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Efficacy of amoxicillin or amoxicillin and clavulanic acid in reducing infection rates after third molar surgery: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The current review was designed to assess the efficacy of amoxicillin (AMX) and amoxicillin-clavulanic acid (AMX-CLA) for reducing infection rates after third molar surgery.

MATERIALS AND METHODS: PubMed, Embase, ScienceDirect, and Google Scholar were searched for double-blind randomized controlled trials (RCTs) assessing the efficacy of AMX/AMX-CLA for infection control after third molar surgery.

RESULTS: 13 RCTs were included. Our meta-analysis demonstrated a statistically significant reduced risk of infections with AMX/AMX-CLA (RR: 0.29, 95% CI: 0.18, 0.45 I^2=0% p<0.00001). The meta-analysis demonstrated that the risk of infections was significantly reduced only in parallel-arm trials but not in split-mouth trials. Sub-group analysis based on antibiotic type indicated that the risk of infections was reduced with both AMX and AMX-CLA. A subgroup analysis based on the timing of AMX/AMX-CLA administration indicated that the risk of infections was significantly reduced with both preoperative (RR: 0.41, 95% CI: 0.21, 0.81 I^2=0% p=0.01) and postoperative (RR: 0.18, 95% CI: 0.09, 0.35 I^2=0% p<0.00001) administration of AMX/AMX-CLA. Meta-analysis indicated no increased risk of adverse events with the use of AMX/AMX-CLA (RR: 1.47, 95% CI: 0.41, 5.22 I^2=77% p=0.55).

CONCLUSIONS: The use of AMX/AMX-CLA is associated with a significant reduction in the risk of infections after impacted third molar surgery. The risk of infections is reduced with both AMX and AMX-CLA. Our results also indicated that the infection risk was reduced with preoperative and postoperative antibiotic administration and there is no significant increase in the risk of antibiotic-related adverse events.

Key Words:
Third molar, Impaction, Amoxicillin, Infection.

Introduction

Surgical extraction of impacted third molars is one of the most common procedures in oral and maxillofacial surgery practice. Third molars are often impacted due to inadequate eruption space and frequently require surgical intervention for their removal[1]. Most of the time, these impacted third molars are asymptomatic, however, pathologies like recurrent pericoronitis, caries, bone loss, and resorption of second molars may compel early removal of these teeth[2].

Flap elevation and bone removal during impaction surgeries frequently result in pain, swelling and trismus in the immediate postoperative period. However, such complications can be aggravated by a supervening infection which can severely deteriorate postoperative recovery[3]. Given the high frequency of third molar surgeries, adequate interventions must be applied to reduce the risk of infection to limit patient morbidity and healthcare costs. In this context, antibiotics are frequently prescribed either before, after, or during the entire perioperative period[4]generally performed by general dental practitioners, are dental caries and periodontal infections. Systemic antibiotics may be prescribed to patients undergoing extractions to prevent complications due to infection. This is an update of a review first published in 2012. Objectives: To determine the effect of systemic antibiotic prophylaxis on the prevention of infectious

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complications following tooth extractions. Search methods: Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health Trials Register (to 16 April 2020. However, despite several clinical trials[4-6], there has been no consensus in literature whether prophylactic antibiotics can reduce the risk of infections after third molar surgeries, except for those prescribed for other medical reasons. One reason for this is the wide variation in the incidence of infections after third molar surgeries ranging from 1-16%[7]. Indeed, many factors, such as patient characteristics, medical comorbidities, the complexity of the surgery, surgical time, different perioperative anti-infective protocols, and the use of antibacterial mouthwashes can influence the rates of infections[8]. A survey of Spanish dental professionals has shown that around 82.7% of clinicians prescribe antibiotics after third molar surgeries[9]. Similar high prescription rates have been reported from other countries as well[10,11]. A major reason for such figures is the fear of surgical site infection which outweighs the adverse effects caused by the use of antibiotics. Research has demonstrated that antibiotics not only lead to immediate adverse events like diarrhea, intestinal pain, and nausea but also lead to the widespread development of antimicrobial resistance[12]. The misuse of antibiotics in dentistry especially in dentistry has reached alarming proportions and there is an urgent need to devise guidelines based on high-quality evidence[13].

Amoxicillin (AMX) and amoxicillin-clavulanic acid (AMX-CLA) are one of the most frequently prescribed antibiotics after third molar surgeries[9]. In the recent past two systematic reviews[5,6] have assessed evidence on the efficacy of AMX/AMC-CLA on infection rates after third molar surgeries. However, these could include only a limited number of studies. Hence, the current updated review was designed to assess the efficacy of AMX and AMX-CLA for reducing infection rates after third molar surgery.

Materials and Methods

The reporting guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[14] and the Cochrane Handbook for Systematic Reviews of Intervention[15] were followed for this review. We registered the study protocol prospectively on PROSPERO (No. CRD42022313604).

Database Search

We conducted an electronic literature search on the databases of PubMed, Embase, ScienceDirect, and Google Scholar to search for studies relevant to the review. We sought the aid of a medical librarian to formalize the search strategy. The databases were searched by two reviewers separately while defining the search limits from the inception of the databases to March 10, 2022. The search was restricted to English-language publications. Both MeSH and free-text keywords were used, and these were: "third molar", "infection", "antibiotic", "amoxicillin", "clavulanic acid", and "augmentin". Details of the literature search common to all databases are presented in the **Supplementary Table I**. The primary search results were assessed initially by their titles and abstracts to identify citations requiring full-text analysis. The full texts of the articles were reviewed by the two reviewers independently based on the inclusion and exclusion criteria. All disagreements were resolved with consensus. We also searched the bibliography of included studies to look for any additional articles.

Inclusion Criteria

Inclusion criteria were defined as per the PICOS (Population, Intervention, Comparison, Outcome, and Study design) framework, which included:

Population: Patients undergoing surgical extraction of third molars;
Intervention: Use of oral AMX/AMX-CLA in any dose either preoperative or postoperatively;
Comparison: No systemic antibiotics of any type;
Outcomes: infection rates with or without adverse events;
Study design: Randomized controlled trials (RCTs).

Exclusion criteria were: (1) Retrospective studies, non-randomized studies; (2) Non-double blinded studies; (3) Lack of control group; (4) Use of other antibiotics in combination with AMX/AMX-CLA; (5) review articles, case series, case reports were also excluded.

Data Extraction and Risk of Bias Assessment

A data extraction sheet was used by two reviewers to extract relevant data from the studies. Details of the first author, publication year, study location, study design, sample size, demographic details, the antibiotic protocol, use of ostectomy,

follow-up duration, and study outcomes were extracted. The outcomes of interest for our review were the risk of infection and adverse events. We did not have a pre-define infection and the definition of infection was as per the included studies.

Two reviewers independently assessed the quality of included RCTs using the Cochrane Collaboration's risk of bias assessment tool-2[15]. Every study was assessed for randomization process, deviation from intended intervention, missing outcome data, measurement of outcomes, and selection of reported results. Based on the risk of bias in individual domains, the overall bias was marked as "high risk", "some concerns", or "low risk". Any disagreements related to data extraction or quality assessment were resolved by discussion.

Statistical Analysis

We used "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) for the meta-analysis. Infection and adverse event data were pooled using risk ratios (RR) with 95% confidence intervals (CI). The random-effects model was used for all the meta-analyses. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% indicated low heterogeneity, 50-75% indicated medium heterogeneity, and more than 75% represented substantial heterogeneity in the meta-analysis. We used funnel plots to assess publication bias. A sensitivity analysis was also conducted wherein we sequentially excluded one study at a time from the meta-analysis to recalculate the results. This was done in the meta-analysis software itself. We also conducted a sub-group analysis based on the type of study (split-mouth or parallel design), antibiotic type (AMX or AMX-CLA), sample size (>50 or <50/group), and timing of antibiotic (preoperative only or postoperative only). $p<0.05$ was considered statistically significant.

Results

Details of Included Studies

The PRISMA flowchart of the study is presented in Figure 1. After deduplication of search results and initial screening, we selected 57 arti-

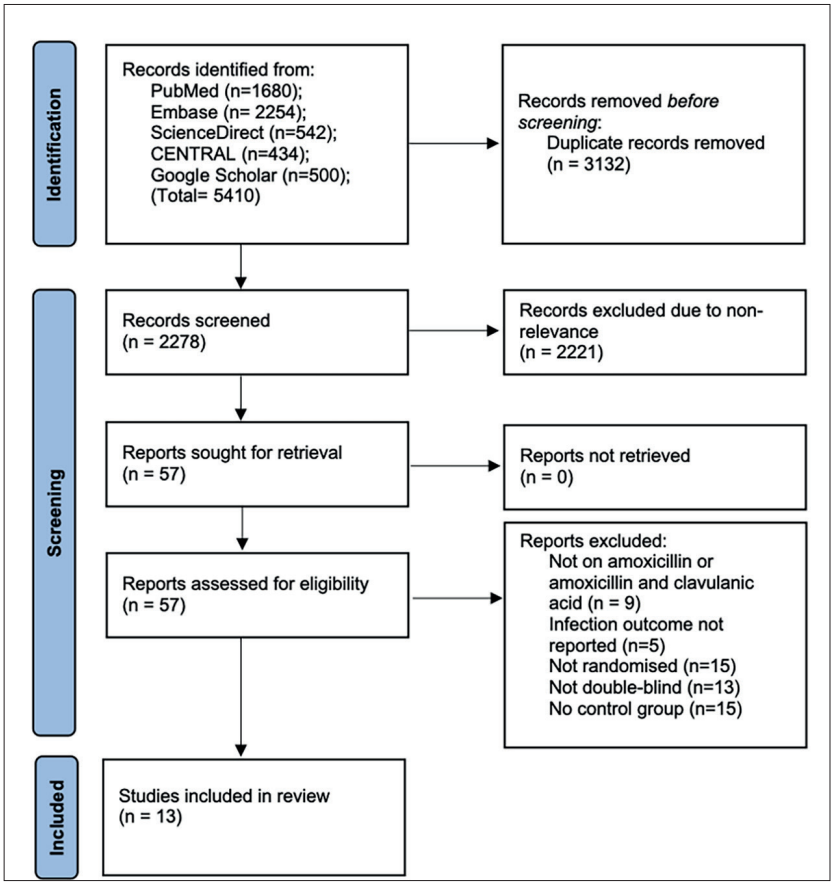

Figure 1. Study flow chart.

cles for full-text analysis. Forty-four studies were excluded with reasons and a total of 13 RCTs were included in this systematic review and meta-analysis[7,16-27].

Details of included studies are presented in Table I. The studies were published between 2005 to 2021. The majority of the studies were conducted in Spain, Brazil, and India. Three studies[17,20,27] were split-mouth clinical trials while the rest used parallel groups. The sample size per group ranged from 12 patients to 259 patients. Three studies[7,19,22] were three arm-trials with two antibiotic groups (depending upon the timing of antibiotic administration) and one control group. Three studies[18,19,23] used AMX-CLA while the rest used only AMX. The follow-up period was variable in the included studies ranging from a minimum of 1 week to a maximum of 8 weeks. The definition of infections used by the included studies is reported in Table II.

Meta-Analysis

Comparing data of 1104 patients in the antibiotic group and 924 patients in the control group, our meta-analysis demonstrated a statistically significant reduced risk of infections with AMX/AMX-CLA (RR: 0.29, 95% CI: 0.18, 0.45 I^2=0% p<0.00001) (Figure 2). There was no evidence of publication bias on the funnel plot (Figure 3). There was no change in the significance of the results on sensitivity analysis.

The results of the subgroup analysis are presented in Table III. The meta-analysis demonstrated that the risk of infections was significantly reduced only in parallel-arm trials but not in split-mouth trials. Sub-group analysis based on antibiotic type indicated that the risk of infections was reduced with both AMX and AMX-CLA. We also conducted a subgroup analysis based on the sample size of the studies. Our meta-analysis indicated that studies with a larger sample size, i.e., >50 patients/group demonstrated a statistically significant reduced risk of infections with AMX/AMX-CLA, but not studies with a sample size of <50 patients/group.

There was also variability in the included studies on the timing of antibiotic administration. A subgroup analysis based on the timing of AMX/AMX-CLA administration indicated that the risk of infections was significantly reduced with both preoperative (RR: 0.41, 95% CI: 0.21, 0.81 I^2=0% p=0.01) and postoperative (RR: 0.18, 95% CI: 0.09, 0.35 I^2=0% p<0.00001) administration of AMX/AMX-CLA (Figure 4). The risk of adverse events was reported in only five studies[7,18,19,22,23]. Meta-analysis indicated no increased risk of adverse events with the use of AMX/AMX-CLA (RR: 1.47, 95% CI: 0.41, 5.22 I^2=77% p=0.55) (Figure 5).

Risk of Bias

Details of risk of bias analysis in the included studies are presented in Table IV. Majority of studies were high-quality.

Discussion

Third molar surgery is one of the most frequently performed clean-contaminated operations. Since the oral cavity is inhabited by more than 400 types of aerobic, as well as anaerobic bacteria, historically, clinicians have frequently advised the use of antibiotics to prevent surgical site infections[28]. However, there has been no consensus on the type, timing, and even on the need for antibiotics with third molar surgeries. Indeed, prescription of antibiotics is not completely safe and can lead to the development of resistant bacteria, disruption of healthy and beneficial microbial flora, leading to overgrowth of yeast and *Clostridioides difficile* causing inadequate absorption of vitamins and other nutrients in the gut[29,30]. Of these, the development of acquired antimicrobial resistance is of particular concern due to the overuse of antibiotics in current clinical practice. Unnecessary exposure to antibiotics builds an evolutionary pressure on bacteria and bestows a selective survival benefit for the bacteria that have developed resistance mutations[31]. Therefore, the prescription of antibiotics should be based on strong evidence derived from high-quality clinical trials to avoid such adverse outcomes.

The inclusion criteria of our review were formulated to include only RCTs with double-blind design to generate such high-quality evidence on the efficacy and safety of AMX/AMX-CLA for preventing infections after third molar surgeries. From a pooled analysis of data from more than 2000 patients, we noted that AMX/AMX-CLA results in a 71% reduced risk of infections after third molar surgeries. The lack of heterogeneity in the meta-analysis (I^2=0%) and the absence of publication bias enhance the credibility of our results. Furthermore, no singular study was found to significantly influence the effect size and the overall results were stable on sensitivity analysis. On close examination of the forest plot, it can be

Table I. Details of included studies.

Study	Location	Split-mouth design	Antibiotic group	Control group	Groups	Sample size	Mean age (years)	Male gender (%)	Ostectomy (%)	Follow-up
Arteagoitia 2005[18]	Spain	No	Postoperative AMX–CLA 500/125 mg three times daily, oral for 4 days	Placebo tablets same size and appearance	AB CN	259 231	24.3 24	38.2 42.4	94.6 97.4	7 days, 8 weeks
Lacasa 2007[19]	Spain	No	G1: single pre-surgical dose of two tablets 1000/62.5 mg G2: post-surgery therapy of two tablets AMX-CLA1000/ 62.5 mg twice daily for 5 days	Placebo	AB CN	G1: 75 G2: 75 75	29.5 29.7 28.2	G1: 49.3 G2: 44 34.7	G1: 48 G2: 45.3 53.3	1, 3, 7, 15 days
Siddiqi 2010[17]	South Africa	Yes	Oral AMX 1 g at 1 hour preoperative	Placebo (glucose) 1 g at 1 hour preoperative	AB CN	190 190	26 26	33 33	NR	3 days, 1 week and 2 weeks
Bezerra 2011[27]	Brazil	Yes	AMX two 500 mg capsules 1 h before surgery	Placebo (starch) two 500 mg capsules before surgery	AB CN	68 68	21.3 21.3	32.4 32.4	NR	3 days, 1 week and 2 weeks
Lopez-Cedrun 201[17]	Spain	No	G1: AMX 500 mg 4 tablets 2 hours before surgery G2: AMX 500 mg three times a day for 5 days after surgery	Placebo	AB CN	G1: 39 G2: 44 40	21.9 22.3 22.2	28.2 29.5 22.5	82.1 95.5 95	4 weeks
Pasupathy 2011[26]	India	No	Oral AMX 1g at 1 hour before surgery	Placebo	AB CN	31 29	30.7 28.2	54.8 68.9	NR	1 week
Adde 201225	Brazil	No	Oral AMX 500 mg three times daily for 7 days	No antibiotic	AB CN	24 24	NR	NR	NR	1 week
Bortoluzzi 2013[24]	Brazil	No	Oral AMX 2 g before surgery	Placebo	AB CN	12 12	22.8 22.5	50 16.7	66.7 41.7	5 days
Arteagoitia 2015[23]	Spain	No	Oral 2 g AMX–CLA 2 g/125 mg 2 hours before surgery and postoperative two times daily for 4 days	Placebo	AB CN	60 58	25.6 31.5	53.3 44.8	100 100	1 week up to 8 weeks
Cazalla 2020[22]	Spain	No	G1: Oral AMX 750 mg every 8 hours for 2 days before surgery and for 5 days after surgery G2: Oral AMX 750 mg every 8 hours for 5 days after surgery	Placebo	AB CN	G1: 30 G2: 32 30	27.5 24.7 24.5	40 43.8 36.7	63.7 50 70	1 week
Mohan 2020[21]	India	No	Oral AMX 750 mg every 8 hours for 5 days after surgery	No antibiotic	AB CN	68 69	25.2 24.5	60.3 65.2	NR	3, 7, 15 days and 1 month
Ganga 2021[20]	Brazil	Yes	Oral AMX 1 g before surgery	Placebo	AB	23	20.9	13	NR	1 week
Yanine 2021[16]	Chile	No	Oral AMX 2 g before surgery	Placebo	AB CN	74 75	21.9 21.1	29.7 33.3	68.9 64	3, 7, 30 days

AMX, amoxicillin; CLA, clavulanic acid; AB, Antibiotic group; CN, control group; G1, group 1; G2, group 2.

Table II. Definition of infections in the included studies.

Study	Definition of infection	Number of infections
Arteagoitia 2005[18]	Oral temperature 37.8°C after 24 hours for no other justifiable cause; presence of pus; dry socket; severe pain persisting or increasing 48 hours surgery accompanied by intraoral inflammation and/or intraoral erythema; severe pain after 7th day accompanied by intraoral inflammation and/or intra-oral erythema for no other justifiable reason which improves with antibiotic treatment	AB: 5/259 CN: 30/231
Lacasa 2007[19]	Presence of purulent discharge in the extraction socket and/or excessive swelling with fluctuation, with or without pain; presence of a local abscess; onset of facial or cervical cellulitis plus other signs suggesting infection such as pain, increased heat, erythema and/or fever; presence of osteitis of dental alveolus defined as absence of the haematic clot of the orifice and presence of a putrid smell and intense neuralgic type pain	AB G1: 4/75 G2: 2/75 CN: 12/75
Siddiqi 2010[17]	Using accepted methods employed in the scientific literature, but not clearly defined	AB: 2/190 CN: 4/190
Bezerra 2011[27]	Presence of purulent secretion, alveolitis, and body temperature > 37.5°C	AB: 1/68 CN: 4/68
Lopez-Cedrun 2011[7]	Presence of purulent discharge in the socket and/or excessive swelling, with or without pain, presence of palpable cervical lymph nodes and evidence of facial or cervical cellulitis	AB G1: 0/39 G2: 0/44 CN: 5/40
Pasupathy 2011[26]	Systemic rise of temperature and purulent discharge	AB: 2/31 CN: 3/29
Adde 2012[25]	Body temperature > 37.8°C without other discernible causes, intraoral abscess with drainage floating point, alveolitis, persistent severe pain or pain intensified 48 hours after surgery and accompanied by inflammation and/or erythema, and severe pain after the seventh day accompanied by inflammation	AB: 0/24 CN: 0/24
Bortoluzzi 2013[24]	Oral temperature 37.8°C after 24 hours for no other justifiable cause; presence of pus; dry socket; severe pain persisting or increasing 48 hours surgery accompanied by intraoral inflammation and/or intraoral erythema; severe pain after 7th day accompanied by intraoral inflammation and/or intra-oral erythema for no other justifiable reason which improves with antibiotic treatment	AB: 1/12 CN: 1/12
Arteagoitia 2015[23]	Oral temperature 37.8°C after 24 hours for no other justifiable cause; presence of pus; severe pain persisting or increasing 48 hours surgery accompanied by intraoral inflammation and/or intraoral erythema; severe pain after 7th day accompanied by intraoral inflammation and/or intra-oral erythema for no other justifiable reason which improves with antibiotic treatment	AB: 2/60 CN: 5/58
Cazalla 2020[22]	Abscess, diagnosed by fluctuation or pus discharge; body temperature greater than 37.8℃ for longer than 24 hours with no other identifiable cause; and severe pain or swelling at 48 hours or later after surgery, with no other identifiable cause that could be alleviated with antibiotic treatment	AB G1: 3/30 G2: 0/32 CN: 5/30
Mohan 2020[21]	Presence of purulent discharge in the extraction socket with or without swelling or pain, presence of local abscess, onset of any facial or cervical cellulitis or any space infections	AB: 2/68 CN: 3/69
Ganga 2021[20]	Pus, increased local and facial volume, ecchymosis, bleeding and flushing	AB: 0/23 CN: 0/23
Yanine 2021[16]	Purulent drainage from the surgical wound or abscess; isolation of pathogenic microorganisms in liquid or tissue cultures from the surgical site; spontaneous dehiscence of the incision site in patients who exhibit at least one of the following signs or symptoms: (1) fever (> 38°C), (2) pain from palpation or spontaneous, (3) localized swelling, facial erythema or local heat; severe pain after a week, together with moderate or severe intraoral inflammation and/or moderate or severe intraoral erythema with no other apparent cause, that improves with antibiotic treatment	AB: 1/74 CN: 1/75

AB, Antibiotic group; CN, control group.

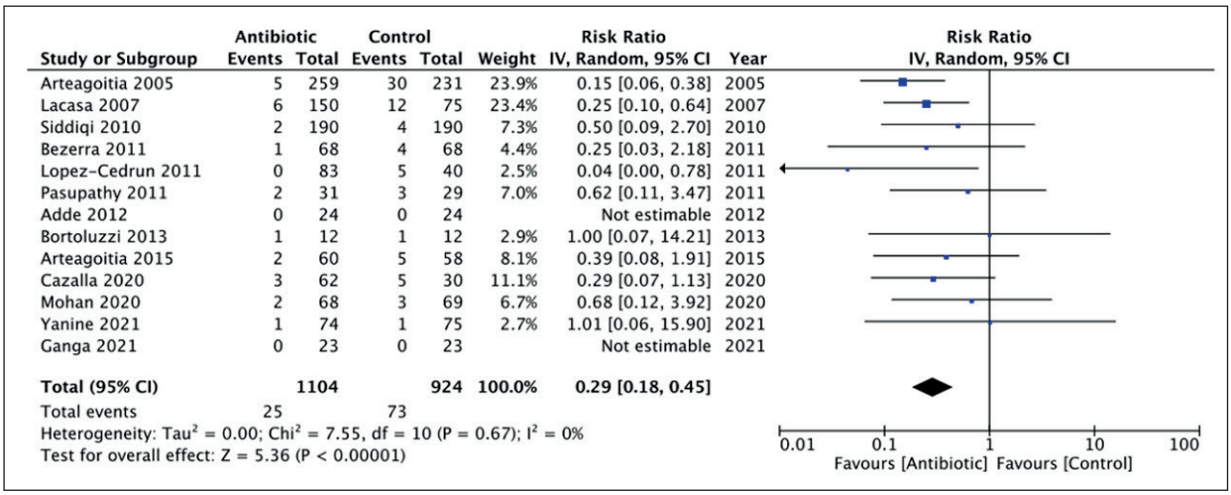

Figure 2. Meta-analysis of risk of infections with and without AMX/AMX-CLA after third molar surgeries.

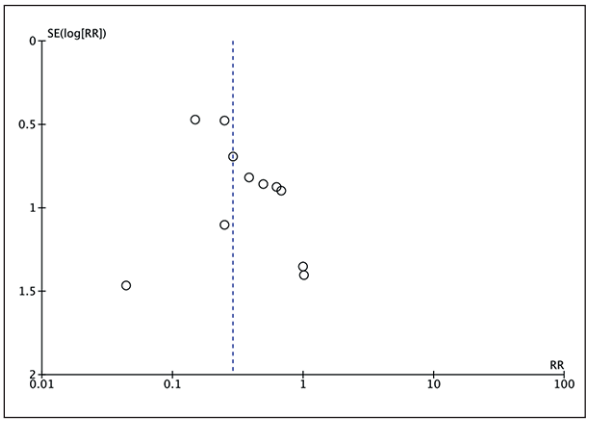

Figure 3. Forest plot of risk of infections with and without AMX/AMX-CLA after third molar surgeries.

seen that individually majority of the studies found no difference in the risk of infections between the antibiotic and control groups and only a limited number of studies[7,18,19] noted a statistically significant difference in the risk of infections. However, we believe that this may be attributable to the small sample size of the studies in the meta-analysis. Indeed, from a subgroup analysis based on sample size, we noted that the difference in the risk of infections was not statistically significant in studies with <50 patients/group but was significant for studies with >50 patients/group.

The results of our review concur with prior systematic reviews[5,6] on this topic. Menon et al[5] in a similar meta-analysis of 8 trials found that AMX/AMX-CLA leads to reduced risk of infections after third molar surgeries (RR: 0.25, 95% CI: 0.15, 0.42). Similarly, Arteagoitia et al[6] in a meta-analysis of 10 studies also noted a statistically significant 75% reduced risk of infections with AMX/AMX-CLA after third molar surgeries (RR: 0.35, 95% CI: 0.21, 0.57). However, our review represents a significant update of these prior studies[5,6]. We not only included four new trials[16,20-22] in the meta-analysis thereby increasing the sample size but also excluded trials like that of Xue et al[28] wherein clindamycin was used instead of AMX for allergic patients. Our results

Table III. Subgroup analysis.

Variable	Groups	No of studies	Risk ratio
Study type	Split-mouth	3	0.38 95% CI: 0.10, 1.46 $I^2 = 0\%$ $p = 0.16$
	Parallel	10	0.28 95% CI: 0.17, 0.45 $I^2 = 0\%$ $p < 0.00001$
Antibiotic type	Amoxicillin	10	0.42 95% CI: 0.21, 0.83 $I^2 = 0\%$ $p = 0.01$
	Amoxicillin+ Clavulanic acid	3	0.21 95% CI: 0.12, 0.39 $I^2 = 0\%$ $p < 0.00001$
Sample size	> 50/group	9	0.26 95% CI: 0.16, 0.42 $I^2 = 0\%$ $p < 0.00001$
	< 50/group	4	0.72 95% CI: 0.17, 3.03 $I^2 = 0\%$ $p = 0.65$

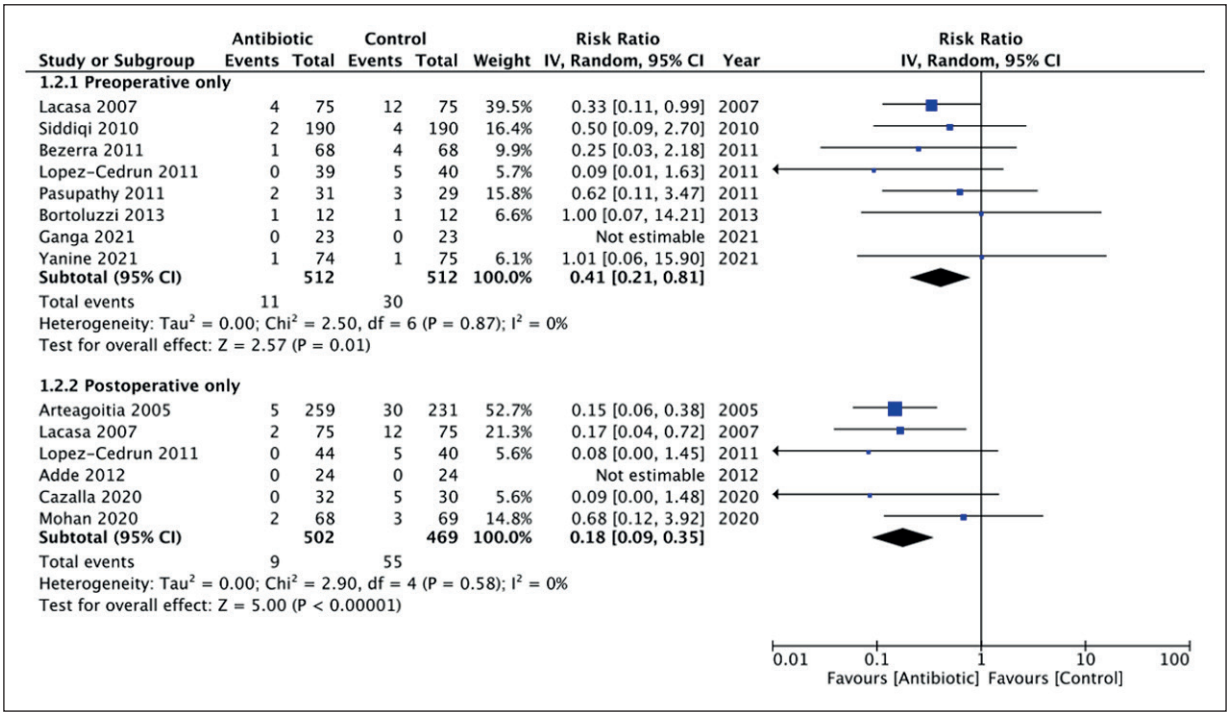

Figure 4. Meta-analysis of risk of adverse events with and without AMX/AMX-CLA after third molar surgeries.

concur with evidence from other oral surgical procedures as well. Salgado-Peralvo et al[32] in a recent systematic review have demonstrated that the use of antibiotics reduces early failure rates in immediate oral implants and recommended the use of 2-3 g AMX before surgery followed by 500 mg every 8 hours for five to seven days. Similarly, the use of AMX has been found to reduce failure rates in patients undergoing bone augmentation with implant placement[33]. Lodi et al[4] in a meta-analysis of 12 RCTs have also noted a reduced risk of infections with the use of antibiotics in patients undergoing third molar extractions (RR: 0.34, 95% CI: 0.19, 0.64).

In the subgroup analysis based on study design, we noted no difference in the risk of infection in split-mouth studies, but the difference was significant for parallel arm trials. Split-mouth studies have the advantage of balancing baseline factors between the intervention and control arms as the drug and placebo are administered to the same patient. While parallel-arm RCTs may balance major confounding factors, there may be some unknown clinical factors like the patient's normal bacterial flora or baseline immunity which could impact infection rates. However, it should be noted that only three split-mouth trials[17,20,27] were available for the meta-analysis and these may not have been adequately powered to

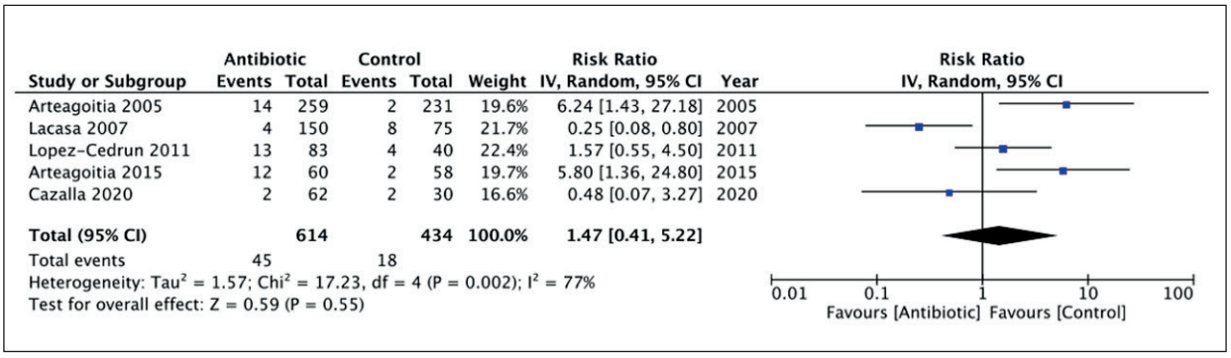

Figure 5. Meta-analysis of risk of adverse events with and without AMX/AMX-CLA after third molar surgeries.

Table IV. Risk of bias in included RCTs.

Study	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of outcomes	Selection of reported result	Overall risk of bias
Arteagoitia 2005[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lacasa 2007[19]	Some concerns	Low risk	Some concerns	Low risk	Low risk	High risk
Siddiqi 2010[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bezerra 2011[27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lopez-Cedrun 201[17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pasupathy 2011[26]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Adde 2012[25]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Bortoluzzi 2013[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Arteagoitia 2015[23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cazalla 2020[22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mohan 2020[21]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ganga 2021[20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yanine 2021[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

detect statistically significant differences even after the pooled analysis. Another important factor is that antibiotics frequently alter the normal oral microbial flora which may be reestablished only after three months or longer[5,34]. The small-time period between the two extractions in split-mouth trials may not have allowed for regeneration of the oral microbiome which could also have affected the overall results[5]. Future studies should take this factor into account while planning split-mouth trials.

Our meta-analysis noted the reduced risk of infections with AMX as well as with AMX-CLA. However, it must be noted that only three studies[18,19,23] reported the use of AMX-CLA, and therefore, the results should be interpreted with caution. Iglesias-Martín et al[35] in a clinical trial comparing AMX *vs.* AMX-CLA have noted no difference in the risk of infections after third molar surgeries, indicating that either drug may be used for antibiotic prophylaxis. Retrospective data from patients with respiratory disorders have also indicated that AMX and AMX-CLA may be equally efficacious in managing patients with acute exacerbations of chronic obstructive pulmonary diseases[36]. Indeed, the addition of clavulanic acid increases the spectrum of action of AMX and may prevent infections from resistant bacteria. However, due to limited trials directly comparing AMX and AMX-CLA for oral surgical procedures, strong conclusions cannot be derived at this point.

The timing of antibiotic administration has been another contentious issue in oral surgical procedures[19]. Pre-operative antibiotic administration is regarded as prophylactic wherein the drug is administered a few hours before the procedure to achieve high blood concentrations of the antibiotic during surgery[19]. Nevertheless, postoperative antibiotics are frequently prescribed due to the fear of surgical site infections[37]. In our review, on subgroup analysis based on the timing of antibiotic exposure, we noted a statistically significant reduction in the risk of infections with both preoperative and postoperative AMX/AMX-CLA administration. However, studies[7,19] directly comparing preoperative *vs.* postoperative antibiotic exposure have produced variable results. Lacase et al[19] have demonstrated a better reduction of infection rates after third molar surgeries with postoperative AMX-CLA therapy as compared to prophylactic alone. Similar results have been noted by López-Cedrún et al[7]. On the other hand, a recent systematic review and meta-analysis by Oppelaar et al[37] have demonstrated no difference in the risk of infection between short course (≤24 hours) *vs.* extended course (≥72 hours) antibiotic prophylaxis for ear, nose, throat, and oral and maxillofacial surgical procedures. The authors[37] suggested that shorter antibiotic courses should be used unless there are documented conditions that would be better treated with longer courses of antibiotics. Using short-course antibiotics may avoid side-effects events, antibiotic resistance development, and higher healthcare costs.

Lastly, our meta-analysis failed to demonstrate any significant increase in the risk of adverse events related to AMX/AMX-CLA use after third molar surgeries. Similar results have been reported by Arteagoitia et al[6]. However, Menon et al[5] have noted

higher rates of adverse events with AMX-CLA. The authors also noted a reduction in bacterial diversity in the gut, saliva, and skin after amoxicillin use for up to 6 months. There is a need for further studies on the effect of AMX/AMX-CLA on normal bacterial flora and its long-term effects.

Our review has some limitations. Firstly, there was heterogeneity in the studies concerning the definition of infections. While the majority of the studies used similar signs and symptoms to identify infections, no standardized definition was followed. Secondly, the perioperative protocol of surgery, like patient preparation, use of anti-inflammatory drugs, etc. would have differed across trials. However, its impact should have been minimal as only RCTs were included in our review. Thirdly, there were a limited number of studies using a split-mouth design and using AMX-CLA. We therefore could not generate adequate evidence on the use of AMX-CLA through our review. Lastly, the majority of the studies were from a few specific countries which limit the generalizability of evidence.

Conclusions

The results of our systematic review and meta-analysis have demonstrated that the use of AMX/AMX-CLA is associated with a statistically significant reduction in the risk of infections after impacted third molar surgery. The risk of infections is reduced with both AMX and AMX-CLA. Our results also indicated that the infection risk was reduced with preoperative and postoperative antibiotic administration and there is no significant increase in the risk of antibiotic-related adverse events.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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