-week course is less preferable, as the same benefits can be achieved using a one-week course.[16,17,23] However, more trials directly comparing regimes are needed to confirm this. Mínguez-Serra et al[12] supports this conclusion, reporting that the optimum regime was twice daily for seven days postoperatively using 0.2% CHX. Our results do not support the use of 0.2% over 0.12% as both studies that utilised 0.2% failed to show any benefit. This is most likely due to the methodological heterogeneity discussed as it is probable that a higher concentration would offer the same benefits. Nonetheless, when increased adverse effects are taken into consideration, 0.12% seems to be the most sensible choice.

Our final aim was to describe the potential adverse reactions that can occur when using CHX rinse to gain an understanding of whether the benefits of CHX rinse outweigh its potential adverse reactions. A total of 45/1043 (4.3%) participants exposed to CHX experienced an adverse event. Bad taste, dysgeusia and staining were commonly reported, which is consistent with the findings by Gürgan et al.[26] There were no reports of major adverse events such as hypersensitivity or anaphylaxis. However, it is likely that these results do not reflect the true prevalence of adverse events within the population if CHX was to be implemented widely as the protocol of four studies was not designed to detect the presence of adverse events[16,19,18,24] and a further four studies excluded participants with a CHX allergy.[16,17,19,21] The prevalence of a perioperative hypersensitivity to CHX is stated to be 9–10%,[27] yet only two major adverse events due to CHX have been recorded in dentistry within the UK.[6] The evidence suggests CHX rinse is safe to use and serious adverse reactions to CHX are rare. However, clinicians must be aware of the potential for CHX to induce both minor and major adverse events when prescribing CHX.

Strengths and limitations

This review provided a focused, comprehensive assessment of the current literature regarding the use of a CHX rinse to prevent AO. Robust statistical analysis, via meta-analyses and sensitivity analyses, and critical appraisal, using the CASP checklist and Cochrane RoB2 tool, was undertaken. The quality of evidence was graded to provide a clear clinical recommendation for practitioners. The systematic methods employed to identify the included studies were stringent, with the inclusion of published literature in all languages, alongside grey literature searching, to avoid publication bias.

Our quality assessment highlighted the limitations within the current evidence, notably the high risk of performance bias. Consequently, the treatment effect of CHX is likely to be overestimated. Interestingly, the studies at greatest risk of performance bias are those that do not support the use of CHX over saline, supporting the conclusion that CHX offers no benefit over saline. However, caution must be exercised with this conclusion. Two out of three of the studies using saline failed to account for risk factors at baseline,[18,19] notably tobacco use. Tobacco use increases the likelihood of acquiring AO by 3–4 times.[28] It is possible these risk factors were unevenly distributed between treatment and control groups in favour of the control, giving a higher incidence of AO in the treatment arm. In contrast, all studies that support the use of CHX excepting Ahmed et al[24] accounted for some risk factors at baseline, of which all include tobacco use, and so are at lower risk of producing spurious results. However, the risk factors accounted for were far from exhaustive in all studies. This highlights the need for future RCTs to comprehensively account for risk factors to minimise potential extraneous variables.

The loss to follow-up (LTF) in most studies was minimal, most probably owing to the short duration of these trials. However, two studies present a high risk of attrition bias.[18,22] Importantly, Berwick and Lessin[18] excluded and replaced participants that were LTF. Although they state that this affected the treatment and control groups evenly, this was not supported by quantitative data. This is a particular limitation in this trial design as those who were LTF were more likely to be asymptomatic and were potentially replaced by symptomatic patients. It is possible the incidence of AO was higher amongst participants within the sample and whether this affected the groups evenly is uncertain.

Conclusively, owing to the factors discussed, the evidence which does not support the use of CHX rinse is significantly weaker. However, the RCTs supporting the use of CHX rinse are not free from methodological concerns, as performance bias and a lack of comprehensive risk factor analysis is a significant limitation in all studies.

Moreover, the statistical methods of two studies fail to account for clustering effects in their extraction site analysis,[22,23] potentially leading to an inappropriate reduction of p-values.[29] Therefore, caution must be exercised when inferring conclusions from this data. This is most notable for the data reported by Larsen[22] as no subject-level analysis was performed. Additionally, only one study reported 95% confidence intervals[17] and so the precision of these results is unclear.

Finally, although the scope of this review was not limited to M3M extractions, only one study reported data for teeth from other locations. Therefore, care must be taken when applying these results to teeth from other sites.

Implication for practice

Current guidelines emphasise smoking cessation advice and oral hygiene education as the best prevention for AO.[30] Unfortunately, AO can still occur despite patients' efforts, especially after M3M extraction. In these cases, we rely on intra-socket obtundents, costing around £45 per pot, and mild analgesics. This diagnostic approach means patients present already in intense pain and adds to the financial burden of the NHS. CHX rinse is a useful preventative tool and is readily available, affordable (around £4) and requires little patient education to be implemented effectively. However, whether CHX rinse is superior to hot salty mouth rinses is uncertain. Therefore, clinicians should make a judgement on which treatment they advise considering the patient's presenting risk factors and any previous tolerance or reactions to CHX.

Conclusion

There is sufficient evidence to recommend the use of 0.12% CHX rinse to prevent AO. CHX is no more effective than saline, although this is supported by poor quality evidence. There is no evidence to suggest that 0.2% CHX offers any benefit over 0.12%. The use of CHX twice daily for seven days postoperatively may be optimum, however this is unable to be corroborated by the data. The adverse reactions caused by CHX are largely benign, yet clinicians must be prepared for a medical emergency in the event of anaphylaxis. This review has highlighted the high risk of performance bias and failure to comprehensively account for risk factors in current RCTs. Further trials are required accounting for these limitations before CHX can be recommended as a suitable preventative treatment to prevent AO.

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Declaration of Interest None

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I am currently completing my Dental Foundation Training in Bristol. I am currently enjoying the variation that dental practice brings but I look forward to future academic roles where I can continue to improve my academic capabilities. My hobbies include swimming, running and going to the cinema.

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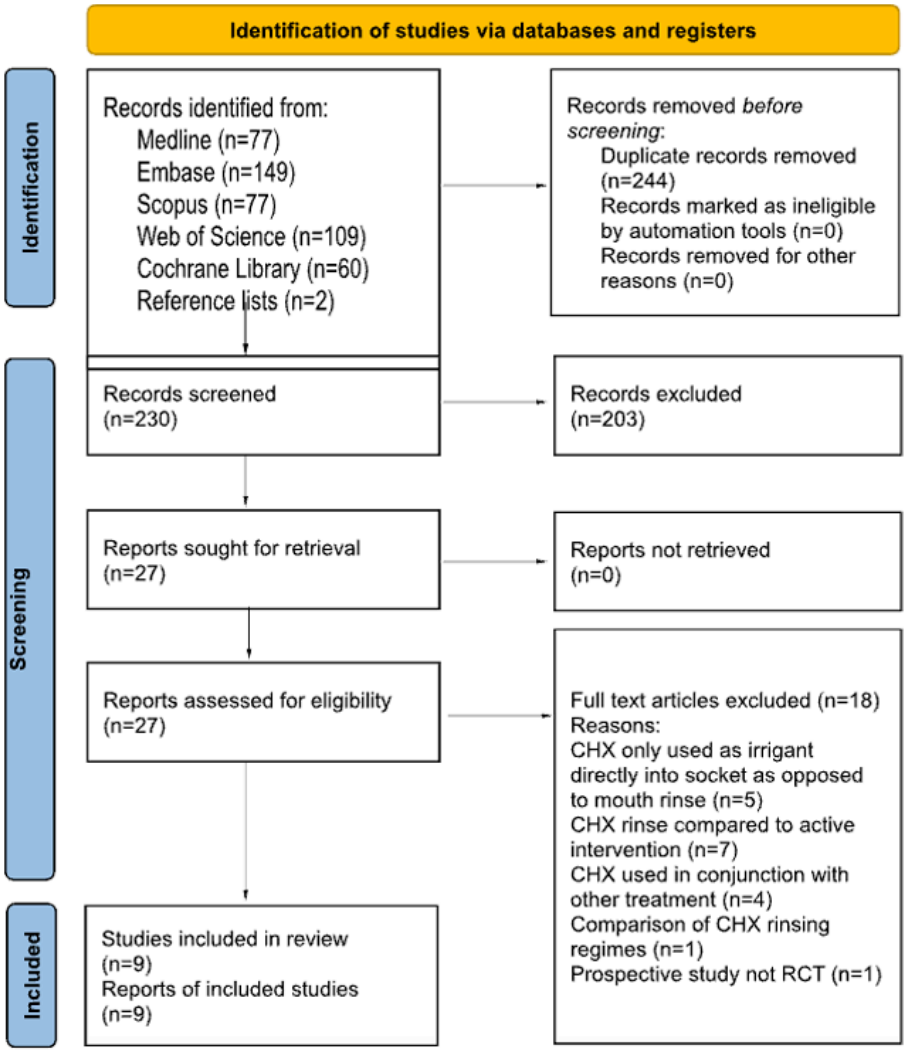
I am currently completing Dental Foundation Training in Bristol. I am completing a two-year post and am currently working in Primary Dental Care Services. This role allows me to treat patients with additional needs which I find extremely rewarding. My hobbies include watching television, going to the gym and spending time with my Vizsla, Chester.

CHX, chlorhexidine. RCT; randomised controlled trial, PICO; patient-intervention-comparison-outcome.



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

Figure 2. PRISMA flowchart showing the selection process of articles.

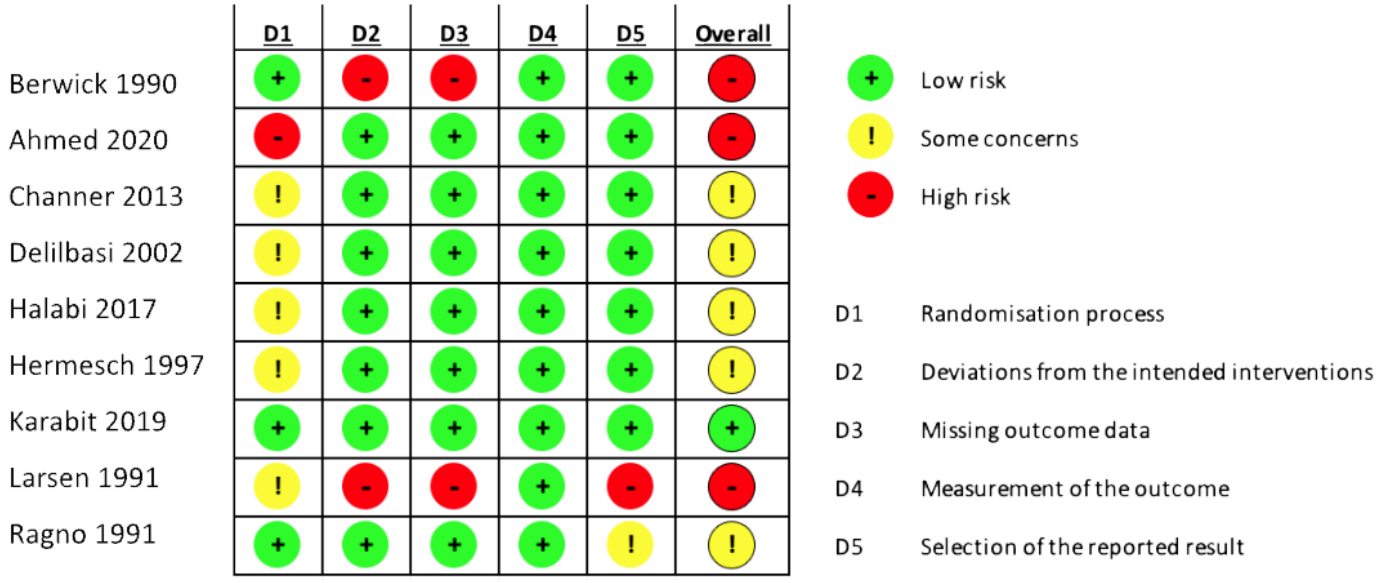

Figure 3. Risk of Bias Assessment of included studies.

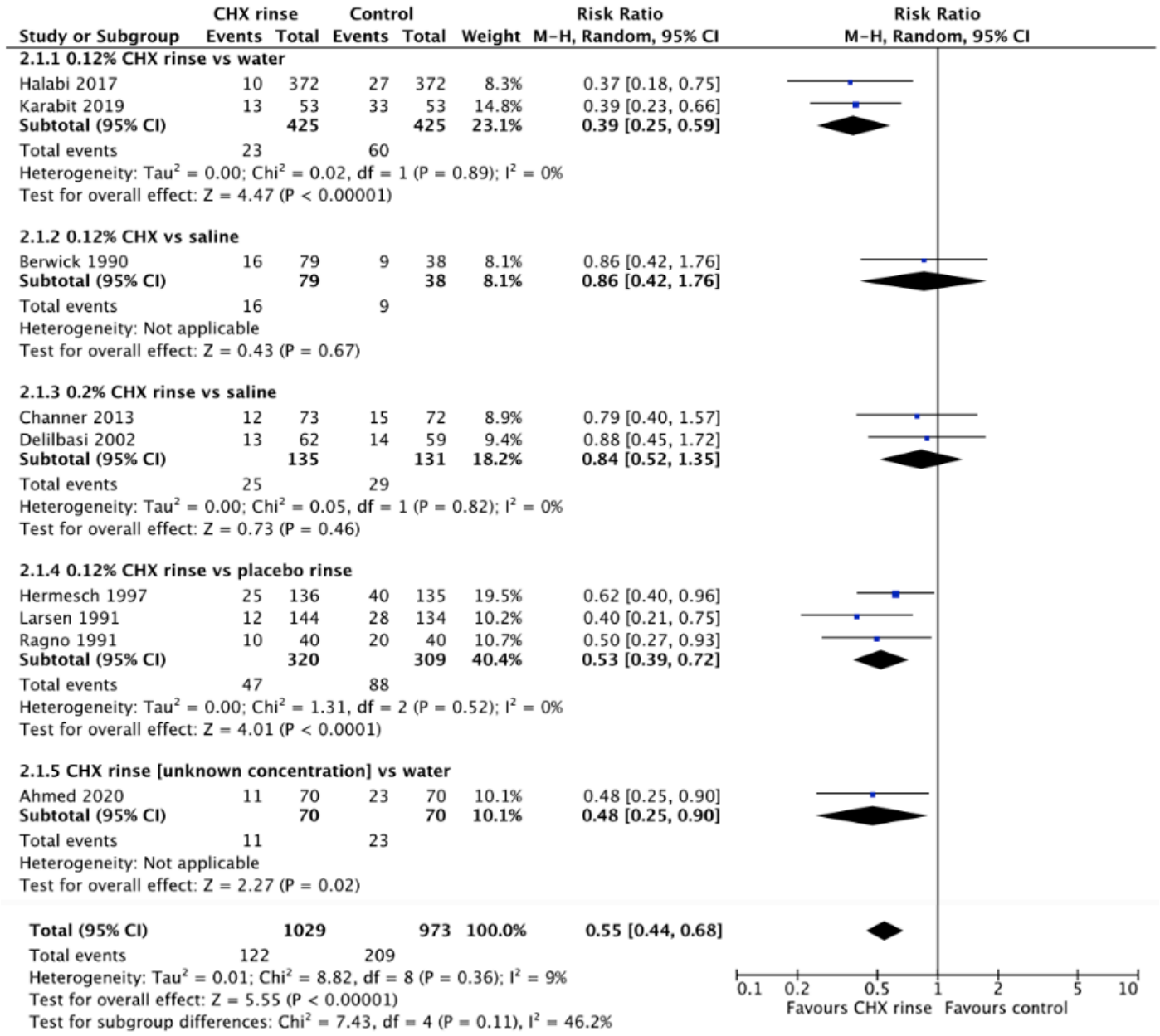

Figure 4. Meta-analysis for CHX rinse (0.12% or 0.2%) versus the control for risk ratio of alveolar osteitis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHX mouth rinse	no treatment, a placebo rinse or saline	Relative (95% CI)	Absolute (95% CI)		
Incidence of alveolar osteitis												
9	randomised trials	very serious	not serious	not serious	serious[a]	none	122/1029 (11.9%)	209/973 (21.5%)	**RR 0.55** (0.44 to 0.68)	**97 fewer per 1,000** (from 120 fewer to 69 fewer)	⨁◯◯◯ Very low	IMPORTANT
Dose and regime analysis												
9	randomised trials						Due to a variation in population selection criteria, controls used, methodological quality and the use of intraoperative irrigation in some studies, we were unable to identify a preferred rinsing regime				-	IMPORTANT
Adverse events												
5	randomised trials	not serious	serious[b]	not serious	not serious	none	45/1043 (4.3%)		not estimable		⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk ratio 0.55, 95% CI [0.44, 0.68]
b. Incidence of adverse events varied significantly despite similar sample sizes.

Figure 5. Certainty of evidence for primary and secondary outcomes.

Table 1. Characteristics of the Randomised Controlled Trials Selected

Author, Date, and Location	Study Design	Participants			Inclusion criteria	Exclusion criteria	Stratification Variables	Treatment		Regime	Outcome(s) Measured		Follow up
		Number (Extraction site no.)	Age range (Mean± SD)	Male/ female				Intervention(s)	Control		Outcome	Definition	
Ahmed, T. et al., 2020 Karachi, Pakistan	Parallel group RCT	140 I: 70 C: 70	I: (33.7±8.8) C: 34.8±9.2)	56/84	20-50 years of age with asymptomatic mesioangular impacted M3M	NR	Not used	CHX rinse	Water	20ml 30s twice -1min total-preoperatively	Incidence of PO AO	Exposed alveolar bone accompanied by moderate to severe pain within 3 days PO	3rd day PO
Berwick, M. J. E. and Lessin, C. M. E., 1990 (Unknown location)	Parallel group RCT	80 I (group 1): 20 I (group 2): 20 I (group 3): 20 C: 20	16-40 (21.4)	40/40	Healthy patients requiring M3M XLA	Pericoronitis; abx treatment; pregnant females	Not used	**Group 1**: 0.12% CHX rinse + IO irrigation using 15/15ml CHX/ saline dilution **Group 2**: 0.05% Cetylpyridium rinse + IO irrigation using 15/15ml cetylpyridium/ saline dilution **Group 3**: 0.12% CHX rinse + IO irrigation using 30ml saline	30 ml IO saline irrigation (0.09% NaCl) (no rinse)	10ml 1min preoperatively	Incidence of PO AO	Denuded socket with or without necrotic debris or fetid breath.	Between 3rd and 7th day PO
Channer, K., A., et al., 2013 Jamshoro, Pakistan	Parallel group RCT	214 I (Group 1): 73 I (Group 2): 69 C: 72	20-40 (30.44± 5.20)	129/85	Healthy patients with impacted M3M between 20-40 years of age	Acute pericoronitis; CHX allergy and penicillin	Not used	**Group 1**: 0.2% CHX rinse **Group 2**: 0.2% CHX rinse + Augmentin* (bid 7d PO)	Saline rinse (0.09% NaCl)	15ml 30s bid 7d PO	Incidence of PO AO	Loss/ necrosis of blood clot or exposed alveolar bone and throbbing pain at surgical site not relived by mild analgesia	3rd and 7th day PO

Delilbasi, C. et al., 2002 Ankara, Turkey	Parallel group RCT	177 I (group 1): 62 I (group 2): 56 C: 59	(24)	82/95	Patients in good general health requiring at least 1 M3M XLA	Pericoronitis; abx treatment; females who were pregnant, lactating or taking oral contraceptives	Not used	**Group 1**: 0.2% CHX rinse + IO irrigation using 15/15ml CHX/ saline dilution **Group 2**: 0.2% CHX rinse + IO irrigation using 15/15ml CHX/ saline dilution + Augmentin (bid 5d PO)	Sterile saline rinse (0.09% NaCl) + 30ml IO saline irrigation	15 ml 30s preoperatively followed by bid 7d commencing 24hrs PO	Incidence of PO AO Adverse reaction to CHX	Pain unrelieved by analgesia and presence of exposed/ necrotic debris	3rd and 7th day PO†
Halabi, D. et al., 2017 Valdivia, Chile	Parallel group RCT	744 I: 372 C: 372	(43.4)	363/ 381	Adults requiring XLA (any tooth) with one of the following RF: smoker; previous surgical site infection; and/or traumatic XLA	CHX allergy; abx treatment; abx prophylaxis requirement; pts living in rural areas; pts needing XLA in operating theatre	Tobacco use; previous infection; traumatic XLA	0.12% CHX rinse	Sterile water rinse	15ml 30s bid 7d commencing 24hrs PO	Incidence of PO AO Adverse reactions to CHX	Increasing PO pain intensity for 4d within/ around the socket and total/ partial breakdown of blood clot +/- bone exposure Hypersensitivity, dysgeusia or pigmentation	7th day PO (phone call 4th day PO to encourage attendance)
Hermesch, C. B. et al., 1997 Texas, USA	Parallel group RCT	271 (479) I:136 (239) C: 135 (240)	18-52 (22.3)	101/170	Healthy pts ≥ 18 years of age requiring at least one impacted M3M XLA	Pregnant or lactating females; Abx treatment within preceding 2w; abx prophylaxis requirement; pericoronitis; CHX allergy	Gender; tobacco use; no. of impacted M3M; tobacco use	0.12% CHX rinse with 11.6% alcohol	Placebo rinse identical to intervention minus CHX	15ml Bid 30s 15d commencing 7d prior to XLA	Incidence of PO AO Adverse reactions to CHX	One or more of the following: loss/ necrosis of blood clot, exposed alveolar bone, persistent or increasing pain at surgical site not relieved with mild analgesics	7th day PO (telephone evaluation 3rd- 4th day PO) †

Karabit, Z.Z., Al Kattan, F. Z., 2019 Damascus, Syria	Split mouth RCT	53 (106) I: 53 (53) C: 53 (53)	18-26	31/22	Smokers (over 20 cigarettes per day) requiring XLA of bilaterally symmetrical mesially impacted M3M	Abx prophylaxis requirement; CHX allergy; systemic disease; adrenaline contraindication; females who are lactating or taking oral contraceptives		0.12% CHX mouthwash	Distilled water	Bid 7d commencing 1d preoperatively and resuming 1d PO	Incidence of PO AO	Presence of pain, blood clot or whether socket was covered or uncovered	3rd and 5th day PO
Larsen, P. E., 1991 Ohio, USA	Parallel group RCT	139 (278) I: 72 (144) C: 67 (134)	≥ 18	61/78	Pts requiring surgical XLA of bilaterally impacted M3M	Acute infection; abx treatment; abx prophylaxis requirement	Gender; females taking oral contraception; tobacco use	0.12% CHX rinse	Placebo rinse (identical to intervention minus CHX)	15ml 30s bid 14d commencing 7d preoperatively and resuming 1d PO	Incidence of PO AO Adverse reaction to CHX	Persistent or increasing PO pain beginning after the 3rd day with necrotic tissue in socket, exposed bone, loss of blood clot or abnormal healing	7th day PO †
Ragno, J.R., and Szkutnik, A.J., 1991 Washington, D.C., USA	Parallel group RCT	80 (160) I: 40 (80) C: 40 (80)	≥ 18	51/29	Healthy pts ≥ 18 years of age and have at least 2 M3M	Pts taking mediation (except birth control pills)	Gender; tobacco use; females taking oral contraception	0.12% CHX rinse + IO irrigation using 15ml CHX	Placebo solution + IO irrigation using 15ml placebo solution	15ml 30s preoperative rinse followed by bid 7d commencing 1d PO	Incidence of PO AO Adverse reactions to CHX	Loss/ necrosis of blood clot, foul odour, increased PO pain unrelieved by mild analgesia and absence of gross infection Any adverse reactions reported by patients	3rd and 7th day PO

AO; alveolar osteitis, M3M; mandibular 3rd molar, Abx; antibiotic, bid; twice daily, s; seconds, min; minute, hrs; hours, d; days, w; weeks, no.; number, XLA; extraction, I; intervention, C; control, ml; millilitres, NR; not reported, IO; intraoperatively, PO; postoperatively RF; risk factors, SD; standard deviation, G1; group 1, G2; group 2, G3; group 3

*Augmentin= Amoxicillin 500mg + clavulanic acid 125mg

†Patients who experienced symptoms prior to the planned follow up were seen earlier for clinical evaluation

Table 2. Results for outcomes of interest: incidence of alveolar osteitis and adverse reactions to CHX.

Study	Subject based incidence of Alveolar Osteitis						Extraction-site based incidence of Alveolar Osteitis						Adverse effect of CHX: number (%)
	Intervention(s) (%) †	Control (%)	Magnitude of Treatment effect [95% CI]				Intervention(s) (%)	Control (%)	Magnitude of Treatment effect [95% CI]				
			ARR (%)	RRR (%)	NNTB	P-value			ARR (%)	RRR (%)	NNTB	P-value	
Ahmed, T. et al., 2020	11/70 (15.7)	23/70 (32.8)	17.1	52.1	5.8	0.018							NR
Berwick, M. J. E. and Lessin, C. M. E., 1990	**G1:** 7/39 (17.9) **G3:** 9/40 (22.5)	9/38 (23.7)	**G1:** 5.8 **G3:** 1.2	**G1:** 24.5 **G3:** 5.1	**G1:** 17.2 **G3:** 83.3	NR							NR
Channer, K., A., et al., 2013	12/73 (16.4)	15/72 (20.8)	4.4	21.2	22.7	>0.05							NR
Delilbasi, C. et al., 2002	13/62 (20.9)	14/59 (23.7)	2.8	11.8	35.7	>0.05							Staining of dentures/ oral mucosa: 10/118 (8.5) Dysgeusia: 18/118 (15.3) Reports of bad taste: 12/118 (10.2) Total number with adverse event 40/ 118 (34))
Halabi, D. et al., 2017	10/372 (2.7)	27/372 (7.3)	4.57 [1.5-7. 7]	62.6	21.88 [13.0-69. 3]	0.006							No adverse effects
Hermesch, C. B. et al., 1997	25/136 (18.4)	40/135 (29.6)	11.2	37.8	8.9	0.031, 0.041‡	31/239 (13.0)	56/240 (23.3)	10.3	44.2	9.7	0.014	Stomatitis: 1/ 136 (0.7) *
Karabit, Z.Z., Al Kattan, F. Z., 2019							13/53 (24.5)	33/53 (62.3)	37.8	60.7	2.6	0.039, 0.041‡	NR
Larsen, P. E., 1991							12/144 (8)	28/134 (21)	13.0	61.9	7.7	0.01	No adverse effects
Ragno, J.R., and Szkutnik, A.J., 1991	10/40 (25)	20/40 (50)	25.0	50	4	0.04	14/80 (17.5)	29/80 (36.3)	18.8	56.8	5.3	0.008	Reports of bad taste: 3/40 (7.5) Brief stomach upset: 1/40 (2.5) Total number with adverse event 4/ 40 (10)

BCP; birth control pill, NR; not reported, CI; confidence interval. G1; group 1, G3; group 3, ARR; absolute risk reduction, RRR; relative risk reduction, NNTB; number needed to treat to benefit

*Hermesch et al. (1997) reports several adverse events following surgery and treatment including paraesthesia, infection, trismus, gingivitis, glossitis, abnormal healing, nausea, sinusitis, headache, dysphagia, oedema, haemorrhage, pain, pharyngitis, and a rash. It is acknowledged that the majority of these are a result of surgery. The one incident of stomatitis in the intervention arm was deemed to be definitely/ possibly attributed to CHX.

‡Karabit and Kattan (2019) and Hermesh et al. (1997) are ambiguous in there reporting of p-values, reporting two values instead of one when comparing AO incidence between the treatment and control.

†Data only reported for intervention groups that satisfy the PICO Question.

Appendices

Appendix A

A screenshot showing an example of the search strategy used in Medline on Ovid and the number of articles found. A table format is included for ease of reading.

	Search term	Number of articles
1	Dry socket/	825
2	(Dry socket* or alveolar osteitis or alveolalgia or alveolalgias or alveolar osteitides or alveolar periostitides or alveolar periostitis).ab,ti.	671
3	Chlorhexidine/	9127
4	(Chlorhexidine or CHX).ti,ab.	13652
5	Tooth Extraction/	20281
6	(Extract* or remov*).ti,ab.	1580276
7	1 or 2	1059
8	3 or 4	15435
9	5 or 6	1587978
10	7 and 8 and 9	77

# ▲	Searches	Results	Type
1	Dry Socket/	825	Advanced
2	(dry socket* or alveolar osteitis or alveolalgia* or alveolar osteitides or alveolar periostitides or alveolar periostitis).ab,ti.	671	Advanced
3	Chlorhexidine/	9127	Advanced
4	(Chlorhexidine or CHX).ab,ti.	13652	Advanced
5	Tooth Extraction/	20281	Advanced
6	(Extract* or remov*).ab,ti.	1580276	Advanced
7	1 or 2	1059	Advanced
8	3 or 4	15435	Advanced
9	5 or 6	1587978	Advanced
10	7 and 8 and 9	77	Advanced

Appendix B

Excluded articles after full text assessment along with their reason and justification for exclusion.

Articles Excluded	Reason for Exclusion	Rationale for Exclusion
Sridhar, V. et al., 2011	Nonrandomized prospective study	Level of evidence insufficient
Metin, M. et al., 2006	Comparison of CHX rinsing regimes	Does not satisfy comparator aspect of PICO question.
Reddy, P. A. et al, 2020 Jadhao, V. A. et al, 2018 Chong, J. K. H., et al., 2016 Haupt, A. M. et al., 2015 Field, E. A. et al, 1986	CHX used as irrigant directly into socket as opposed to mouth rinse	Irrigation post-operatively by a clinician would allow better access of the CHX solution into the socket. This method of application does not reflect what could be achieved with mouth rinsing alone.
Mohanty, R. and Jha, C., 2020 Abu-Mostafa, N. et al., 2019 Divya, R. et al., 2019 Cho, H. et al, 2018 Abu-Mostafa, N. et al., 2015 Younus, S. et al., 2014 Hita-Iglesias, P. et al., 2008	CHX rinse compared to an active intervention rather than a control	Does not satisfy comparator aspect of PICO question.
Osunde, O. D. et al., 2017 Istvan, K. et al., 2017 Bonine et al., 1995 Tjernberg, A. et al., 1979	CHX rinse used in conjunction with other treatment	Addition of another treatment would confound the contribution of CHX in the treatment arm.

CHX; chlorhexidine, PICO; population, intervention, control, outcome.

Appendix C

Sensitivity analysis showing fixed effects forest plot the for CHX rinse (0.12% or 0.2%) versus the control for risk ratio of alveolar osteitis.