Journal section: Oral Surgery
Publication Types: Review

doi:10.4317/medoral.21139
http://dx.doi.org/doi:10.4317/medoral.21139

Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis

María-Iciar Arteagoitia [1], Luis Barbier [2], Joseba Santamaría [3], Gorka Santamaría [4], Eva Ramos [5]

[1] MD, DDS, PhD, Associate Professor, Stomatology I Department, University of the Basque Country (UPV/EHU), BioCruces Health Research Institute, Spain; Consolidated research group (UPV/EHU IT821-13)
[2] MD PhD, Chair Professor, Maxillofacial Surgery Department, BioCruces Health Research Institute, Cruces University Hospital, University of the Basque Country (UPV/EHU), Spain; Consolidated research group (UPV/EHU IT821-13)
[3] MD, DDS, PhD, Professor and Chair, Maxillofacial Surgery Department, Bio Cruces Health Research Institute, Cruces University Hospital, University of the Basque Country (UPV/EHU), Bizkaia, Spain; Consolidated research group (UPV/EHU IT821-13)
[4] DDS, PhD, Associate Professor, Stomatology I Department, University of the Basque Country (UPV/EHU), BioCruces Health Research Institute, Spain; Consolidated research group (UPV/EHU IT821-13)
[5] PhD, Degree in Farmacy, BioCruces Health Research Institute, Cruces University Hospital. Spain

Correspondence:
Servicio Cirugía Maxilofacial
Hospital Universitario de Cruces
Plaza de Cruces s/n
Barakaldo, Bizkaia, Spain
jsz@clinicaimd.com

Arteagoitia MI, Barbier L, Santamaría J, Santamaría G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2016 Jul 1;21 (4):e494-504.
http://www.medicinaoral.com/medoralfree01/v21i4/medoralv21i4p494.pdf

Received: 02/11/2015
Accepted: 23/12/2015

Article Number: 21139 http://www.medicinaoral.com/

eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Emcare
Indice Médico Español

Abstract

Background: Prophylactic use of amoxicillin and amoxicillin/clavulanic acid, although controversial, is common in routine clinical practice in third molar surgery.

Material and Methods: Our objective was to assess the efficacy of prophylactic amoxicillin with or without clavulanic acid in reducing the incidence of dry socket and/or infection after third molar extraction. We conducted a systematic review and meta-analysis consulting electronic databases and references in retrieved articles. We included double-blind placebo-controlled randomized clinical trials published up to June 2015 investigating the efficacy of amoxicillin with or without clavulanic acid on the incidence of the aforementioned conditions after third molar extraction. Relative risks (RRs) were estimated with a generic inverse-variance approach and a random effect model using Stata/IC 13 and Review Manager Version 5.2. Stratified analysis was performed by antibiotic type.

Results: We included 10 papers in the qualitative review and in the quantitative synthesis (1997 extractions: 1072 in experimental groups and 925 in controls, with 27 and 74 events of dry socket and/or infection, respectively). The overall RR was 0.350 (p<0.001; 95% CI 0.214 to 0.574). We found no evidence of heterogeneity (I^2=0%, p=0.470). The number needed to treat was 18 (95% CI 13 to 29). Five studies reported adverse reactions

(RR=1.188, 95% CI 0.658 to 2.146, p =0.567). The RRs were 0.563 for amoxicillin (95% CI 0.295 to 1.08, p=0.082) and 0.215 for amoxicillin/clavulanic acid (95% CI 0.117 to 0.395, p<0.001).
Conclusions: Prophylactic use of amoxicillin does not significantly reduce the risk of infection and/or dry socket after third molar extraction. With amoxicillin/clavulanic acid, the risk decreases significantly. Nevertheless, considering the number needed to treat, low prevalence of infection, potential adverse reactions to antibiotics and lack of serious complications in placebo groups, the routine prescription of amoxicillin with or without clavulanic acid is not justified.

Key words: *Meta-analysis, amoxicillin, infection, removal, dry socket, third molar.*

Introduction

Third molar extraction is a common procedure in oral surgery. There still is controversy over the need to routinely use systemic antibiotics for the prevention of infectious and inflammatory complications associated with this type of surgery (1,2).

In a survey in 2014 (3), we found that 83% of dentists in our region (Bizkaia) would administer antibiotics prophylactically for surgery of fully impacted third molars fully covered by bone in healthy patients, the drugs most commonly prescribed being amoxicillin (58.3%) and amoxicillin/clavulanic acid (34.5%). Most reviews and meta-analyses on this topic question the routine use of antibiotics in healthy patients, given that these drugs may cause adverse reactions and that their inappropriate use leads to the development of resistant bacteria (4-9). In order to assess the scientific evidence on the widespread clinical practice among dentists of administering amoxicillin with or without clavulanic acid before or during surgery, we have designed a meta-analysis including all available high quality clinical trials on the prophylactic use of amoxicillin with or without clavulanic acid.

The objectives of this study were; 1: to assess the efficacy of the use of amoxicillin with or without clavulanic acid to prevent infection and/or dry socket, compared to a control group given placebo, in third molar surgery patients; and 2: to carry out stratified analysis of the efficacy of amoxicillin and amoxicillin/clavulanic acid. We designed a meta-analysis testing the null hypothesis that the use of amoxicillin with or without clavulanic acid is not effective.

Material and Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Institute of Medicines' guidelines. The literature search was based on questions structured in the Patient, Intervention, Comparison, and Outcome (PICO) format.

- Eligibility criteria: We selected studies including patients of any age and sex who underwent extraction of third molars with any degree of impaction. Regarding type of intervention, we included trials that analysed the efficacy of amoxicillin with or without clavulanic acid at any dose or regimen, and regarding comparisons, we exclusively included randomized double-blind placebo-controlled (RDBPC) clinical trials, not excluding those with split-mouth designs. With respect to outcome, we excluded studies that did not investigate the incidence of dry socket, infection, and both conditions concurrently, but did not apply restrictive criteria for the definition of infection or dry socket. Results of interest: The search was not restricted by language. The last search date was 1 June 2015.

- Sources of information. The electronic databases consulted were: Medline/PubMed, Scopus, ScienceDirect, Web of Science, Evidence-Based Dentistry, ClinicalTrials.gov, the EU Clinical Trials Register, the Cochrane Central Register of Controlled Trials, the Spanish General University Board database of doctoral theses in Spain (TESEO) and Spanish National Research Council (CSIC) bibliographic databases.

- Search strategy: The search terms selected are descriptors of each of the PICO components: extraction, removal; third molar; antibiotic, amoxicillin, clavula*; infection; and dry socket. The filters used were: humans, clinical trials, meta-analysis, randomised, and controlled trials. The electronic search in the Medline/PubMed database was carried out using MeSH strings and search algorithms connected with Boolean operators as key words for titles and abstracts. Specifically, we used the following search strategy: (randomized controlled trials OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR clinical trial OR clinical trials OR) ("clinical trial") OR (doubl* OR trebl* OR tripl*) AND (mask* OR blind*) OR ("Latin square") OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR prospectiv* (OR volunteer* NOT animal) AND (third molar) AND (antibiotic OR amoxicillin OR clavula*) AND (infection OR dry socket) AND (extraction OR removal). For the Spanish language databases, we used the following Spanish terms: (antibiótico OR amoxicilina OR clavulan*) AND (infección OR alveolitis seca) AND (exodoncia OR extracción). The references

in each paper were reviewed, and we also searched for conference abstracts.

- Selection of studies: Two researchers independently performed the searches in the databases with the aforementioned criteria. After applying the filters, we obtained the following: 26 papers from PubMed; 123 from SCOPUS; 668 from ScienceDirect; 69 from the Web of Science; 65 from Evidence-Based Dentistry, 42 from the Cochrane Library, 4 from TESEO, and 2 from IME-Biomedicina (a CSIC database). The databases not listed did not yield any relevant publications. Having removed duplicate publications and any for which it was clear from the title and abstract that they did not met the inclusion criteria, 75 papers were retrieved, and these were reviewed by two of the authors. Table 1 summarises the 65 studies excluded and the reasons for their exclusion. Qualitative and quantitative analysis was conducted considering the remaining 10 papers (RDBPC studies).

- Data extraction process: Data were extracted on 13 variables from each of the studies (10-19). Each study was examined independently by two researchers.

- List of data: The types of data collected are listed in table 2 and 2 continue.

Risk of bias in individual studies. Qualitative and quantitative data were collected on potential sources of bias in each of the studies (Table 2 and 2 continue). To assess bias in each study, we considered the following factors:

1- Generation of the random sequence: we assessed whether the method for generating the random sequence was appropriate.

2- Concealment of allocation: we assessed how patients were allocated to each group (experimental and control) and how allocation was concealed.

3- Blinding of participants and personnel: all the studies included claimed to be double blind, but they did not report the method for blinding of participants and personnel.

4- Blinding of outcome assessment: as above, though all the studies included claimed to be double blind, they did not specify the method for blinding assessment of the outcome.

5- Handling of data: we identified whether patients lost to follow-up were included in the analysis and whether the analysis was carried out on an intention-to-treat basis.

6- Selective reporting: we checked whether data were in fact reported for all the variables and outcomes that authors had planned to report a priori.

7- Other sources of bias: we sought to identify other potential sources of bias.

For each study, all of these factors were analysed and the study was then assigned to one of three categories (low risk, unclear risk, high risk) based on the estimated risk of bias.

- Summary measure of efficacy: the analysis of efficacy was based on the relative risk (RR) or cumulative incidence ratio in the treatment vs. control groups. In clinical trials that compared several experimental groups using the same antibiotic under different regimens with a single control group, the data considered were the total numbers of surgical interventions and complications in the experimental groups, without considering them as independent clinical trials. To assess the clinical significance of the treatment effect, we used the difference in the incidence or attributable risk of infection and calculated the number needed to treat (NNT) to prevent one case of infection.

- Synthesis of results: All the analyses were carried out using StataCorp 2013 Stata Statistical Software: Release 12 (College Station, TX: StataCorp LP) and Review Manager (RevMan) Version 5.2 (Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2012). We studied the heterogeneity of the different studies using the I^2 statistic, an expression related to Cochran's Q test. The overall relative risk, the result from combining data from the different studies, was calculated using an inverse-variance approach with a random effect model. Empirical correction was used for the studies with zero effect sizes in one of their arms. Any studies with a zero effect size in both arms were excluded. The clinical significance was analysed by calculating the NNT for each study and overall.

- Risk of between-study bias. The publication bias was assessed graphically using a funnel plot and quantitatively with the methods of Egger and Macaskill. The number of unpublished studies was estimated with Rosenthal's method.

- Additional analysis: We also carried out meta-analysis stratified by the type of antibiotic and cumulative meta-analysis by publication date, as well as analysing adverse reactions.

Results

- Selection of studies: Out of the 75 studies retrieved, qualitative and quantitative analysis was performed on 10 RDBPC studies. Table 1 lists the studies excluded and the reasons for their exclusion.

- Characteristics of the studies: Table 2 and 2 continue lists the main characteristics of the 10 RDBPC studies published between 2001 and June 2015 that were included in the qualitative and quantitative analyses.

- Risk of bias in the studies: (Fig. 1) illustrates the estimated risk of bias in each of the studies. Despite potential sources of bias having been identified, none of the RDBPC studies were excluded for this reason.

- Results of the individual studies: The forest plot (Fig. 2) is a graphical representation of the estimates of the RRs and 95% CIs based on the samples in each of the studies, together with their relative weights. Forest plots

Table 1. Studies excluded from the meta-analysis and the reasons for their exclusion.

1	Abu-Mowais 1990	Not a double-blind study
2	Adde 2012	No placebo control group
3	Agrawal 2012	Did not assess the response variable infection
4	Al-Asfour 2009	Retrospective study
5	Ariza 1999	Not a randomised study
6	Arora 2014	No control group exclusively treated with placebo
7	Ataoglu 2008	Not a double-blind study
8	Barclay 1987	Used metronidazole
9	Bargnesi 1995	Surgical procedures included other than just third molar extractions
10	Bergdahl 2004	Used metronidazole
11	Bystedt 1980	Used azidocillin, erythromycin, clindamycin and doxycycline
12	Bystedt 1981a	Used phenoxymethylpenicillin and azidocillin
13	Bystedt 1981b	Used tinidazole
14	Calvo 2012	Did not assess the effect of the antibiotic
15	Cubas-Jaeger 2015	No placebo control group
16	Curran 1974	No placebo control group
17	De Moura 2011	No placebo control group
18	Delibasi 2002	Not a double-blind study
19	Foy 2004	Not a randomised study
20	Fernández 2002	No control group
21	Fridrich 1990	Not a randomised study
22	Graziani 2005	Not a double-blind study
23	Grossi 2007	Did not consider infection as a response variable
24	Halper2007	Used penicillin IV
25	Happonen 1990	Used phenoxymethylpenicillin and tinidazole
26	Head 1984	Did not consider infection as a response variable
27	Iglesias-Martin 2014	No control group
28	Ishihama 2006	Retrospective study
29	Kaczmarzyk 2007	Used clindamycin
30	Kaziro 1984	Did not consider infection as a response variable
31	Kremanov 1980	Not a double-blind study
32	Kremanov 1981	Not a double-blind study
33	Kremanov 1986	Not a double-blind study
34	Laird 1972	No control group
35	Lee 2013	Retrospective study
36	Leon Arcila 2001	Not indexed in PubMed
37	Limeres 2009	No control group
38	Lloyd 1994	No control group
39	Lombardia Garcia 1987	Not a double-blind study
40	Lopes 2011	Not a double-blind study
41	Luaces-Rey 2010	No control group
42	Lyall 1991	Not a double-blind study
43	MacGregor 1973	Used topical antibiotic
44	Milani 2015	No control group exclusively treated with placebo
45	Mitchell 1986	Used timidazole
46	Mitchell 1987	No control group
47	Monaco 1999	Not a double-blind study
48	Monaco 2009	Not a double-blind study
49	Olusanya 2011	No control group
50	Osborn 1979	Not a randomised study
51	Poeschl 2004	Not a double-blind study
52	Ritzau 1992	Used metronidazole
53	Reekie 2006	Used topical antibiotic
54	Rohit 2014	No placebo control group
55	Rood 1979	Not a randomised study
56	Samsudin 1994	Not a randomised study
57	Sane 2014	No placebo controlled group
58	Sekhar 2001	Used metronidazole
59	Sisalli 2012	No control group
60	Stavropoulos 2006	Used a topical antibiotic
61	Sulejmanagic 2005	Not a randomised study
62	Swanson 1989	Used a topical antibiotic
63	Uluibau 2005	Not a double-blind study
64	Yoshii 2002	Not a double-blind study
65	Xue 2014	Pilot study

Table 2. Main characteristics of the 10 randomized double-blind placebo-controlled studies included in the qualitative analysis.

Main author (Year) Study location Recruitment period	Antibiotic Analgesic/ Anti-inflammatory/ antiseptic drugs	Criteria for diagnosis of infection	Antibiotic regimen	Quantitative outcome measure Scheduled postoperative appointments Randomisation method	Adverse reactions	Losses to follow-up
Arteagoitia (10) (2015) Spain February 2010 to June 2013	Amoxicillin /clavulanic acid Ibuprofen 600 mg q8h for 7 days after surgery Chlorhexidine mouthwash 0.12% 15 ml q8h for 7 days after surgery	Concentration of C reactive protein >2.2 mg/dL; Oral temperature >37.8º intraoral abscess draining pus; severe pain that persists or increases 48 h after surgery together with intraoral inflammation and/or intraoral erythema; severe pain 7 days after surgery together with intraoral inflammation and/or intraoral erythem	**E** (n=60): oral amoxicillin /clavulanic acid 2000/125 mg 2 hours before surgery + oral amoxicillin / clavulanic acid 2000/125 mg q12h for 4 days after surgery **C** (n=58): oral placebo 2 hours before surgery + oral placebo q12 h for 4 days after surgery	**E** : 3.33% (2/60) **C** : 8.62% (5/58) 7 days after surgery Using C4-SDP software (Glaxo S.A., Tres Cantos, Madrid, Spain)	**E**: 12 patients (nausea and vomiting 1; diarrhoea 8; abdominal pain 1; vaginal candidiasis 2; others 0) **C**: 2 patients (nausea and vomiting 0; diarrhoea 1; abdominal pain 0; vaginal candidiasis 0; Others 1)	4 patients lost to follow-up, C:3 and E:1
Arteagoitia (11) (2005) Spain March 2001 to February 2003.	Amoxicillin /clavulanic acid Diflunisal 500 mg q12h for 2 days. Metamizole 575mg q8h (if moderate to severe pain). Chlorhexidine mouthwash 0.12% 15ml q8h for 7 days after surgery	Oral temperature >37.8º; intraoral abscess draining pus; severe pain that persists or increases 48 h after surgery together with intraoral inflammation and/or intraoral erythema; severe pain 7 days after surgery together with intraoral inflammation and/or intraoral erythema	**E** (n=259): oral amoxicillin /clavulanic acid 500/125 mg q8h for 4 days after surgery **C** (n=231): placebo following the same regimen	**E** : 1.93% (5/259) **C** : 12.99% (30/231) 7 days after surgery Using C4-SDP software (Glaxo S.A., Tres Cantos, Madrid, Spain	**E**: 14 patients **C**: 2 patients All adverse reactions were mild: 2 people with vomiting, 2 stomach ache, 1 mycosis, and 11 with diarrhoea.	4 patients lost to follow-up, (2 in each group): all for failing to attend postoperative appointments
Bezerra (12) (2011) Brazil January 2008 to November 2008	Amoxicillin Nimesulide 100 mg q12h for 4 days after surgery. Paracetamol 500 mg q6h for 2 days after surgery.	Infection: purulent discharge, alveolitis and body temperature >37.5ºC Dry socket: postoperative pain at the extraction site, that increases between day 1 and 3 after surgery, together with total or partial disintegration of the blood clot in the socket, with or without halitosis	**E** (n=68): oral amoxicillin 1 g 1 h before surgery **C** (n=68): oral placebo 1 h before surgery	**E** : 1.47% (1/68) **C** : 5.88% (4/68) 3, 7 and 14 days after surgery By the tossing of a coin by a blinded researcher	Not described	9 declined to participate, 1 for failed to attend postoperative appointmentsr1 for pregnancy
Bortoluzzi (13) (2013) Brazil Not specified	Amoxicillin Paracetamol 750 mg q6h for 2 days after surgery. Diclofenac 50 mg q8h for 2 days after surgery	Criteria applied for the diagnosis of dry socket and alveolar infection are the same as those previously described by other authors (Arteagoitia *et al*. and Bouloux *et al*.).	**E1** (n=12): oral amoxicillin 2 g + dexamethasone 8 mg 60-90 min before surgery **E2** (n=12): oral amoxicillin 2 g + placebo 8 mg 60-90 min before surgery **E3** (n=14): oral placebo 2 g + dexamethasone 8 mg 60-90 before surgery **C** (n=12): oral placebo 2 g + placebo 8 mg 60-90 min before surgery	**E1** : 0% (0/12) **E2** : 8.33% (1/12) **E3** : 7.14% (1/14) **C** : 8.33% (1/12) Not specified By draw	Not described	Not described
Bulut (14) (2001) Turkey Not specified	Amoxicillin Paracetamol (not specifying treatment regimen).	Post-operative C reactive protein levels >10 mg/l and alpha-1 antitrypsin levels >370 mg/dl in blood considered indicators of infection	**E** (n=30): oral amoxicillin 1000 mg 60 min before surgery (8:00 a.m.) + amoxicillin 500 mg at 4:00 p.m. and 12:00 p.m. after surgery + oral amoxicillin 500 mg q8h for 4 days after surgery **C** (n=30): placebo	**E** : 6.67% (2/30) **C** : 6.67% (2/30) 1,3 and 7 days after surgery Not described	Not described	Not described

Table 2 Continue. Main characteristics of the 10 randomized double-blind placebo-controlled studies included in the qualitative analysis.

Lacasa (15) (2007) Spain January 2002 to December 2002	Amoxicillin /clavulanic acid Metamizole 575 mg q8h for at least 2 days after surgery.	Purulent discharge in the alveolus and/or excessive inflammation with fluctuation with/without pain - Local abscess. - Facial or neck cellulitis and other signs of infections such as pain, heat, redness and/or fever - Osteitis defined as absence of absence of blood clot of the orifice and presence of a putrid smell and intense neuralgic type pain	**E1** (n=75): oral amoxicillin/clavulanic acid 2000/125 mg before surgery + placebo for 5 days after surgery **E2** (n=72): oral placebo before surgery + oral amoxicillin/clavulanic acid 2000/125 mg for 5 days after surgery **C** (n=75): placebo before and after surgery, under the same conditions as experimental groups	**E1** : 5.33% (4/75) **E2** : 2.78% (2/72) **C** : 16.00% (12/75) 1, 3 and 7 days after surgery Described as randomised, randomisation method not specified	**E1**: 48% of patients had some type of adverse reaction **E2**: 54.7% of patients had some type of adverse reaction **C**: 69.3% of patients had some type of adverse reaction	**E2**: 3 patients lost to follow-up at day 1, as they withdrew their consent (before day 1 assessment)
Lopez-Cedrún (16) (2011) Spain Not specified	Amoxicillin Ibuprofen 600 mg immediately after surgery + ibuprofen 600 mg q12h for 5 days. Metamizole 2 g (rescue analgesia) Salt water mouth rinse after meals	- Infection: purulent discharge and/or excessive inflammation with or without pain. Palpable nodules in neck and facial or neck cellulitis. - Dry socket: disintegration of blood clot in the alveolus and halitosis, as well as severe neuropathic pain	**E1** (n=39): amoxicillin 2000 mg orally 2 h before surgery + placebo q8h for 5 days after surgery **E2** (n=44): placebo 2 hours before surgery + amoxicillin 500 mg q8h for 5 days after surgery **C** (n=40): placebo 2 h before surgery + placebo q8 h for 5 days after surgery	**E1** : 0% (0/39) **E2** : 0% (0/44) **C** : 12.50% (5/40) 7 days after surgery By a pharmacists using a random alphanumeric code	**E1**:nausea 1;diarrhoea 2; stomachache 3;cutaneous eruption 1, headache 1,others 5 **E2**:vomiting 1; nausea 1; diarrhoea 1; stomach ache 2; cutaneous eruption 1;headache 1, others 3. C: nausea 2;diarrhoea 1; stomach ache 1; headache 3;others 7	**E1**: 3 lost to follow-up,2 for technical problems; **C**: 4 lost to follow-up,1 for technical problems; **E2**:1 lost to follow up
Pasupathy (17) (2011) India Not specified	Amoxicillin and metronidazole Ibuprofen 600mg q8h for 5 days after surgery.	- Increase in body temperature - Purulent discharge from the wound	**E1** (n=31): oral amoxicillin 1g 1 h before surgery **E2** (n=29): oral metronidazole 800 mg 1h before surgery **C** (n=29): placebo	**E1** : 6.45% (2/31) **E2** : 0% (0/29) **C** : 10.33% (3/29) 7 days after surgery Using a table created using Random Software (version 2, Social Psychology)	Not described	9 patients were excluded from the analysis: 8 lost to follow-up and 1 for using antibiotics during the follow-up period.
Siddiqi (18) (2010) New Zeeland Not specified	Amoxicillin Ibuprofen 400 mg before surgery + ibuprofen 400 mg q6h for 2 days after surgery Paracetamol 500 mg + codeine phosphate 8 mg q6h for 2 days after surgery Chlorhexidine mouthwash 0.2% 10 ml before surgery + 10 ml q8h for 3 days after surgery	- Dry socket: halitosis, pain and lack of blood clot together with bone tissue necrosis	Group 1(n=192): 1st appointment: oral amoxicillin 1 g 1 h before surgery, 2nd appointment: placebo under the same regimen or vice versa Group 2(n=188): 1st appointment: oral amoxicillin 1 g 1 h before surgery + amoxicillin 500 mg q8h for 2 days after surgery; 2nd appointment: placebo under the same regimen or viceversa	**E** (Group 1 + Group 2): 1.05% (2/190) **C** (Group 1 + Group 2): 2.10% (4/190) 1, 3, 7 and 14 days after surgery By asking patients to select one of two sequentially-numbered	Not described	5 patients lost to follow-up for failing to adhere to the follow-up protocol
Xue (19) (2015) China January to December 2013	Amoxicillin (clindamycin, if allergy to amoxicillin) Loxoprofen before or after operation as necessary.	Not specified	**E** (n=192): oral amoxicillin 500 mg 1h before surgery + oral amoxicillin 500 mg q 8h for 3 days after surgery (or oral clindamycin 300 mg if allergy to amoxicillin) **C** (n=192): placebo at the same times before and after surgery	**E**: 3.13% (6/192) **C**: 4.17% (8/192) 2 and 10 days after surgery Using computer-generated random numbers	**E**: 12 patients (gastrointestinal adverse reactions 4; ulcers 2, fever 6) **C**: 16 patients (gastrointestinal adverse reactions 0; gastrointestinal adverse reactions 2, fever 14)	15 patients excluded, but the reasons were not specified

E: experimental group, C: control group, n=number of third molars extracted.
- In studies with a split-mouth design (those of Bezerra, Siddiqi, Bulut and Xue), the rates of infections have been calculated taking n as the number of third molars removed, rather than the number of patients in the study.
- In studies using antibiotics other than amoxicillin for patients allergic to this drug, if it was not specified how many patients were treated with alternative antibiotics, calculations have been based on assuming that all patients were treated with amoxicillin or amoxicillin/clavulanic acid.

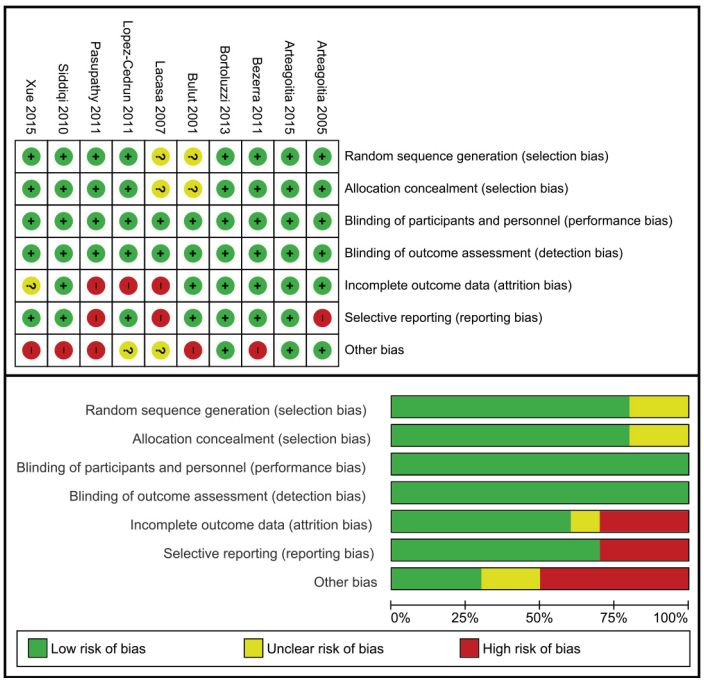

Fig. 1. Risk of bias in studies included in the systematic review.
- All the studies were considered low risk in terms of performance and detection bias, given that a double-blind design was a selection criterion for the meta-analysis.
- In studies with a split-mouth design, it was considered that that there might be other sources of bias given the duration of the washout period (no more than 4 weeks in all cases).

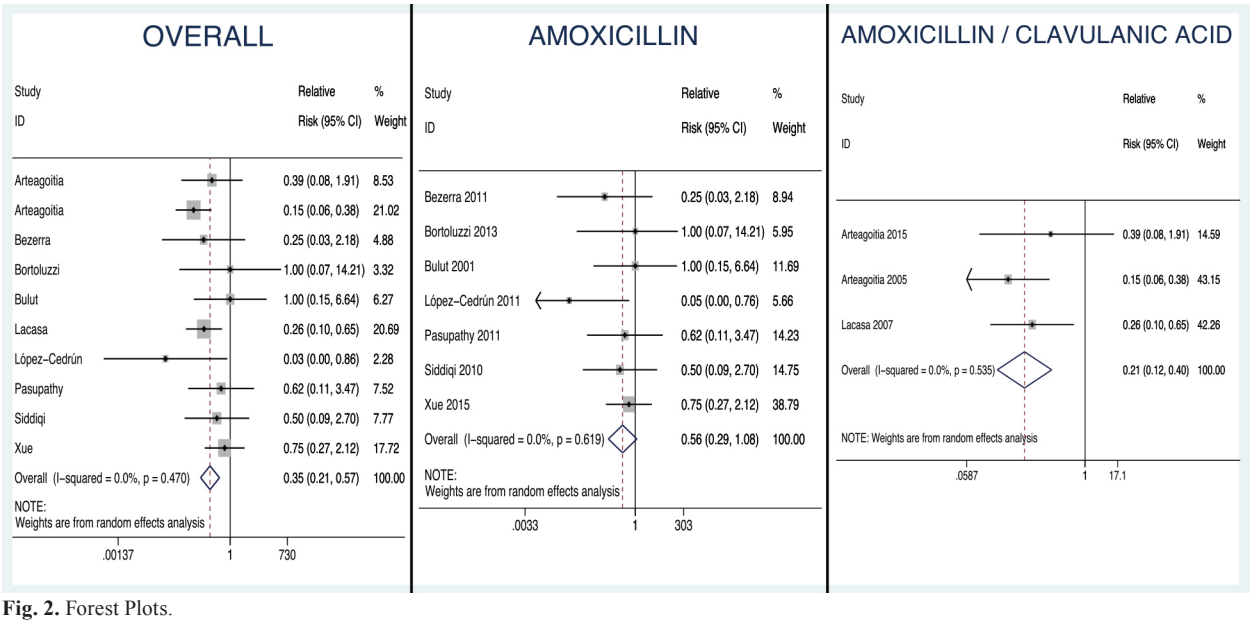

Fig. 2. Forest Plots.
Overall forest plot: graphical representation of the estimates of the RRs and 95% CIs based on the samples in each of the studies, including both those that used amoxicillin and those that used amoxicillin/clavulanic acid, together with their relative weights.
Amoxicillin forest plot.
Amoxicillin/clavulanic acid forest plot.

are shown for the overall analysis and for the analysis stratified by antibiotic (amoxicillin or amoxicillin/clavulanic acid).

- Synthesis of the results:

Analysis of the overall efficacy of amoxicillin with or without clavulanic acid: The quantitative analysis included 1997 extractions: 1072 in experimental groups and 925 in control (placebo) groups, with 27 and 74 reported events of dry socket and/or infection respectively. The overall RR was found to be 0.350, with a 95% CI of 0.214 to 0.574, this being significant (p<0.0001) and different from 1, indicating that treatment with amoxicillin with or without clavulanic acid prevents the development of infectious complications (dry socket, infection, or both conditions concurrently).

Analysis of the heterogeneity: The Q statistic was 8.65 and I^2 was 0% (p=0.470), supporting the assumption of homogeneity among the studies. Further, there is no sign of heterogeneity in the L'Abbé plot (Fig. 3), all the circles being grouped close together, independently of their size and baseline risk.

Analysis of clinical significance: The NNT for each of the studies is reported in table 3 and the overall NNT, adjusting for the weight of each study, was estimated to be 18 (95% CI 13 to 29). This means that we would need to treat between 13 and 29 patients with amoxicillin with or without clavulanic acid to prevent one case of infection.

- Risk of publication bias: The funnel plot (Fig. 3) is not absolutely symmetrical around the summary estimate RRw, and hence, given the suspicion that there may be publication bias, we carried out the corresponding quantitative analysis.

The Begg method suggested a lack of publication bias (Kendall´s Tau being 0.1556; p=0.59), and Egger´s more sensitive method also suggested a lack of publication

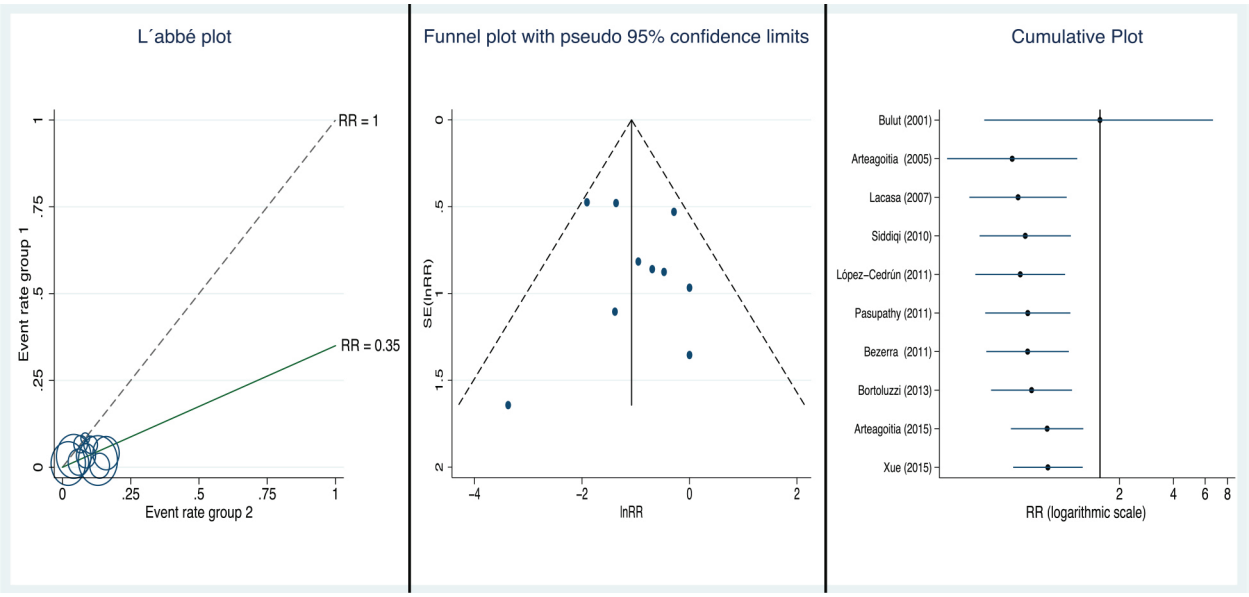

Fig. 3. L'Abbé plot, Funnel plot, Cumulative plot.

Table 3. Number needed to treat (NNT) for each individual study included in the meta-analysis.

AUTHOR	YEAR	NNT	Lower limit	Upper Limit
Bulut (14)	2001	*	*	*
Arteagoitia (11)	2005	9.04	6.37	15.60
Lacasa (15)	2007	8.39	4.81	33.05
Siddiqi (18)	2010	95.00	28.11	-68.87
Bezerra (12)	2011	22.67	9.35	-53.47
Pasupathy (17)	2011	14.26	5.27	-20.13
Lopez Cedrun (16)	2011	8.00	4.40	44.43
Bortoluzzi (13)	2013	*	*	*
Arteagoitia (10)	2015	18.91	7.24	-30.81
Xue (19)	2015	96.00	20.88	-36.95

* Since control and experimental groups have identical results, it is impossible to compute the NNT.

bias (with an intercept value of 0.4772, which is not significant, p=0.627). Macaskill's more specific procedure yielded a slope that was close to 0 and non-significant (p=0.489), confirming the lack of publication bias, both when using the sample size (n) as the independent variable, as proposed by Peters, and when the regression uses the inverse of the sample size (1/n) as the independent variable (p=0.330). Lastly, with Rosenthal's method, it was estimated that it would be necessary to add 79 non-significant studies to cause the results of this meta-analysis to become non-significant.

- Additional analysis:

Stratified analysis: We analysed independently the studies in which the treatment was amoxicillin or amoxicillin/clavulanic acid:

- Amoxicillin: We included 7 studies (1167 extractions: 606 in experimental groups and 561 in controls with 14 and 27 events of dry socket and/or infection respectively). The RR was 0.563 (p=0.082, 95% CI 0.295 to 1.08). We found no evidence of heterogeneity (I^2=0.00%, p=0.619). The NNT was 40, meaning that about one in every 40 patients would benefit from the treatment. The 95% confidence interval for the NNT ranged from 22 to 274.
- Amoxicillin/clavulanic acid: We included 3 studies (830 extractions: 466 in experimental groups and 364 in controls with 13 and 47 events of dry socket and/or infection respectively). The RR was 0.215 (p<0.001, 95% CI 0.117 to 0.395). Again, we found no evidence of heterogeneity (I^2=0.00%, p=0.535). The NNT was 10, meaning that about one in every 10 patients would benefit from the treatment, and the 95% confidence interval for the NNT ranged from 7 to 16.

Cumulative analysis: Figure 3 shows the evolution of the 95% CI of the weighted estimate in the cumulative meta-analysis by year of publication, that is, as we added RDBPC studies to the analysis in date order. It can be observed that the first study found a non-significant association but that with the progressive addition of the studies conducted to date the RR increased towards 1.

Analysis of adverse reactions: Five studies reported adverse reactions (Table 2 and 2 continue) with a total follow-up of 1337 patients (741 in experimental groups and 596 controls). A total of 222 patients had some type of adverse reaction associated with the antibiotic given (136 in experimental groups and 86 controls). The RR was 1.188 (95% CI 0.658 to 2.146; p=0.567). The adverse reactions were generally mild and short lived. The number needed to harm (NNH) was 26, meaning that 1 in 26 patients given the prophylactic antibiotics would have an adverse reaction.

Discussion

Our meta-analysis includes 10 RDBPC clinical trials that assess the efficacy of amoxicillin with and without clavulanic acid to prevent dry socket, infection and both conditions concurrently after third molar extraction. These studies yielded a total of 1997 third molar extractions. We only selected trials that used placebo in the control group. It is important to highlight that we have not taken into account the antibiotic regimen used. As noted in the qualitative analysis, the studies included are not free from individual bias, but we have not detected publication bias. Adverse reactions were more frequent in the experimental group but were generally mild.

In the quantitative analysis, we used a multiplicative relative risk model and estimates were weighted by the inverse of the variance. We opted to use a random effect model, which assigns a fixed constant coefficient of variability to all studies, and this gives more importance to studies with smaller sample size; however, this is the most appropriate type of model when analysing fewer than 20 studies, provided there is no publication bias.

We have carried out analysis stratifying by the type of antibiotic (amoxicillin or amoxicillin with clavulanic acid), finding this variable to be relevant. The hypothesis of the analysis by subgroups was established a priori and the variable type of antibiotic used for weighing was defined prior to randomisation in all of the studies. This stratified meta-analysis has found that the statistical significance of the RR differs between the subgroups: in the case of amoxicillin alone, the CI of the RR (95% CI 0.295 to 1.08) includes 1 and the result was not significant (p=0.082), while for amoxicillin and clavulanic acid, the result was statistically significant (p<0.001, 95% CI 0.117 to 0.395). We should emphasize that only three studies were included in the amoxicillin/clavulanic acid subgroup analysis, and that two of these were conducted by the same research team (10,11), which could be a source of bias.

We have not used restrictive criteria in the definition of infection or dry socket. We found significant differences in the rate of infection and/or dry socket in the groups treated with placebo. This may be attributable to differences in the diagnostic criteria, or factors related to the technique used, surgeon experience, asepsis or patient characteristics. In our meta-analysis, the mean rate of infection in the control group was 8%, with very different results across the clinical trials included. The mean rates of infection in the placebo group were 5% in studies using amoxicillin and 13% in studies using amoxicillin/clavulanic acid.

The rate of infection was not significantly different in patients given amoxicillin (2.31%) or amoxicillin/clavulanic acid (2.79%). In contrast, there were notable differences analysing absolute risk reduction, with values of 2.50% (95% CI 0.37 to 4.64%) in the amoxicillin group and 10.12% (95% CI 6.37 to 13.88%) in the amoxicillin/clavulanic acid group. This discrepancy is understandable given the difference in rates of the conditions considered in patients treated with placebo in

the two subgroups, with higher rates of infection in the case of studies using amoxicillin/clavulanic acid than those using amoxicillin (Table 2 and 2 continue). This underlines the fact that failing to include placebo groups in trials of antibiotics may lead to different conclusions regarding drug efficacy (4).

Other meta-analyses have been published on the efficacy of antibiotics for the prevention of inflammatory and infectious complications after third molar extraction. In 2007, Ren *et al*. (9) studied the efficacy of antibiotic prophylaxis including 15 clinical trials. They did not limit the search to double-blind studies, included different families of antibiotics and analysed the efficacy taking into account the treatment regimen, concluding that the antibiotic treatment is effective only when used before surgery. In 2012, Lodi *et al*. (6) included 18 double-blind randomised clinical trials and analysed different families of antibiotics and several different response outcomes (infection, dry socket, pain, inflammation, trismus and high temperature). They concluded that, compared to placebo, antibiotics (without specifying which) reduce the risk of infection by 70%, a very similar result to ours (65%), and that of dry socket by 38%. On the other hand, they found that antibiotics are associated with an increase in adverse effects compared to placebo (RR 1.98; 95% CI 1.10 to 3.59; $p = 0.02$). In our case, the relative risk was somewhat lower, but only half of the studies had recorded adverse reactions (RR = 1.188; 95% CI 0.658 to 2.146; $p = 0.567$). Lodi *et al*. (6) estimated that, despite the results obtained, physicians should consider whether treating 12 patients with antibiotics to prevent one case of infection does more harm than good.

In our case, the results should also make us think. To avoid one patient having an infectious complication using amoxicillin prophylactically, we would need to treat 40 patients. Moreover, as mentioned earlier, amoxicillin does not significantly reduce the risk of infection and/or dry socket. For this reason, we believe that its use is not justified.

In the case of amoxicillin/clavulanic acid, we would have to treat 10 patients to avoid 1 case of infectious complication. It is important to analyse the clinical significance of these results. First, we should take into account the low rate of infectious complications and the lack of serious complications. On the other hand, the risks of antibiotic use are widely documented, in relation to increases in antibiotic resistance at the population level (20,21), as well as adverse reactions at the individual level. In this meta-analysis, 1 out of 26 patients treated with amoxicillin with or without clavulanic acid had some type of adverse reaction.

For all these reasons, and given our results, we conclude that there no basis for recommending the prophylactic use of amoxicillin without clavulanic acid for preventing infection and/or dry socket after third molar extraction in healthy patients. Regarding amoxicillin/clavulanic acid, although the null hypothesis was rejected and prophylactic use was statistically significantly effective, taking into account the NNT, low rate of infectious complications, adverse reactions in experimental groups and lack of serious complications reported in controls, the prescription of this combination of antibiotics cannot be justified either.

References

1. Rodrigues WC, Okamoto R, Pellizzer EP, dos Carrijo AC, de Almeida RS, de Melo WM. Antibiotic prophylaxis for third molar extraction in healthy patients: Current scientific evidence. Quintessence Int. 2015;46:149-61.

2. Rohit S, Reddy BP. Efficacy of postoperative prophylactic antibiotic therapy in third molar surgery. J Clin Diagn Res. 2014;8:14-6.

3. Arteagoitia MI, Ramos E, Santamaría G, Álvarez J, Barbier L, Santamaría J. Survey of Spanish dentists on the prescription of antibiotics and antiseptics in surgery for impacted lower third molars. Med Oral Patol Oral Cir Bucal. 2016;21:e82-7.

4. Iglesias-Martín F, García-Perla-García A, Yañez-Vico R, Aced-Jiménez E, Arjona-Gerveno E, González-Padilla JD, et al. Comparative trial between the use of amoxicillin and amoxicillin clavulanate in the removal of third molars. Med Oral Patol Oral Cir Bucal. 2014;19:e612-5.

5. Oomens MA, Forouzanfar T. Antibiotic prophylaxis in third molar surgery: a review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114:e5-12.

6. Lodi G, Figini L, Sardella A, Carrassi A, Del Fabbro M, Furness S. Antibiotics to prevent complications following tooth extractions. Cochrane Database Syst Rev. 2012;11:CD003811.

7. Arora A, Roychoudhury A, Bhutia O, Pandey S, Singh S, Das BK. Antibiotics in third molar extraction; are they really necessary: A non-inferiority randomized controlled trial. Natl J Maxillofac Surg. 2014;5:166-71.

8. Calvo AM, Brozoski DT, Giglio FP, Gonçalves PZ, Sant'ana E, Dionísio TJ, et al. Are antibiotics necessary after lower third molar removal? Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(5 Suppl):S199-208.

9. Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg. 2007;65:1909-21.

10. Arteagoitia I, Ramos E, Santamaria G, Barbier L, Alvarez J, Santamaria J. Amoxicillin/clavulanic acid 2000/125 mg to prevent complications due to infection following completely bone-impacted lower third molar removal: a clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:8-16.

11. Arteagoitia I, Diez A, Barbier L, Santamaría G, Santamaría J. Efficacy of amoxicillin/clavulanic acid in preventing infectious and inflammatory complications following impacted mandibular third molar extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:e11-8.

12. Bezerra TP, Studart-Soares EC, Scaparo HC, Pita-Neto IC, Batista SH, Fonteles CS. Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: a split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). J Oral Maxillofac Surg. 2011;69:e333-9.

13. Bortoluzzi MC, Capella DL, Barbieri T, Pagliarini M, Cavalieri T, Manfro R. A single dose of amoxicillin and dexamethasone for prevention of postoperative complications in third molar surgery: a randomized, double-blind, placebo controlled clinical trial. J Clin Med Res. 2013;5:26-33.

14. Bulut E, Bulut S, Etikan I, Koseoglu O. The value of routine antibiotic prophylaxis in mandibular third molar surgery: acute-phase protein levels as indicators of infection. J Oral Sci. 2001;43:117-22.

15. Lacasa JM, Jiménez JA, Ferrás V, Bossom M, Sóla-Morales O, García-Rey C, et al. Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: a randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000/62.5 mg). Int J Oral Maxillofac Surg. 2007;36:321-7.
16. López-Cedrún JL, Pijoan JI, Fernández S, Santamaria J, Hernandez G. Efficacy of amoxicillin treatment in preventing postoperative complications in patients undergoing third molar surgery: a prospective, randomized, double-blind controlled study. J Oral Maxillofac Surg. 2011;69:e5-14.
17. Pasupathy S, Alexander M. Antibiotic prophylaxis in third molar surgery. J Craniofac Surg. 2011;22:551-3.
18. Siddiqi A, Morkel JA, Zafar S. Antibiotic prophylaxis in third molar surgery: A randomized double-blind placebo-controlled clinical trial using split-mouth technique. Int J Oral Maxillofac Surg. 2010;39:107-14.
19. Xue P, Wang J, Wu B, Ma Y, Wu F, Hou R. Efficacy of antibiotic prophylaxis on postoperative inflammatory complications in Chinese patients having impacted mandibular third molars removed: a split-mouth, double-blind, self-controlled, clinical trial. Br J Oral Maxillofac Surg. 2015;53:416-20.
20. Loyola-Rodriguez JP, Garcia-Cortes JO, Martínez-Martinez RE, Patiño-Marin N, Martinez-Castañon GA, Zavala-Alonso NV, et al. Molecular identification and antibiotic resistant bacteria isolated from primary dentition infections. Aust Dent J. 2014;59:497-503.
21. Chopra R, Merali R, Paolinelis G, Kwok J. An audit of antimicrobial prescribing in an acute dental care department. Prim Dent J. 2014;3:24-9.

Conflict of Interest

The authors of this paper have no conflict of interest to report regarding this publication.