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Is Clindamycin Effective in Preventing Infectious Complications After Oral and Maxillofacial Surgical Procedures – A Systematic Review and Meta-Analysis

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KEYWORDS

Clindamycin, Infection, Oral surgery, Third molar surgery, Antibiotic prophylaxis, Systematic review

ABSTRACT:

Objective: To determine the effect of clindamycin in the prevention of infection after oral and maxillofacial surgery.

Material and Methods: This systematic review and meta-analysis followed the PRISMA statement, the PICO-framework and included only randomized controlled clinical trials. In all studies clindamycin was administered to prevent infections in patients who underwent oral surgery. An independent researcher conducted the search, data extraction and risk of bias assessment. Included studies were classified by the type of oral surgery. Besides, data of patients, procedures and outcome variables were collected. The combined results were expressed as proportions for the dichotomous data assessed as risk ratio using Mantel-Haenszel test at 95% confidence intervals (CIs) at $P<0.05$ considered as significant. Chi-square and Tau-square were used to assess whether the observed difference was homogeneous or heterogeneous among the studies. Statistical heterogeneity was assessed by the I^2 test at $\alpha=0.10$.

Results: Five studies were included in the pooled assessment. A total of 318 participants were in clindamycin and control groups. The pooled relative risk obtained was 0.29[0.16, 0.51]. As the relative risk is less than 1, it can be implied that use of clindamycin is associated with reduction of post-operative inflammatory complications. Overall, the results were statistically significant ($p<0.05$) with low heterogeneity ($I2=20\%$).

Conclusion: It can be implied that use of clindamycin is associated with reduction of post-operative inflammatory complications. The null hypothesis that oral clindamycin is minimally effective in preventing infection in third molar surgery regardless of the dosage used may be accepted.

Clinical Relevance: There is a lack of high quality evidence supporting the prescription of clindamycin to prevent infections after oral surgery, despite being frequently prescribed as an alternative for penicillin-allergic patients. Oral clindamycin has been shown to be very minimally effective after third molar extractions.

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1. Introduction

Despite the well-known economic and public health effects of the non-selective use of antibiotics, doctors and clinicians prescribe preventive antibiotics very frequently in common oral surgical procedures such as third molar extractions and oral implant placements in healthy patients.[1,2]

Besides, several surveys conducted in different parts of the world have shown that many medical and health professionals continue to prescribe prophylactic antibiotics after different oral surgeries, in order to prevent post-operative complications due to infection.[8]

Plenty of clinical trials have been carried out to assess the efficacy of different antibiotics in preventing infection post-surgical and non-surgical extractions, as we can acknowledge in the Cochrane Review update of 2021.[2-4] However, there is no general opinion on the use of antibiotics for the prevention of infection associated with the placement of oral implants in healthy patients.[1]

Penicillin and other antibiotics from the same group are the most routinely advised in dentistry and oral surgery. However, some important concern is raised for patients allergic to them. Clindamycin is widely used in oral surgical procedures as an alternate preventive treatment in patients allergic to amoxicillin.[5-7] In fact, many past studies reported exceptional effectiveness of clindamycin in reducing the occurrence of infectious and inflammatory complications after third molar surgery such as alveolar osteitis.[8] However, recent studies also suggest a lack of satisfactory results.[2]

Indeed, the current literature is not enough to exactly determine the benefit of clindamycin in oral surgery regardless of being commonly used as an alternative in penicillin-allergic patients.[9] For the above reasons, it was considered a necessity to carry out a systematic review and, to conduct a meta-analysis on this topic.

The aim of this study was to evaluate the effect of clindamycin (with any kind of route of administration, dosage, or regimen) in preventing infectious complications when used in patients who underwent any type of oral surgical procedure.

2. Methodology

Protocol and Registration

A systematic review of the literature and meta-analysis was performed. This study followed the (PRISMA 2020) Preferred Reporting Items for Systematic Review 2020, the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. and 4th Edition of the JBI Reviewer's Manual and was registered at PROSPERO under registration code CRD42023471247. The following focused question in the Patient, Intervention, Comparison and Outcome (PICO) format was proposed "Is Clindamycin effective in preventing infectious complications after oral and maxillofacial surgical procedures?"

Eligibility Criteria:

Inclusion Criteria:

a. Population

Studies patients of any age, gender, previous pathologies, or habits undergoing any oral surgical procedure.

b. Intervention

Studies including clindamycin administered through any route, regimen, or dosage before or after the oral surgical procedure.

c. Comparison

Studies including a placebo group or control group without any treatment.

d. Outcome

- Studies giving information about post-operative complications, and adverse events in both groups.

e. Study design

- Studies published in any language where English translation is possible.
- Studies published between 1-1-2010 to 30-6-2023
- Clinical trials, in-vivo studies, randomized clinical trials, controlled clinical trials, only
- Studies with full-text articles were included.

Exclusion Criteria:

- Studies not fully available in the database.

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- Single intervention studies without the comparative group were excluded
- Non-randomized clinical trials, Observational studies, Review reports, case series, in-vitro, and animal studies were excluded.
- Studies providing only abstract and not full text.
- Trials involving participants who had a history of significant medical conditions, or took any medication that could have influenced the results of the study.

Search Strategy

Studies were selected based on the PICOS inclusion criteria in the review protocol. Two reviewers assessed titles and abstracts to identify potentially eligible studies. Any queries were discussed with a third reviewer.

- The preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for conducting a meta-analysis were followed.
- The electronic data resources consulted for elaborate search were Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL, EMBASE, PsycINFO, Scopus, ERIC, Science Direct with controlled vocabulary and free text terms. (Table 1)
- Articles published from 01/01/2010 until 30/06/2023 were searched, without any restriction concerning the publication's language.
- Following keywords and MeSH terms were used in combination with Boolean operators in the advanced search option.

Table 1: The search strategy and PICOS tool

Search strategy	
Focused Question	Is Clindamycin effective in preventing infectious complications after oral and maxillofacial surgical procedures?
Search strategy	
Population	(("oral"[All Fields]) OR "oral surgery"[All Fields] OR ("oral"[All Fields] AND "surgery"[All Fields]) OR "oral surgery"[All Fields] OR "oral surgical procedures"[MeSH Terms] OR ("oral"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "oral surgical procedures"[All Fields] OR ("oral"[All Fields] AND "surgery"[All Fields]))
Intervention (#1)	(("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]))
Comparisons (#2)	((Control" [Text Word] OR "Placebo" [Text Word] OR "no treatment" [Text Word]))
Outcomes (#3)	("post-operative complications" [Text Word] OR "Adverse Events" [Text Word] OR pain [Text Word] OR fever [Text Word] OR Dry socket [Text Word] OR Swelling [Text Word] OR Infection [Text Word]))
Study design (#4)	((Randomized controlled studies [Text Word] OR randomized control trials [MeSH] OR randomized control clinical trial [MeSH]))
Search Combination	#1 AND #2 AND #3 AND #4
Database search	
Language	Articles in English language
Electronic Databases	PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Scopus, DOAJ
Period of Publication	Studies published between 1-1-2010 to 30-09-2023

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Selection of Studies

The title and the abstract of each study were reviewed and critically assessed by two independent reviewers. The methods used to apply the selection criteria were the following:

- Integration of the searched outcomes to delete duplicate entries
- Examination of titles and abstracts to delete clearly irrelevant articles
- Recovery of the full text of potentially relevant articles
- Binding and gathering of multiple articles of the very same study
- Examination of the articles' full text to verify the degree of compliance that the studies had with the eligibility criteria
- Establishing connection with researchers, if necessary, to clarify the study's eligibility
- Deciding about the study's inclusion and proceeding with data gathering.

Data Extraction

Two reviewers independently extracted data from the included studies. Disagreements were again resolved through discussion. Data gathered was carried out using a verification list of items that were considered for data extraction. The main items of this list were as follows:

- Authors, Year and Title of study
- Country
- Study design
- Sample size
- Age group of participants
- Gender
- Intervention
- Comparison
- Outcomes
- Methods of outcome assessment
- Conclusion and other items

Details regarding the publication and the study, the participants, settings, the interventions, the comparators, the outcome measures, study design, statistical analysis and results, and all other relevant data (funding; conflict of interest etc.) were carefully and accurately extracted from all included studies. Data extraction was done and accurately recorded in the excel sheets for all the primary outcomes separately.

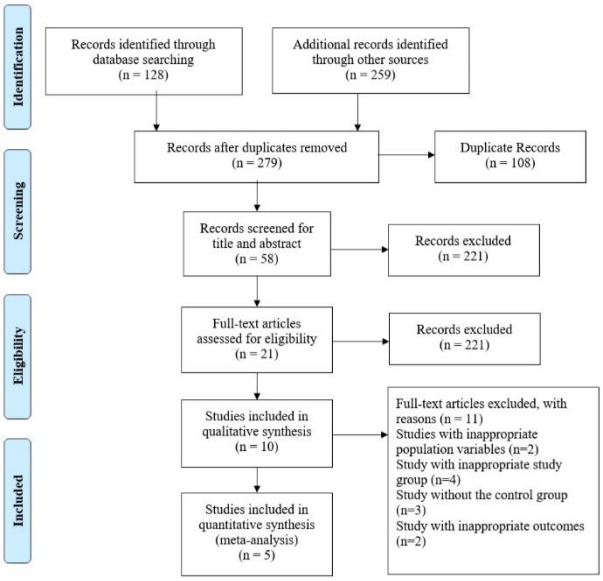

Figure 1: PRISMA Flow diagram indicating the selection process of the articles in the present systematic review

Critical Appraisal of Retrieved Studies

For randomized controlled trials, Cochrane RoB-2 tool[2] was used for quality assessment.

According to this tool, risk of bias is assessed at study level under seven domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

The overall risk for individual studies was assessed as low, moderate or high risk based on domains and criteria.

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The study was assessed to have a low overall risk only if all domains were found to have low risk. High overall risk was assessed if one or more of the six domains were found to be at high risk. A moderate risk assessment was provided to studies when one or more domains were found to be uncertain, with none at high risk.

Risk of bias was evaluated using RevMan (Review Manager Version 5.3) software.

Statistical Analysis for Quantitative Synthesis

Review Manager (RevMan) 5.3 was used for statistical analysis. The combined results were expressed as proportions for the dichotomous data assessed as risk ratio using the Mantel-Haenszel test at 95% confidence intervals (CIs) at $P<0.05$ considered as significant. Chi-square and Tau-square were used to assess whether the observed difference was homogeneous or heterogeneous among the studies. Statistical heterogeneity was assessed by the I^2 test at $\alpha=0.10$.

Assessment of Heterogeneity:

Clinical heterogeneity refers to differences between studies with regards the participants, interventions, comparators, settings, and outcomes. Methodological heterogeneity refers to the study design and the methodological quality of the studies (risk of bias).

The I square statistic (I^2) represents the percentage of the variability in effect estimates that is due to heterogeneity. I^2 is the proportion of observed dispersion of results from different studies included in a meta-analysis that is real, rather than spurious.

3. Results

Literature Search

The initial electronic database search on PubMed/MEDLINE, Cochrane Library, and DOAJ resulted in 387 titles, out of which 108 were cited as duplicates. After screening 279 abstracts, 58 relevant titles were selected by two independent reviewers. Following examination and discussion by the reviewers, 21 articles were selected for full-text evaluation. Hand-searching of the reference lists of the selected studies did not deliver additional papers. After pre-screening, application of the inclusion and exclusion criteria, and handling of the PICO questions, 10 studies were included in the qualitative synthesis and 5 were included for quantitative assessment (Figure 1).

Study Characteristics

Ten studies were included in this systematic review whose general characteristics are mentioned in Table 2.[1,3-8,10,11,13] All the included studies were parallel double-blind RCTs except for Poeschi 2004 and Posse 2016 which were single-blind RCTs.[7,10] Two dosages of clindamycin were used in the included studies – 300mg and 600mg. Most of the studies used clindamycin orally in the form of a tablet or capsule 1 hour before the procedure. The most common oral procedure was third molar surgical extraction in eight studies followed by implant placement and endodontic surgery in one study each respectively. These studies were conducted in different parts of the world including Spain (3 studies), and Austria, Netherlands, Spain, Boston, Poland, Brazil, South Africa, and Kosovo (1 study each respectively).

The conclusions of all studies indicated that the use of clindamycin reduces the chances of dry socket formation as compared to placebo control.

Table 2: Characteristics of included studies

Study ID	Place of study	Study design	Sample size	Age	Gender	Intervention	Control	Surgical procedure conducted	Follow-up	Author conclusions
Poeschl et al. (2004)[10]	Austria	RCT	352 teeth 180/172	14-61	N/A	300 mg clindamycin for 5 days	no medication	third molar removal	30 months	antibiotics used in our protocol could not reduce the overall postoperative infection rate and did not contribute to a decrease in non–infection related side

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Study ID	Place of study	Study design	Sample size	Age	Gender	Intervention	Control	Surgical procedure conducted	Follow-up	Author conclusions
										effects like dry socket, pain, and reduced mouth opening.
Lindeboom et al. (2005)[11]	Netherlands	RCT double-blind	256 128/128	44.1+-10.8	109/147	single dose of 600 mg clindamycin orally 1 h before incision	single dose of placebo orally 1 h before incision	endodontic surgery	1,2,4 weeks	No statistically significant difference was found between clindamycin] rophylaxis and placebo with regard to the prevention of postoperative infection in endodontic surgical procedures.
Dios et al. (2006)[5]	Spain	RCT	221	24.9+-5.7	126/95	a standard prophylactic regimen of 600 mg of CLIorally 1 to 2 h before anesthesia induction	No treatment	third molar removal	N/A	CLI prophylaxis was noneffective as compared to amoxicillin and moxifloxacin.
Halpern and Dodson, 2007[4]	Boston	RCT double blind	122 Lost to follow-up -4 59/59	25.4+-7.2	57/65	Penicillin (15,000 units per kilogram) or, for penicillin-allergic subjects, clindamycin (600 mg)	Placebo 0.9% NS	third molar	N/A	In the setting of third molar removal, these results suggest that the use of intravenous antibiotics administered prophylactically decrease the frequency of SSIs. The authors cannot comment on the efficacy of intravenous antibiotics in comparison to other antibacterial treatment regimens.
Kaczmarzyk et al. (2007)[13]	Poland	RCT double blind	86 31/28/27	23.4+-0.6	23 /63	1. single-dose group: patients receiving 600 mg clindamycin hydrochloride orally 60 min preoperatively, 2. 5-day group: patients receiving 600 mg clindamycin hydrochloride orally 60 min preoperatively, followed by a dose of 300 mg clindamycin hydro chloride every 8 h for 5 days	300 mg placebo	third molar surgery	1,2,7 days	Clindamycin applied in a single preoperative dose of 600 mg with or without subsequent 5-day therapy does not demonstrate efficacy in prophylaxis for postoperative inflammatory complications after third molar surgery.
Adde et al. (2012)[3]	Brazil	RCT double blind	71	18-45	49/22	300 mg clindamycin every 6 hours for 7 days	No treatment	third molar surgery	7 days	This study demonstrated that antibiotic prophylaxis should not be indicated in all cases of third molar surgery. The evaluation of factors, such as sys emic conditions of the patient, skill of the operator, and contamination of the surgical environment should be conducted correctly.
Maharaj et al. (2012)[6]	South Africa	RCT	80 40/40	18-60		600mg clindamycin orally	No treatment	third molar surgery	N/A	This study showed that none of the treatments prevented post-extraction bacteraemia and confirmed earlier reports that bacteraemia is not

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Study ID	Place of study	Study design	Sample size	Age	Gender	Intervention	Control	Surgical procedure conducted	Follow-up	Author conclusions
										completely eliminated by antibiotics.
Hamiti-Krasniqi et al. (2014)[8]	Kosovo	RCT double-blind	30/30	N/A	N/A	300mg clindamycin	No treatment	third molar surgery	N/A	The use of local intra-alveolar Clindamycin after a removal of third mandibular molar. This will improve the patients' quality of life by reducing the chances of developing dry socket which is known to be a very painful experience.
Posse et al. (2016)[7]	Spain	RCT single blind	55/52	18-51	N/A	[standard prophylactic regimen with 600 mg of clindamycin	no antibiotic prophy laxis before the dental procedure)	third molar surgery	N/A	Bacteraemia following dental extractions was undetectable with amoxicillin/clavulanate prophylaxis as compared to clindamycin.
Arrieta et al. (2023)[1]	Spain	RCT double blind	32 31/31	48.6+-10.1	22/40	a single dose of 600-mg clindamycin (two capsules of 300 mg) 1 h before surgery	two capsules of placebo 1 h before surgery	implant placement	1,7,14,28,56 days	The use of preoperative clindamycin in oral implant surgery under straightforward conditions in healthy adults may not be beneficial in reducing oral implant failures.

Quality Assessment of RCTs

Among the included studies, four[4,5,11,12] studies showed low risk of bias, two[6,8] showed moderate risk and three[3,7,10] showed high risk of bias.

In the study by Poeschl et al. (2004)[10] and Hamiti-Krasniqi et al. (2014)[8], information related to randomization, allocation concealment, and blinding was not mentioned while in the study by Kaczmarzyk et al. (2007)[12], incomplete outcome data was seen. Hence these studies showed a high risk of bias.

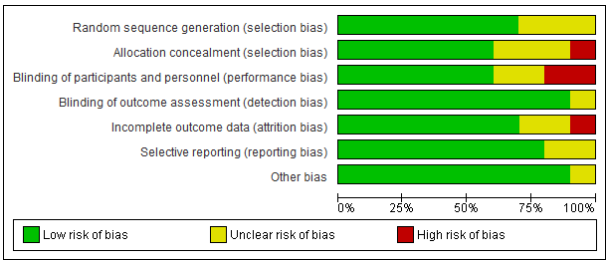

Figure 2: Risk of bias graph

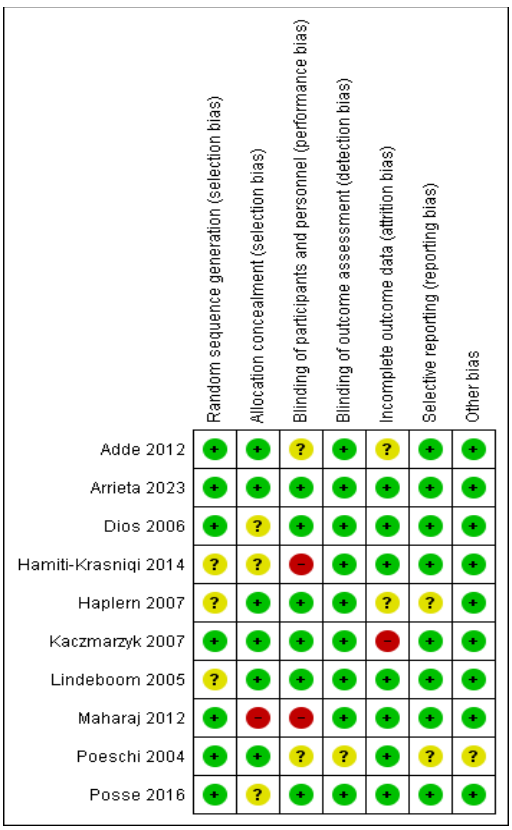

Figure 3: Risk of bias summary

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Meta-Analysis

Data synthesis was carried out using a descriptive synthesis, with a summary of the characteristics of each included study. For quantitative synthesis, a summary of the combined estimate related to the intervention effect was calculated as several events and the total sample size of individual studies.

Effect Measures

Effect measures refer to statistical constructs that compare outcome data between two intervention groups. For this study, relative risk was used as an effect measure. Studies were included in the meta-analysis irrespective of the dosage of clindamycin used.

Post-Operative Inflammatory Complications

Five studies were included in the pooled assessment. A total of 318 participants were in clindamycin and control groups. The pooled relative risk obtained was 0.29[0.16, 0.51]. As the relative risk is less than 1, it can be implied that the use of clindamycin is associated with the reduction of postoperative inflammatory complications. Overall, the results were statistically significant ($p<0.05$) with low heterogeneity (I^2=20%).

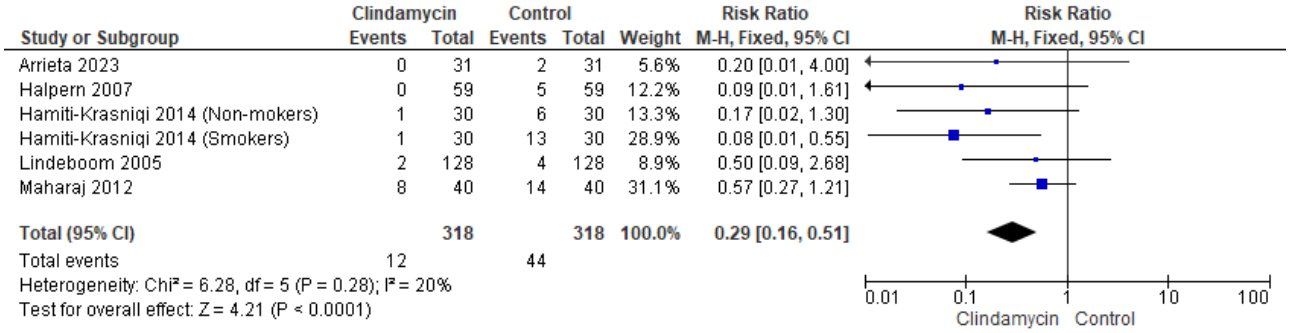

Figure 4: Forest plot for postoperative inflammatory complications.

4. Discussion

The principal findings of this systematic review and meta-analysis were that despite being the antibiotic of choice in patients with hypersensitivity reactions to penicillins, only a small number of studies are available that focus on the effect of prophylactic clindamycin in oral surgery procedures.[10]

The quantitative analysis carried out on five studies evaluating the effect of oral clindamycin in third molar extractions showed the effectiveness of clindamycin in preventing infection complications post-operatively as compared to placebo control.

However, the main weakness of this study is the small number of publications available indicating the use of clindamycin in procedures other than 3rd molar extractions. Ten clinical trials met the inclusion criteria: eight on third molar extractions, one in endodontic surgery, and one on oral implant surgery.[11] In the rest of oral surgical interventions, the authors did not use a control group with placebo or no treatment which might be due to ethical reasons or non-compliance of patients. However, the absence of a control group makes it difficult to assess the efficacy of the tested treatment modality.

One RCT analyzed the preventive effect of penicillin, replacing it with clindamycin if the patient was allergic to penicillin.[2] Some studies did not specify the number of infected patients or the sample size of each antibiotic according to the antibiotic that was finally used. Nevertheless, there was also a difference in the route of administration of Clindamycin, its dose, and whether it was given preoperatively, postoperatively, or both.

The sample size of each study is another aspect that can be taken into consideration. In the quantitative analysis, a total of 318 participants were in the clindamycin and control groups. In addition, we must keep in mind that each of the trials studied a different antibiotic prescription pattern in different surgical procedures and different sample sizes.

Besides, we must consider the risk of bias in each of the studies discreetly. Four studies showed a low risk of bias, two showed a moderate risk and three showed a high risk of bias.[13]

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Moreover, there may be important suggestions for clinicians emerging from the present study. Nowadays, there is no generalized agreement on the need to prescribe precautionary antibiotics in oral surgical procedures such as third molar extractions or oral implant placements in healthy patients. Most reviews and meta-analyses that have been conducted are by using prophylactic beta-lactam antibiotics. In 2021 a Cochrane review, it was concluded that Prophylactic antibiotics, when given after third molar extractions reduce the risk of dry socket, infection, and pain, and showed an overall decrease in adverse effects and complications post-surgery.[2] However, due to the increasing prevalence of antibiotic resistance in bacteria from currently available antibiotics, clinicians should cautiously consider the benefits and harm in treating multiple healthy patients with antibiotics to prevent one infection (NNT).[12]

Clindamycin is frequently used to treat healthy patients allergic to Amoxicillin in oral surgery.[2] Few results also indicate that oral clindamycin may not only be ineffective in preventing infections after third molar extraction, but it might even have an undetectable or negative effect. No statistically significant difference was found between clindamycin prophylaxis and placebo in the prevention of postoperative infection in endodontic surgical procedures.

The NNT is only a part of the information that is required to make decisions. Therefore, clinicians must also consider other factors such as costs, side effects, patient characteristics, and socio-economic priorities while prescribing antibiotics before and/or after oral surgery to avoid infections.

Educational programs, clinical guidelines, mentors, professionals, and educators should promote the recent advances in the use of prophylactic and empirical antibiotics in oral surgery. They should also attempt to reduce the possible and evident gap between the prophylactic antibiotic usage supported by scientific evidence and the real antibiotic prescriptions advised by professionals.[2]

This review also highlights the need for further research focusing on clindamycin, with different dosages, different routes of administration, and adverse drug reactions, particularly in those surgical procedures where it is frequently prescribed as a prophylactic treatment.[10,11]

It would also be interesting to review the efficacy of other antibiotics such as clarithromycin, azithromycin, and metronidazole that are also used as preventive treatment in oral surgery procedures in patients allergic to amoxicillin. Metronidazole is a synthetic antibiotic that is highly effective against obligate anaerobes but is not effective against facultative anaerobic bacteria. Clarithromycin is another acceptable penicillin substitute. This drug has a more limited spectrum of activity than clindamycin but has some advantages over erythromycin. Clarithromycin is effective against facultative anaerobes and some of the obligate anaerobic bacteria.[5]

Therefore, even though, enough evidence to evaluate the effectiveness of preventive clindamycin in oral surgical interventions other than third molar extraction is not available, the conclusions of all studies still indicate that the use of clindamycin reduces the chances of dry socket formation as compared to placebo control. It can be implied that the use of clindamycin is associated with the reduction of post-operative inflammatory complications. The null hypothesis that oral clindamycin is effective in preventing infection in third molar surgery regardless of the dosage used may be accepted.

5. Conclusion

The present systematic review aimed to evaluate the effectiveness of clindamycin in preventing infectious complications after oral and maxillofacial surgical procedures, particularly in patients undergoing third molar extractions. Despite the widespread use of clindamycin as a prophylactic antibiotic, the evidence gathered from the included studies presents a complex picture.

The results demonstrate that clindamycin, regardless of dosage or regimen, does not consistently prevent post-operative infections or reduce the incidence of complications such as dry socket and pain when compared to placebo or no treatment. While some studies indicated minor benefits, the majority found no statistically significant difference between clindamycin and control groups. This lack of consistent efficacy raises questions about the routine use of clindamycin for such procedures, especially considering the potential for antibiotic resistance and adverse effects.

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Given the heterogeneous results and the limitations of the studies included, such as varying dosages, procedures, and sample sizes, there is a clear need for further high-quality randomized controlled trials. These future studies should aim to standardize protocols and consider the broader implications of antibiotic prophylaxis in oral surgery. Until more definitive evidence is available, the use of clindamycin should be carefully weighed against its potential risks, and alternative strategies for infection prevention should be considered.

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