

Comparative efficacy of pre-operative and post-operative administration of amoxicillin in third molar extraction surgery – A systematic review and meta-analysis

ABSTRACT

To compare the effectiveness of pre-operative and post-operative administration of amoxicillin in patients undergoing third molar extraction surgery. A systematic search was executed according to PRISMA guidelines for studies published till December 2021. Studies were included based on the pre-eligibility criteria. The risk of bias was assessed using the Cochrane risk of bias tool. The heterogeneity was evaluated, and a random effect model was used for meta-analysis. A total of five studies were included from an initial search of 96 studies. The included studies were randomized controlled trials and comparative studies assessing pre-operative and post-operative administration of antibiotics among patients undergoing third molar extraction surgery. For comparison between pre-operative and post-operative groups, interincisal distance, complications, pain, and swelling were systematically reviewed and meta-analysis was done for interincisal distance and complications. The mean change in interincisal distance ranged from 5.5 to 47.9 and from 4.56 to 46.1 in the pre-operative and post-operative amoxicillin groups, respectively. Complications reported were infections, alveolar osteitis, nausea, diarrhea, gastric pain, rash, and headache with a pooled incidence of 4.3–33% in the pre-operative amoxicillin group and 0–22.7% in the post-operative amoxicillin group. Quantitative synthesis of data carried out from meta-analysis shows a significant difference in the pre-operative and post-operative amoxicillin groups in improving the interincisal distance and incidence of complications post surgery. The qualitative synthesis of data derived from systematic review for pain provides favoring results for post-operative amoxicillin administration. In case of swelling, a non-conclusive result was obtained.

Keywords: Amoxicillin, meta-analysis, pre-operative and post-operative, third molar surgery

INTRODUCTION

One of the most frequent surgical procedures in dentistry is third molar disimpaction.^[1-7] It is very common to develop a range of potential infections as well as other complications following surgery.^[2] Post-operative complications include pain, swelling, discomfort, and trismus.^[6,7]

The most common bacteria that cause infections following third molar surgery are streptococci, bacteroides, and fusobacteria. To prevent such infections, dental professionals recommend taking antibiotics before and/or after surgery to prevent systemic and local infections.^[3] Penicillins, cephalosporins, tetracyclines and metronidazole are the most common antibiotics used in dentistry.^[4]

Although the use of antibiotics in third molar surgery has long been a controversial issue, amoxicillin has always been a preferred antibiotic since it is safe, bactericidal, and highly effective.^[5]

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Amoxicillin has a few but well-known side effects too, which include diarrhea, nausea, vomiting, and abdominal discomfort.^[8-12] It is typically prescribed orally every 8 hours or every 12 hours in 500 mg and 1000 mg doses. Blood levels peak in 1–2 hours after oral administration.^[13]

The controversy over the pre- and post-operative amoxicillin arises due to variations in the results of studies.

Hence, the purpose of this meta-analysis was to compare the efficacy of administration of amoxicillin pre-operative and post-operative for third molar extraction surgery regardless of the dosage used.

METHODOLOGY

Protocol registration

The current systematic review and meta-analysis was conducted and written according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Statement) checklist recommendations and is registered in PROSPERO (registration number CRD42021255870).

The screening process of studies is presented in the form of PRISMA flow chart [Figure 1]. From a total of 96 studies identified in the initial search, only five studies were included in the qualitative and quantitative syntheses. Detailed study characteristics of the included studies in this systematic review and meta-analysis are presented in data extraction sheets [Table 1].

Literature search

A systematic search was carried out in PubMed and EBSCOhost databases and Google Scholar search engine. Search terms pertaining to effectiveness of antibiotics in patients undergoing third molar extraction surgery were selected with the help of MeSH library. Additionally, free text terms were also used. An appropriate search strategy was framed using Boolean operators as follows:

- Amoxicillin AND preoperative AND postoperative AND extraction AND molar
- Amoxicillin AND preoperative AND postoperative AND third molar surgery
- Amoxicillin AND preoperative AND postoperative AND tooth extraction.

Filters were set for article type at clinical trial, clinical study, randomized controlled trials, and human species with the best match option. Additionally, chasing of cross references from the relevant articles was done. Specialty journals available in the Institutional library were hand-searched for studies on antibiotics use in third molar surgery.

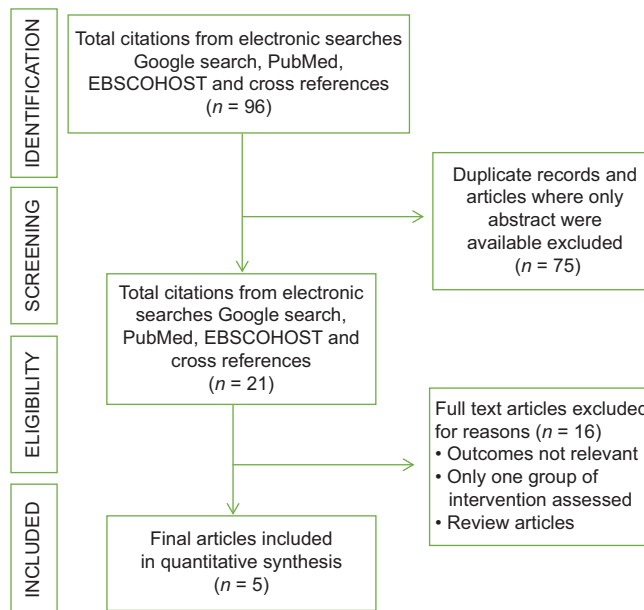


Figure 1: PRISMA flow chart representing screening process of articles

Eligibility criteria

All the randomized controlled trials, quasi-randomized controlled trials, and comparative studies comparing the use of amoxicillin pre-operatively and post-operatively irrespective of dosage were included in the study, along with parameters such as post-operative inflammation, complications, pain, and swelling among males and females above the age of 18 undergoing third molar surgery. Articles published in English language or possible of getting translated into English language and published until year 2021 were eligible for the review. On the other hand, studies with dissimilar parameters for comparison and data reported through retrospective studies, clinical case reports, case series, literature review, abstracts, conference proceedings, books, reports, animal studies, letter to editor, and short communications were excluded.

Study selection

Two authors (first and second author initials) independently conducted the screening process and three steps. In step 1, articles were screened based on titles and irrelevant studies were excluded. In step 2, the abstract of the remaining articles was read to take a further decision on their eligibility. In step 3, the full text of the remaining articles was read and a final decision for their inclusion or exclusion was made. Uncertainties encountered were resolved by the help of the third author. The eligibility criteria were based on PICO (population, intervention, comparators, and outcomes) [Table 1].

Risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool – the Cochrane Handbook for systematic review

Table 1: Data extraction sheet

Sr. no.	Author	Year of publication	Sample		Dosage of drug		Duration of drug	
			Preoperative	Post operative	Preoperative	Post operative	Preoperative	Post operative
1	Lacasa JM <i>et al</i>	2007	68	69	1000 mg amoxicillin + 62.5 mg clavulanate	1000 mg amoxicillin + 62.5 mg clavulanate	2 tablets before surgery	Twice/5 days
2	Ataoglu H <i>et al</i>	2008	50	50	1 gm amoxicillin + clavulanic acid orally	1 gm amoxicillin + clavulanic acid orally	twice/5 days	Twice/5 days
3	Luaces - Rey R <i>et al</i>	2010	70	75	2 gm amoxicillin	1 gm amoxicillin	once before surgery + once after surgery	Once/5 days
4	Lopez - Cedrun JL <i>et al</i>	2011	39	44	500 mg amoxicillin	500 mg amoxicillin	once before surgery	Thrice/5 days
5	Mariscal - Cazalla MM <i>et al.</i>	2020	30	32	750 mg	750 mg	every 8 hrs 2 days before and 5 days after surgery	Every 8 hrs/ 5 days

Sr. no. (cont'd)	Pain		Swelling		Complications		Interincisal Distance	
	Preoperative B/A	Post operative B/A	Preoperative B/A	Post operative B/A	Preoperative B/A	Post operative B/A	Preoperative B/A	Post operative B/A
1	1.7	1.2	Not reported	Not reported	5.3% with infection	2.8% with infection	47.916.3	46.119.3
2	6% with > 40 VAS	4% with > 40 VAS	6%	8%	14% with wound infection	2% with alveolar osteitis, 18% with wound infection	4115/3916	4516/4216
3	2.4	1.8	Not reported	Not reported	4.3% with infection	5.3% with infection	8.5	8.4
4	17.3	11.6	Not reported	Not reported	Total - 33.3% with 2.56% with nausea, 5.12% with diarrhoea, 7.69% with gastric pain, 2.56% with rash, 2.65% with headache, 12.82% with other complications	Total 22.7% with 4.54% with nausea, 2.27% with diarrhoea, 2.27% with gastric pain, 6.81% with headache, 15.9% with other complications	52.1 6.6/ reduced to 16.2%	52.6 6.1/ reduced to 13.6%
5	1.742.1	0.72 1.22	1.13 + 1.5	0.59 + 1.01	10% with infection	0% with infection	5.514.92	4.56 5.35

Interventions Versions 5.1,0 (updated March 2011) The Cochrane Collaboration, 2011.

Statistical analysis

Meta-analysis was performed to estimate the pooled odd's ratio for complications and mean difference for interincisal difference at 95% confidence intervals (CIs). Heterogeneity was quantified using I² statistics, and based on the heterogeneity, the fixed/random effect analysis was performed.

RESULTS

Detailed study characteristics of the included studies in this systematic review and meta-analysis are presented in data extraction sheets [Table 1]. They show qualitative synthesis of four parameters, Interincisal distance, complications, pain,

and swelling, and quantitative synthesis of two parameters, Interincisal distance and complications. The details were obtained from five studies concluded by Lacasa JM *et al.*^[14], Ataoglu H *et al.*^[15], Luaces-Rey R *et al.*^[16], López-Cedrún JL *et al.*^[17], and Mariscal-Cazalla MM *et al.*^[18]

Pain and swelling were assessed through qualitative synthesis. All five studies reported about pain following third molar surgery with the pain score ranging from 1.7 to 17.3 for four studies.^[14-19] A study by Ataoglu H *et al.*^[15] presented 6% patient with >40 VAS score, which decreased to 4% patient with >40 VAS score.

Only two studies reported swelling^[15] demonstrating swelling among 6% pre-operative amoxicillin group and 8% post-operative amoxicillin group, whereas Mariscal-Cazalla MM

et al.^[18] report swelling of 1.13 pre-operative amoxicillin group and 0.59 post-operative amoxicillin group. Both pain and swelling presented improvement after third molar surgery.

Interincisal distance and complications were analyzed via quantitative synthesis. For interincisal distance, only three studies were included for meta-analysis and the heterogeneity was found to be low ($I^2 = 0\%$) with a Q-statistic of 8.367, indicating statistical significance with a P value of 0.015 for 2 degrees of freedom. As depicted in Forest plot 1 [Figure 2] for three estimates, the pooled mean difference denoted by diamond is reported to be 0.302 (-1.752 to 1.149). Since the diamond is crossing the null effect line, there is no significant difference between the two groups with respect to interincisal distance or mouth opening after third molar extraction surgery.

With respect to complications associated with third molar surgery, the data from all five studies were pooled. As depicted in Forest plot 2 [Figure 3], the heterogeneity was found to be high across the studies ($I^2 = 85\%$); thus, the random effect model was used with a Q-statistic of 4.035, τ^2 of 0.004, indicating statistical significance with a P value of 0.015 for 4 degrees of freedom. As depicted by the diamond in the forest plot for five estimates, the odds ratio was reported to be 1.221 (0.67 to 2.22). Since the diamond is crossing the null effect line, there is no significant difference between the two groups with respect to the development of complications after third molar extraction surgery.

Publication bias was assessed using funnel plot. For interincisal distance, since the studies were less in number, a confirmation regarding the presence of publication bias could not be provided. For complications, the studies were equally distributed on the right and the left side of the funnel, thereby representing no publication bias [Figure 4]. Assessment of risk of bias was conducted according to the guidance in Higgins, JPT, Green, S (editors): the Cochrane Handbook for systematic review Interventions Versions 5.1,0 (updated March 2011) The Cochrane collaboration, 2011.

DISCUSSION

Due to the nature and environment of third molar surgery, inflammation and infection are the most commonly observed complications. So, to make third molar surgery as uneventful as possible, clinicians have recommended several interventions.

In dental practice, antibiotics are preferred for limiting post-operative infections as they have a wide range of effectiveness. But it was observed that whether antibiotics should be prescribed before or after surgery, is still a question due to which clinicians often face dilemma.

Hence, this meta-analysis and systematic review attempted to integrate the data on efficacy of administration of antibiotics before or after surgery irrespective of dosages selected by clinicians in the included studies.

Data used for comparison have parameters such as pain, swelling, and interincisal distance and complications following third molar surgery. Systematic review was carried out for parameters such as pain, swelling, interincisal distance, and post-operative complications, while meta-analysis was done for interincisal distance and post-operative complications. These categories of parameters were based on quantitative and qualitative data required for meta-analysis and systematic review, respectively.

Pain

Inflammation caused by trauma often causes pain after third molar surgery. The intensity of pain increases 6–8 hours later. According to Lacasa JM *et al.*,^[9] the post-operative amoxicillin group experienced a pain intensity of 1.2 and 1.7 in the pre-operative amoxicillin group, Ataoğlu H *et al.*^[15] found 6% of the pre-operative group and 4% of the post-operative amoxicillin group, Luaces-Rey R *et al.*^[16] reported the post-operative amoxicillin group as 1.8, compared to those prior to the surgery amoxicillin group as 2.4, and López-Cedrún JL *et al.*^[17] study showed a 17.3 score in the pre-operative group and a 11.6 score in the post-operative group. In addition, Mariscal-Cazalla MM *et al.*^[18] reported significantly less pain in the post-operative group with a

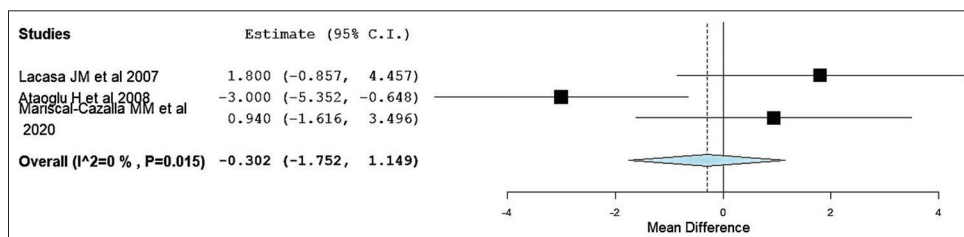


Figure 2: Forest plot representing mean difference in interincisal distance between groups (preoperative amoxicillin and post-operative amoxicillin)

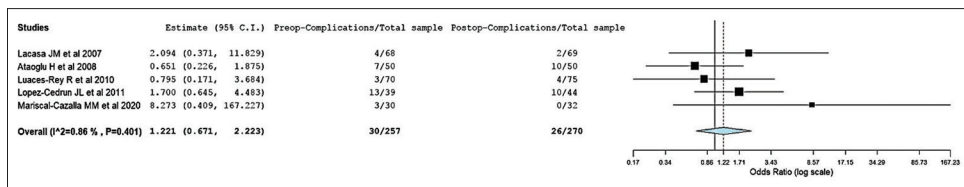


Figure 3: Forest plot representing odds ratio for adverse reaction/complications between groups (preoperative amoxicillin and post-operative amoxicillin)

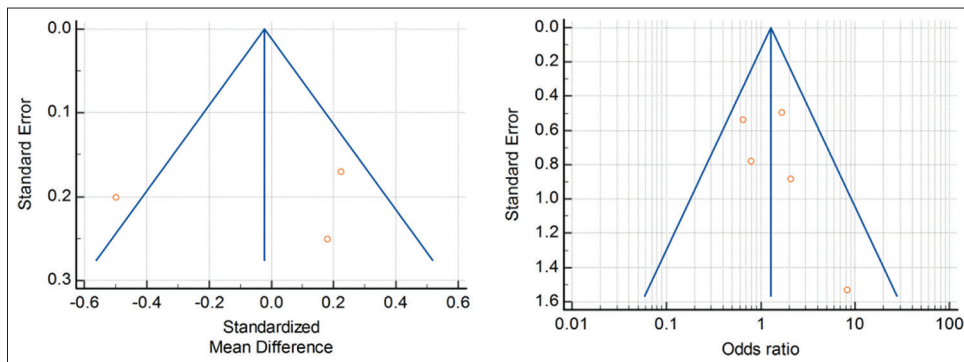


Figure 4: Funnel plots representing publication bias

score of 0.72 as compared to the pre-operative group with a score of 1.7. After statistical analysis, among all five studies, patients who have taken pre-operative antibiotics reported pain perceptions ranging from 1.7 to 17.3, while patients who have taken antibiotics after the surgery reported between 1.7 and 0.72. So, patients who have taken amoxicillin post-operatively reported with less pain.

Swelling

Swelling may be caused by a variety of factors, making its occurrence difficult to predict before surgery gender, weight, body surface, and oral health influence post-operative swelling.^[20] It was observed that swelling is more likely to occur after flap surgery and bone removal to facilitate third molar extraction. It is also affected by factors such as ease of extraction, third molar type, and level of impaction. Only two studies have been conducted on swelling. Ataoglu H *et al.*^[15] reported post-surgery surgical swelling in 6% of patients in the before-surgery amoxicillin group and 8% in the post-operative amoxicillin group. Swelling was graded as present or absent. Mariscal-Cazalla MM *et al.*^[18] observed an increase in swelling of 1.13 mm in the pre-operative group and 0.59 mm in the post-operative group after surgery. Since both the studies reported fewer patients with swelling, no concrete conclusion could be drawn regarding the use of amoxicillin. No significant difference was observed among the studies.

Interincisal distance

Multiple needle penetrations during inferior alveolar nerve block administration are significant factors affecting interincisal distance. Low-grade infections and elevation

of flaps beyond the external oblique ridge during surgery have also been associated with increased interincisal distance. Three of the five studies that evaluated interincisal distance were included in the quantitative analysis. A recent study by Ataoglu H *et al.*^[15] found that after surgery, the interincisal distance decreased from 41 mm to 39 mm in the pre-operative amoxicillin group and 45 mm to 42 mm in the post-operative amoxicillin group. Lopez-Cedrun JL *et al.*^[17] reported 16.2% and 13.6% reductions in interincisal distance in prior and post-operative amoxicillin patients after surgery, respectively. The mean interincisal distance ranged from 5.5 to 47.9 in the pre-operative amoxicillin group and from 4.56 to 46.1 in the post-operative amoxicillin group. Interincisal distances between groups did not differ significantly.

Complications

Most third molar extractions are completed without any intra-operative or post-operative complications. The integration of the surgical technique with surgical principles and effective pre-operative planning are paramount to reducing the risk of complications during surgery. According to literature reviews, third molar surgery complications range from 4.6% to 30.9%.^[21] The complications reported in the five studies were infections, alveolar osteitis, nausea, diarrhea, gastric pain, rash, and headache. According to the study by Lacasa JM *et al.*,^[14] infections were observed in 5.3% of patients receiving pre-operative amoxicillin and in 2.8% of patients receiving post-operative amoxicillin. Ataoglu H *et al.*^[15] also reported 14% of wound infections and 2% of alveolar osteitis, and 18% of wound infections, respectively. Luaces-Rey *et al.*^[16] found 4.3% in the pre-operative

amoxicillin group and 5.3% in the post-operative amoxicillin group. According to López-Cedrún JL *et al.*,^[17] nausea, diarrhea, gastric pain, rash, headache, and nausea were the most common complications. In the post-operative amoxicillin group, 4.54% had nausea, 2.27% diarrhea, 2.27% gastric pain, and 6.81% headaches. Mariscal-Cazalla MM *et al.*^[18] reported complications in the group treated with amoxicillin pre-operatively, but only 10% in the group treated with amoxicillin post-operatively. In all included studies, third molar extraction complications ranged from 4.3 to 33% in pre-operative amoxicillin groups and from 0 to 22.7% in post-operative amoxicillin groups. The post-operative amoxicillin group reported a significantly lower rate of complications in all studies. However, only one study, by Lacasa JM *et al.*,^[14] found a significant difference. Other studies did not show significant differences.

According to literature reports, patients undergoing third molar extraction should undergo a complete examination of the temporomandibular joint. This includes evaluation of joint sound, muscle tenderness, and jaw opening and excursion movements. Post-operative complications can be reduced by using bite blocks and judicious application of force during surgery, along with stabilizing the mandible and lower dentition during surgical mobilization.

The comparable parameters included in pre- or post-operative amoxicillin groups were pain, swelling, interincisal distance, and post-operative complications. A few studies reported standard deviations in quantitative synthesis of these parameters, while others reported outcomes in percentage, limiting the number of studies for comparison.^[22] Studies included in this systematic review and meta-analysis had small sample sizes too. An added limitation was the variation in the follow-up period, which might have affected the final outcome of the study. To evaluate the bias, risk of bias was assessed, which showed heterogeneity in parameters as a limitation of this study. Hence, this study recommends to conduct more standard and uniform clinical trials on a larger population to evaluate the effect of antibiotic administration during third molar surgery.

Ideally, a surgical field is sterile; it is free of all biological contaminants. Despite many efforts to preserve asepsis during surgery, there is a 1–3% chance of surgical site infection. Even in an aseptic state, a condition of sterile infection may develop. Sterile infection manifests as pain, swelling, hemorrhage, paresthesia, and trismus. As the complications associated with third molar surgery can lead to pain and trismus-like conditions, the sufferer's quality of life and productivity are often impaired. These clinical situations may demand the use of antibiotics. Hence, it can be said that

the use of antibiotics has become a choice of clinicians for surgical cases during the third molar surgery.^[23]

CONCLUSION

Within the limitations of this review, it can be concluded that there was no significant difference in effectiveness of pre-operative and post-operative amoxicillin in improving the interincisal distance or reducing post-operative complication, carried out from quantitative synthesis of data. The qualitative synthesis of data for pain provides favorable results for post-operative amoxicillin administration, whereas in the case of swelling following third molar surgery, a non-conclusive result was obtained.

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Conflicts of interest

There are no conflicts of interest.

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