Review

Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis

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1. Introduction

The insertion of dental implants is a routine treatment in the rehabilitation of partially and completely edentulous jaws (American Academy of Implant Dentistry, 2017 December 12). Treatment with dental implants is expected to have a high success rate: implant survival rates of 90–95% have been reported in longitudinal studies with long-term follow-up (Hee-Won et al., 2011).

Despite the high success rates, failures do occur and may be classified as either early failures, occurring prior to prosthetic restoration, or late failures, post-prosthesis placement (Koldsland et al., 2009). Bacterial contamination at implant insertion may be one cause of infection and early implant failure (Pye et al., 2009; Esposito et al., 2013).

In spite of the fact that there are different therapeutic options, if an infection has been established, infected implants usually have to be removed. Both patients and professionals poorly tolerate complications and failures in implantology. For this reason, diverse strategies to prevent implant infection and failure in healthy subjects, such as antiseptic dilutions and oral...
Antibiotic prophylaxis in oral and dental surgery is usually recommended for patients at risk of infectious endocarditis, patients with reduced host response, and when surgery is performed in infected sites (Gould et al., 2006; Wilson et al., 2007; Resnik and Misch, 2008). However, the evidence of antimicrobial protocols in order to prevent implant failure or infection in healthy subjects is limited. In spite of the fact that there are some published articles (Dent et al., 1997; Laskin et al., 2000; Seabera et al., 2000; Morris et al., 2004; Binaimhed et al., 2005; Schwartz and Larson, 2007; Abu-Ta’a et al., 2008; Esposito et al., 2008, 2010; Khoury et al., 2008; Anitua et al., 2009; Ciaiazzo et al., 2011; Givens et al., 2013; El-Kholey, 2014; Hosseini et al., 2014; Tan et al., 2014; Nolan et al., 2014; Arduino et al., 2015; Escalante et al., 2015) and review papers (Ahmad, 2012; Esposito et al., 2013; Ata-Ali et al., 2014; Caiazzo et al., 2011; Arduino et al., 2015; Escalante et al., 2015) with different antibiotic regimens for preventing dental implant failures or postoperative infections, their results remain inconclusive.

Unfortunately, there is still no consensus among professionals about the use and indications of antibiotics for preventing failures or postoperative infections in these surgeries in healthy patients under normal circumstances (Caiazzo et al., 2011; Arduino et al., 2015). Additionally, it remains unclear whether an adjunct use of postoperative antibiotics is beneficial after the use of single preoperative doses of antibiotics (Esposito et al., 2013; Park et al., 2017). Therefore, the widespread use of perioperative antibiotics to prevent such an infrequent complication remains controversial.

The irrational use of antibiotics could potentially cause adverse reactions, and this risk should be seriously considered. Adverse events related to the use of antibiotics range from diarrhea to life-threatening allergic reactions. Another current concern of antibiotic use is the development of bacterial resistance and the risk of superinfection (Resnik and Misch, 2008; Surapaneni et al., 2016).

A rather alarming increased rate of the prescribing of antibiotics by dental practitioners has been documented (Marra et al., 2016). Moreover, there is a significant cost for antibiotic prophylaxis in the dental practice setting, and evidence-based recommendations concerning this practice are needed (Lockhart et al., 2013).

Consequently, the authors considered it important to analyze all of the quality evidence published and to try to keep it up-to-date to support the clinician’s evidenced-based decisions.

The purpose of this systematic review and meta-analysis was to assess the efficacy and effectiveness of antibiotics in preventing dental implant failure or postoperative infection, compared to a control group, among patients undergoing dental implant placements under ordinary conditions. The second purpose was to evaluate which was the most effective and efficacious antibiotic regimen preventing dental implant failure or postoperative infection.

The investigators hypothesize that the use of antibiotics, in any regimen, is neither effective nor efficacious in preventing dental implant failures or postoperative infections after a dental implant placement. The authors also hypothesize that the use of a postoperative antibiotic regimen, used either exclusively postoperatively or in conjunction with a preoperative regimen (adjunct use), is neither more effective nor more efficacious than a solely preoperative antibiotic regimen.

The specific aims of the research were as follows:

- To assess the incidence rate of dental implant failures and postoperative infections after dental implant placements among healthy patients who were treated with or without antibiotics (in any regimen and dosage).
- To contrast the benefits of postoperative antibiotics orally (exclusively postoperative and adjunctive to preoperative antibiotics) versus only preoperative antibiotics orally.

2. Materials and methods

2.1. Protocol and registration

To address the research purpose, the authors designed and implemented a systematic review and meta-analysis. The research was conducted and is reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

Details of the protocol for this systematic review were registered on PROSPERO (CRD42017054364) and can be accessed at (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?id=CRD42017054364).

2.2. Eligibility criteria

The target sample was composed of all published articles presenting an evaluation of the efficacy of antibiotics for preventing postoperative infection or dental implant failure after a dental implant placement.

For inclusion in the study, publications had to be RCTs (with or without placebo) that included patients of any age or gender who underwent a dental implant surgery. Studies were required to have analyzed the efficacy of any antibiotic in any treatment dose or regimen (preoperatively, postoperatively or both) for preventing postoperative infection or dental implant failure after dental implant placement.

Publications were excluded if they were case series, retrospective studies or not randomized clinical trials. Articles were also excluded if they did not assess the postoperative incidence of implant-site infection or dental implant failure, or if they did but the implant was inserted into sites with periapical infection or with apical pathology. The authors did not use restrictive criteria for defining postoperative infection or dental implant failure. There was no restriction by language or year of publication.

2.3. Information sources

Searches were conducted in the following electronic databases up to August 2017: Medline/PubMed, Scopus, Science-Direct, Web of Science, Evidence-Based Dentistry, ClinicalTrials.gov, the EU Clinical Trials Register, and the Cochrane Central Register of Controlled Trials, as well as the Spanish General University Board database of doctoral theses in Spain (TESEO), the Spanish National Research Council (CSIC) bibliographic databases, and the Spanish Medical Index (IME).

2.4. Search

The searched terms were descriptors of each of the Patient, Intervention, Comparison, and Outcome (PICO) components: dental implant surgery, dental implant placement, antibiotics, amoxicillin, implant failure, implant loss, and postoperative infection. The following filters were applied: humans, clinical trials, meta-analysis, and randomized controlled trials. The electronic search in the Medline/PubMed database was carried out using MeSH and search algorithms connected with Boolean operators as key words for titles and abstracts (Robinson and Dickersin, 2002): (randomized controlled trials OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials...
OR ("clinical trial") OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR ("latin square") OR placebo 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 prospective* OR volunteer*) NOT animal) AND (amoxicillin) AND (dental implant failure OR dental implant loss OR postoperative infection) AND (dental implant placement OR dental implant surgery).

For databases in Spanish, we used the following terms: (antibioticos O amoxicilina) AND (fracaso implante O pérdida implante) AND (implante dental).

The authors reviewed the references of all papers retrieved, and when they identified potentially unpublished work, they contacted the corresponding authors to request a copy of the study report.

2.5. Study selection

Three researchers independently carried out the search on the databases applying the aforementioned criteria.

Three records were excluded after the duplicates were removed, since their titles specified that they were retrospective and not randomized (Kashani et al., 2005; Karaky et al., 2011). The third one was a congress abstract without enough information to assess randomization and risk of bias (Seabra et al., 2000). Thereafter, 20 full text articles were assessed for eligibility and 11 were excluded. Two of these were excluded because they were retrospective studies, 6 because no randomization method was performed, one for being an abstract article, another because the implant failure was not the outcome of interest, and 2 articles because they used implants placed in sites with periradicular infection and apical pathology (Fig. 1).

2.6. Data collection process

All selected studies were independently examined by 2 researchers who extracted data from each article. When explicit data on some variables were not stated in the text, they were calculated using data from tables when possible. In the event of uncertainty, the authors were contacted to obtain the necessary information. A third researcher was consulted in cases of disagreement.

2.6.1. Postoperative infection

The authors of the studies included in this meta-analysis applied different diagnostic criteria for the definition of postoperative infection. The most used terms to define this outcome were the presence of suppuration, fistula and abscess or pus exudation with pain, tenderness, edema, swelling, erythema, and heat in the implant site or fever.

The terms suppuration and pus exudation were considered as postoperative infection during the data collection process. The study conducted by Arduino et al. (2015) used the term pus exudation, and 4 studies reported the term suppuration (Esposito et al., 2008, 2010; Nolan et al., 2014; Tan et al., 2014). The RCT implemented by Tan et al. (2014) reported the percentage of patients with suppuration at weeks 1, 2, 4 and 8 after the surgery intervention. Nevertheless, it was not explicit if the data from each week were independently reported. Therefore, it was impossible to distinguish if one patient who had infection signs at one week was the same person with the same signs at another week in the same treatment group. The authors were contacted, and the doubt was resolved, as the percentage of patients with suppuration at each week was found to be independently reported.

2.6.2. Implant failure

Implant failure outcome was essentially defined as a mobile implant that had to be mechanically removed due to lack of osseointegration. The study performed by Arduino et al. (2015) did not report the total number of implants analyzed in each group (test and control) after losses to follow-up and exclusions. Additionally, the RCT carried out by Caiazzo et al. (2011) did not report the total number of patients who had implant failures in each group. For this reason, the authors from both RCTs were contacted and they successfully provided these data (Table 1).

The article published by Nolan et al. (2014) did not report the total number of implants inserted in each group, and the corresponding author was also contacted, but in this case, the raw data were unfortunately not available. For this reason, this study was excluded from the analysis carried out by the number of implant failures. Nevertheless, the authors used the data available in this study for the analyses by the number of patients who had an implant failure and the number of patients who suffered a postoperative infection.

The articles conducted by Caiazzo et al. (2011) and Tan et al. (2014) included 3 treatment groups using amoxicillin and 1 control group. In this meta-analysis, each treatment group was included as an independent RCT using the same control group provided by the researchers.

In 2 articles, patients in the control group were also treated with amoxicillin with a different dose regimen from the treatment group (El-Kholey, 2014; Arduino et al., 2015). These control groups might be considered as treatment groups in different RCTs, for which a new control group would be necessary.

To this end, the authors constructed a new control group for each analysis. The new control groups were based on calculating the mean number of subjects presenting the outcome variables (patients who had an implant failure, total number of implant failures and patients who had a postoperative infection) in the control groups from the other RCTs included in each analysis (Abu-Ta’a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014). Similarly, the mean number of subjects not presenting the outcome variables (successful implants, patients who had no implant failures and patients who had no postoperative infections) in the control groups from the other RCTs was also calculated (Abu-Ta’a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014).

These newly constructed control groups were composed of 4 patients who had an implant failure and 94 patients who had no implant failure for the first analysis (implant failure by patients), 4 implant failures and 130 successful implants for the second analysis (implant failure by implants), and 2 patients who had a postoperative infection and 76 patients without postoperative infections for the last analysis.

The authors imputed the data of these newly constructed control groups for the 2 aforementioned studies (El-Kholey, 2014; Arduino et al., 2015).

2.7. Data items and analysis

The predictor variable was whether or not antibiotics were used in each RCT. The recorded data included the following: type of antibiotic, administration route and treatment regimen (before or after the implant placement). In all studies, the only antibiotic type used was oral amoxicillin.

The authors performed a stratified meta-analysis with 3 different outcome variables: 1.-Number of patients who had an implant failure; 2.- Number of implant failures; and 3.-Number of patients who suffered a postoperative infection. Stratified analysis
was carried out in order to contrast the effect of solely preoperative oral antibiotics versus postoperative antibiotics (used both exclusively postoperatively and as adjunct use in a perioperative regimen).

The authors did not use restrictive criteria for defining postoperative infection and implant failure.

The authors also recorded the presence or absence of adverse effects.

The remaining variables described the characteristics of the sample of each article (sample size, gender, mean age of the patients, number of smokers, and use of contraceptives) and the characteristics of the study design in each article (study type, number of treatment groups, randomization process, secret assignment, blinding, losses to follow-up, test materials, control materials, co-treatment materials, type of implant and type of surgery). The data collected are listed in Table 1.

2.8. Risk of bias in individual studies

The Cochrane Collaboration’s tool was used in order to assess the individual risk of bias of each included RCT at the study level (Higgins and Green, 2011). The risk of bias graph (Fig. 2) and the risk
<table>
<thead>
<tr>
<th>Study, Year and Country</th>
<th>Type of study</th>
<th>Method of randomization</th>
<th>Blinding</th>
<th>Test material (which and dosage)</th>
<th>Control material</th>
<th>Co-intervention (meds and dosage)</th>
<th>Test group patients</th>
<th>Control group patients</th>
<th>Diagnositic criteria</th>
<th>Quantitative outcome measure &amp; LTF</th>
<th>Follow up period</th>
<th>Adverse reactions</th>
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</thead>
<tbody>
<tr>
<td>Abu-Taa et al., 2008, Belgium</td>
<td>Parallel-group RCT</td>
<td>Random sampling</td>
<td>Double-blinded</td>
<td>AMX 1 g per os, 1 h preoperatively and 500 mg 4 times per day, 2 days postoperatively</td>
<td>No antibiotics</td>
<td>Postoperative rinse with 0.02% CLX for 1 min for 7–30 days</td>
<td>n = 40 male: 23 female: 17 MA: 60 Range: 27–82 n implants: 128</td>
<td>n = 40 male: 20 female: 20 MA: 57 Range: 26–88 n implants: 119</td>
<td>Postoperative infection: Pus, drainage (pus) or fistula in the operated region, with pain or tenderness, localized swelling, redness and heat or fever</td>
<td>Test group: Patients with infection: 1/40 Survival rate (implants): 120/128 (100%) Patients who had implant failures: 0/40 Control group: Patients with infection: 4/40 Survival rate (implants): 134/119 (90%) Patients who had implant failures: 3/40</td>
<td>5 months after implant placement</td>
<td>No side effects of the antibiotic were reported</td>
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<td>Eposito et al., 2005, Italy</td>
<td>Parallel-group RCT</td>
<td>Twelve computers-generated restricted randomization list</td>
<td>Double-blinded</td>
<td>2 g AMX orally (2 tablets of 1 g) 1 h prior to implant placement</td>
<td>2 identical placebo tablets 1 h prior to implant placement</td>
<td>Postoperative rinse with 0.2% CLX for 1 min twice a day for at least 1 week in the control group 1 patient was treated with antibiotics because of influenza 2 days after implant placement</td>
<td>n = 158 Female: 78 (49.4%) MA: (range) = 47.8 ± 12.7 Non-smokers = 108 (68.4%) Duration: (range) = 26.4 ± 12 Total number of implants = 341 Took postoperative antibiotics = 2</td>
<td>n = 158 Female: 56 (60.8%) MA: (range) = 47.9 ± 12.7 Non-smokers = 106 (68.4%) Duration: (range) = 26.4 ± 12 Total number of implants = 335 Took postoperative antibiotics = 1</td>
<td>Postoperative infection: Suppuration, fistula, abscess</td>
<td>Test group: Implant failures: 2/344 Patients with infection: 3/248 Control group: Implant failures: 5/335</td>
<td>4 months after implant placement</td>
<td>1 adverse event occurred in the placebo group (itching for 1 day) and 1 in the AMX group (diarrhea and somnolence)</td>
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<td>Antua et al., 2009, Spain</td>
<td>Parallel-group RCT</td>
<td>Random numbers table</td>
<td>Double-blinded</td>
<td>2 g oral AMX 1 h before implant surgery</td>
<td>2 placebo tablets administered orally 1 h before implant surgery</td>
<td>0.2% CLX rinse for 1 min preoperatively and 0.2% CLX for 1 min twice a day for at least 1 week postoperatively</td>
<td>n = 52 Female: 37 (71%) MA: 15 (29%) Non-smokers = 42 (81%) Duration: (mean ± SD) = 41.63 ± 12.99 Anterior Zone = 26 (51%) Mandibular = 25 (49%) Anterior Zone = 11 (22%) Posterior Zone = 19 (37%) Immediate Loading type = 1 (2%)</td>
<td>n = 53 Female: 33 (62%) MA: 20 (38%) Non-smokers = 24 (45%) Duration: (mean ± SD) = 41.71 ± 12.7 Anterior Zone = 21 (40%) Mandibular = 22 (42%) Anterior Zone = 12 (23%) Posterior Zone = 38 (72%) Immediate Loading type = 1 (2%)</td>
<td>Postoperative infection: Inflammation, pain, heat, fever and drainage</td>
<td>Test group: Postoperative infections: 2/652 Implant failures: 2/652 Control group: Postoperative infections: 6/571 Implant failures: 5/571</td>
<td>3 months after implant placement</td>
<td>NR</td>
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<td>Eposito et al., 2010, Italy</td>
<td>Parallel-group RCT</td>
<td>Computer generated restricted randomization list</td>
<td>Triple-blinded</td>
<td>2 g AMX orally (2 tablets of 1 g) 1 h prior to implant placement</td>
<td>2 identical placebo tablets 1 h prior to implant placement</td>
<td>CLX mouthwash 0.2% for 1 min prior to implant placement and CLX mouthwash 0.2% for 1 min twice a day for at least 1 week postoperatively</td>
<td>n = 256 Female: 138 (54.8%) MA: (range) = 49.0 ± 8.45 Non-smokers = 171 (67.9%) Smoking up to 10 cigarettes/day = 55 (21.8%)</td>
<td>n = 254 Female: 132 (52.0%) MA: (range) = 47.6 ± 8.86 Non-smokers = 166 (65.4%) Smoking up to 10 cigarettes/day = 55 (21.8%) Smoking more than 10 cigarettes/day = 12 (4.7%)</td>
<td>Postoperative infection: Suppuration, fistula, abscess</td>
<td>Test group: Implant failures: 7/489 Patients who had implant failures: 9/252 Patients who had postoperative infections: 4/252</td>
<td>4 months after implant placement</td>
<td>No antibiotic adverse events were noted in any group</td>
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<td>Study</td>
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<td>Success/postoperative infections</td>
<td>Outcome</td>
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<td>Caizzo et al., 2011, Italy</td>
<td>Parallel-group RCT</td>
<td>Computer-generated randomization lists</td>
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<td>Group 1: Single prophylactic antibiotic dose consisting of AMX 2 g 2 h before surgery Group 2: Preoperative and postoperative antibiotic treatment consisting of AMX 2 g 1 h before surgery and 1 g twice a day for 7 days following surgery Group 3: Postoperative antibiotic coverage consisting of AMX 1 g twice a day started after surgery and continued for 1 week after surgery</td>
<td>Implant failures: 2/25</td>
<td>No antibiotic adverse events were noted in any group</td>
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<td>El-Khairy, 2004, Saudi Arabia</td>
<td>Parallel-group RCT</td>
<td>Computer-generated list of random numbers</td>
<td>Saudi Arabia</td>
<td>Group 1: single dose of 1 g oral AMX 1 h preoperatively, and no postoperative antibiotics Group 2: 1 g oral AMX 1 h preoperatively followed by postoperative oral AMX 500 mg every 8 h for 3 days</td>
<td>Implant failures: 4/43</td>
<td>No antibiotic adverse events were noted in any group</td>
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<tr>
<td>Nolan et al., 2018, Ireland</td>
<td>Parallel-group RCT</td>
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<td>Placebo capsules (containing sugar) orally 1 h prior to the surgery 3 g AMX orally 1 h prior to the surgery</td>
<td>Implant failures: 2/29</td>
<td>No antibiotic adverse events were noted in any group</td>
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<tr>
<td>Tan et al., 2014</td>
<td>Parallel-group RCT</td>
<td>Randomization tables. Blocked randomization in blocks of eight, whereby at every block of eight enrolments, there were two subjects randomly assigned to one of the four intervention groups</td>
<td>Single-blinded</td>
<td>Group 1: 2 g of amoxicillin preoperatively, 1 h prior to conventional implant placement. Group 2: 2 g of AMX immediately postoperatively. Group 3: 2 g of amoxicillin preoperatively, 1 h prior to implant placement and 500 mg three times a day (8 hourly) on days 2 and 3</td>
<td>Group 4: 2 g of a placebo CLX rinse for 1 min immediately prior to surgery</td>
<td>Preoperation 0.2% LTF rinse for 1 min</td>
<td>Group 1 (PC)</td>
<td>n = 81 Female = 49.4% Male = 50.6% MA = 48.8 Non-smoker 81.5% Smoker: 18.5% Group 2(T1)</td>
<td>n = 82 Female = 42.7% Male = 57.3% MA = 47.8 Non-smoker 80.5% Smoker: 19.5% Group 3 (T2)</td>
<td>n = 86 Female = 45.3% Male = 54.7% MA = 46.9 Non-smoker 80.2% Smoker: 19.8%</td>
<td>Group 4 (NC)</td>
<td>n = 80 Female = 44.7% Male = 55.3% MA = 45.1 Non-smoker 80.0% Smoker: 20% Alveolar Bone Width B-L (Mean, mm): 7.91 Alveolar Bone Width M-D (Mean, mm): 11.33</td>
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<tr>
<td>Arduino et al., 2015, Italy</td>
<td>Parallel-group RCT</td>
<td>Two computer-generated randomization lists</td>
<td>Double-blinded</td>
<td>Group 1: 2 g of AMX orally (2 tablets of 1 g) 1 h prior to surgery</td>
<td>Group 2: 2 g of AMX orally (2 tablets of 1 g) 1 h prior to surgery and 1 g the evening of the day of surgery and 1 g twice a day for 2 days following surgery</td>
<td>Rinse with 0.2% CLX 1 min immediately prior to surgery</td>
<td>Group 1: n = 180 MA (SD) = 49.3 (13.9) Female = 101 Male = 79 Smokers = 57 (31.7%) Mandibular Implants = 202 Maxillary implants = 76 Number of implants = 278</td>
<td>Group 2: n = 180 MA (SD) = 51.6 (14.4) Female = 88 Male = 92 Smokers = 37 (20.6%) Mandibular Implants = 173 Maxillary implants = 116 Number of implants = 289</td>
<td>Group 3: n = 180 MA (SD) = 51.6 (14.4) Female = 101 Male = 79 Smokers = 57 (31.7%) Mandibular Implants = 202 Maxillary implants = 76 Number of implants = 278</td>
<td>Group 4: n = 180 MA (SD) = 51.6 (14.4) Female = 101 Male = 79 Smokers = 57 (31.7%) Mandibular Implants = 202 Maxillary implants = 76 Number of implants = 278</td>
<td>Group 1: Implant failures: 5/81 Patients with implant failures: 0/81 Patients with postoperative infections: 2/81</td>
<td>Group 2: Implant failures: 0/82 Patients with implant failures: 0/82 Patients with postoperative infections: 0/82</td>
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</tbody>
</table>

AMX: Amoxicillin; CLX: Chlorhexidine; N: Newton’s; n: population; RCT: Randomized Controlled Trial; n: sample size; MA: mean age; SD: standard derivation; NR: Not reported; LTF: Lost to follow-up. *Indicates studies whose data have been imputed from the calculated control group.
of bias summary (Fig. 3) were generated using Review Manager 5.3 (The Cochrane Collaboration, 2014). Quantitative and qualitative data were collected on losses to follow-up, the randomization process, blinding and other factors that could be potential sources of bias (Table 1).

2.9. Summary measure

The efficacy of the treatment was assessed using Risk Ratio (RR) (Fig. 4). The effectiveness of the treatment with antibiotics was assessed using the number needed to treat (NNT). The overall NNTs adjusted for the weight of each study for all analyses were estimated.

2.10. Synthesis of results

All analyses were carried out using STATA 14 (StataCorp LP, College Station, TX) (Sterne, 2009). The authors assessed the heterogeneity among different studies using the I² statistic, and graphically with the I’Abbe plots (Fig. 5). The overall RR, resulting from combining different studies, was calculated with a fixed-effects model with weights calculated using the Mantel–Haenszel method (Delgado, 2015).

2.11. Risk of bias across the studies

Publication bias was assessed graphically using funnel plots (Fig. 6).

The quality of the evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considering each outcome variable independently (Tables 2 and 3). GRADE was developed for rating the quality of evidence and strength of recommendations (Guyatt et al., 2008, 2011).

3. Results

3.1. Study selection

Overall, 9 articles published since 2008 were included in this meta-analysis. Fig. 1 presents a flow diagram of the study selection process with a list of the excluded studies and the reasons for their exclusion.
Fig. 4. Combined Forest plots. RR: Risk Ratio, CI: Confidence Interval.
Fig. 5. Combined l’Abbé plots. RR: Risk Ratio; AMX: amoxicillin.
The final analyses, by the number of patients who had an implant failure and by the number of postoperative infections, were performed on 15 RCTs corresponding to 9 articles (Abu-Ta’a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014; Arduino et al., 2015).

Furthermore, 14 RCTs corresponding to 8 articles were finally included in the meta-analysis by the number of implant failures (Abu-Ta’a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014). 3.2. Study characteristics

In the studies reviewed, only one antibiotic type was assessed: amoxicillin. It is used in various dosages and therapeutic regimens. Preoperative regimens were as follows: single dose of 1 g (Abu-Ta’a et al., 2008; El-Kholey, 2014), 2 g (Esposito et al., 2008, 2010; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014; Arduino et al., 2015), or 3 g 1 h before surgery (Nolan et al., 2014). Postoperative regimens were as follows: 2 g immediately after the surgery (Tan et al., 2014), 1 g two/three times a day for one week (Caiazzo et al., 2011) or for two days after implant placement (Arduino et al., 2015), and 500 mg three times a day for two (Abu-Ta’a et al., 2008) or three days after surgery (El-Kholey, 2014; Tan et al., 2014). Several studies combined preoperative and postoperative antibiotics (Abu-Ta’a et al., 2008; Caiazzo et al., 2011; El-Kholey, 2014; Tan et al., 2014; Arduino et al., 2015).

The risk of bias graph (Fig. 2) illustrates the proportion of studies with each of the judgments (Low risk, High risk, Unclear risk of bias). The risk of bias summary (Fig. 3) presents all of the judgments in a cross-tabulation of study by entry.

The RCT carried out by Anitua et al. (2009) might present a possible risk of information bias, as the Biotechnology Institute (BTI®, Vitoria, Spain) provided funding and controlled the analysis and results of the trial.

3.4. Results of individual studies

The forest plots presented in Fig. 4 are graphical representations of the estimates of the RR and 95% confidence intervals (CIs) obtained using the samples from each of the studies. The area of gray squares around the RR is proportional to the weight of the study in the analysis. CIs, indicated by a continuous horizontal line that crosses the vertical line at a RR equal to 1, correspond to studies with non-significant results. The graph also indicates the overall RR based on all the studies with a rhombus and a dotted line.
### Table 2

**Evidence table.**

<table>
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<th>Quality assessment</th>
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<td>Low (0.47, 1.22)</td>
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<td>Treatment Group</td>
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<td></td>
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<td></td>
<td>Very Low (0.29, 1.19)</td>
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#### 3.5. Synthesis of results

#### 3.5.1. Implant failure analysis by patients

A single dose of oral amoxicillin preoperatively (SDOAP) before implant surgery was found to significantly \( (P = .012) \) prevent patients from developing dental implant failures \( (RR = 0.50, CI: 0.29–0.86) \), while the postoperative use of oral amoxicillin (exclusively postoperative and adjunct with preoperative amoxicillin) did not significantly \( (P = .197) \) achieve a prophylactic effect \( (RR = 0.60, CI: 0.28–1.30) \).

The overall RR from the analysis carried out by the number of patients who had an implant failure was 0.53 (95% CI, of 0.34–0.82), which is significantly different from 1 \( (P = .005) \).

The overall NNT estimated for the analysis carried out by the number of patients who had an implant failure was 55. Considering the 95% CI, 33 to 167 patients would need to be treated with amoxicillin to prevent just 1 patient from suffering an implant failure. The NNT for SDOAP was 67 (95% CI, of 26–125), and the NNT for the postoperative use of oral amoxicillin was 53 (95% CI, of 30–200).

#### 3.5.2. Implant failure analysis by implants

SDOAP before implant surgery was found to be significantly \( (P = .024) \) effective at preventing dental implant failures \( (RR = 0.52, CI: 0.30–0.92) \). However, the postoperative use of oral amoxicillin (exclusively postoperative and adjunct with preoperative amoxicillin) was not found to significantly \( (P = .137) \) prevent dental implant failures \( (RR = 0.58, CI: 0.28–1.19) \).

The overall RR from the analysis performed by the number of implant failures was 0.54 (95% CI, of 0.35–0.85), which is also significantly different from 1 \( (P = .007) \).

The overall NNT from the analysis by the number of implant failures was estimated to be 77. If its 95% CI is also considered, 43 to 250 dental implants would need to be treated with amoxicillin to prevent 1 implant failure. The NNT for SDOAP was 77 (95% CI, of 32–250), and the NNT for the postoperative use of oral amoxicillin was also 77 (95% CI, of 42–500).

#### 3.5.3. Postoperative infection analysis

Neither postoperative oral amoxicillin \( (RR = 0.64, CI 0.27–1.51) \) nor SDOAP \( (RR = 0.82, CI: 0.46–1.45) \) was found to significantly \( (P = .309 \) and \( P = .488 \), respectively) prevent postoperative infections after dental implant surgery.

The overall RR from the analysis carried out by the number of postoperative infections was 0.76 (95% CI, of 0.47–1.22), which is not significantly different from 1 \( (P = .250) \).

The overall NNT calculated for the analysis performed by the number of patients who had postoperative infection was 143. The 95% CI reveals that 50 to 200 patients would need to be treated with amoxicillin to prevent just 1 case of postoperative infection. The
NNT for SDOAP was 100 (95% CI of 32–100), and the NNT for the postoperative use of oral amoxicillin was 143 (95% CI, of 50–200).

3.5.4. Heterogeneity analysis

The heterogeneity, as indicated by the $I^2$ statistic, was 0.0 for the 3 analyses, as the $P$ values were next to 1. This fact provides sufficient evidence to accept the null hypothesis of a lack of heterogeneity among the results of the studies included in this meta-analysis. In the I$^2$Abbe plots (Fig. 5), each circle corresponds to each study included in the analyses, with the area of the circle being proportional to the weight of the study. In the graphics, the authors did not observe any relevant pattern of heterogeneity, with all the circles being grouped in the same region, regardless of their size and baseline risk.

3.5.5. Adverse reactions

The study conducted by Esposito et al. (2008) reported 1 adverse event that occurred in the placebo group (itching for 1 day) and 1 in the antibiotic group (diarrhea and somnolence), but the difference was not significant ($P = 1$). The research performed by Arduino et al. (2015) reported no adverse events in group 1. However, in group 2, two men (aged 53 and 73) reported abdominal swelling with bloating and heartburn and 1 female patient (aged 78) reported skin rash and laryngeal edema. This patient, who did not report in the anamnesis any possible allergy to any type of antibiotic, experienced a profoundly severe reaction requiring discontinuation of therapy and temporary hospital admission. The authors found no significant differences between the two groups.

No adverse reactions to amoxicillin were reported in the 3 included articles (Abu-Ta’a et al., 2008; Esposito et al., 2010; Caiazzo et al., 2011), and there is no information on adverse reactions to amoxicillin in 4 of the included articles (Anitura et al., 2009; El-Kholey, 2014; Nolan et al., 2014; Tan et al., 2014).

3.6. Risk of bias across the studies

The funnel plots (Fig. 6) suggest a lack of publication bias considering the symmetrical dispersion of the points in reference to a RR equal to 0.53, 0.54 and 0.74, respectively. The results of the quality of evidence (GRADE) analysis are presented in Table 2.

4. Discussion

4.1. Summary of evidence

This systematic review and meta-analysis suggests that the use of SDOAP might be the only beneficial regimen for preventing dental implant failures after a dental implant placement. The use of postoperative oral amoxicillin regimens might not significantly prevent dental implant failures or postoperative infections after dental implant surgeries. For this reason, the use of postoperative amoxicillin orally might not add any benefits to SDOAP and may be considered overtreatment.

The effectiveness analysis suggests that 67 patients would need to be treated with a SDOAP to prevent 1 patient from suffering an implant loss. Additionally, the effectiveness analysis also suggests that 77 dental implants would need to be treated with preoperative amoxicillin orally to prevent 1 implant failure. This might result in a slight reduction of almost 1.30% in the risk for implant failure. Unfortunately, there is still no consensus on the use of antibiotics in healthy patients in order to prevent dental implant failures and complications or which prophylactic regimen should be used. Several of the last published reviews and meta-analyses are chronologically listed below.

The systematic literature review conducted by Ahmad (2012) found no significant difference between the success rate of implants with and without the use of antibiotics. Implants performed with the use of antibiotics had a success rate of 96.5%, while surgeries performed without antibiotics had a slightly lower success rate of 92%. This review concluded that there is no clear evidence pointing to the need for prophylaxis antibiotics in conjunction with dental implant surgery.

The Cochrane systematic review and meta-analysis conducted by Esposito et al. (2013) included 6 RCTs and suggested that short-term antibiotics, e.g., 2 or 3 g of amoxicillin administered 1 h prior to implant placement or 1 g of amoxicillin administered 1 h prior to implant placement and 500 mg four times a day for two days postoperatively, significantly decrease early implant failures in ordinary conditions (RR = 0.33; 95% CI 0.16 to 0.67). The use of antibiotics in this way would prevent one person from experiencing an early implant loss for every 25 people receiving antibiotics. There were no significant differences for any of the other outcomes: infections (RR 0.69; 95% CI 0.36 to 1.35) or adverse events (RR = 1; 95% CI 0.06 to 15.85). However, it remained unclear whether an adjunct use of postoperative antibiotics is beneficial and which antibiotic is the most effective.

The survival systematic review and meta-analysis performed by Ata-Ali et al. (2014) included 4 RCTs, and the results showed that antibiotic treatment significantly reduced the risk of implant failure (OR = 0.331, 95% CI 0.157–0.696) (P = 0.003, QA = 8.49). The NNT to prevent one patient from having an implant failure was 48 (95% CI 31–109). The result of the $X^2$ test applied to the four included RCTs showed antibiotic administration not to be associated with a decrease in the incidence of postoperative infection (OR = 1.091, 95% CI 0.629–1.893), and this result failed to reach significance (P = 0.754, QA = 8.49) (Ata-Ali et al., 2014).

The systematic review and meta-analysis conducted by Chrcanovic et al. (2014) included 6 RCTs rated as low risk of bias assessing the event “implant failure” and 7 RCTs rated as low risk of bias assessing the postoperative infections. The results showed that the difference between the procedures (use versus non-use of antibiotics) significantly reduced (P = 0.003) the implant failure rates in ordinary conditions (RR = 0.37, 95% CI 0.19–0.72). On the other hand, the meta-analysis showed that there were no apparent significant effects of prophylactic antibiotics on the occurrence of post-operative infections in healthy patients receiving implants (RR = 0.72, 95% CI 0.38–1.39; P = 0.66). The overall NNT to prevent one patient from having an implant failure was 50 (95% CI 33–100).

The complex systematic review and meta-analysis carried out by Lund et al. (2015) showed that preoperative antibiotic prophylaxis reduced the risk of implant loss (pooled RR 0.39, 95% CI 0.18–0.84; P = 0.02) (pooled RR 0.02, 95% CI 0.04–0.00; P = 0.02). A risk difference of 2% yielded an NNT of 50 to prevent one patient from experiencing implant loss. They concluded that preoperative antibiotics give a modest reduction of 2% for the risk for implant loss, and the results suggested that there was no benefit of antibiotic prophylaxis in uncomplicated implant surgery in healthy patients, while a beneficial effect in complicated cases could not be excluded.

The systematic review implemented by Surapaneni et al. (2016) concluded that prophylactic antibiotics for each implant surgery are not mandatory but that antibiotics are, however, useful in preventing postoperative infections after implant placement and that antibiotic prophylaxis is required to achieve high long-term survival and success rates of dental implants.

The systematic review reported by Park et al. (2017) concluded that the routine use of systemic antibiotics to accompany dental implant placement in healthy patients is not supported. It also suggested that antibiotic use at the time of surgery does not appear to play a major
role in influencing the early incidence of prosthesis failure, implant failure, adverse events or postoperative complications.

The last published systematic reviews and meta-analyses differ in their results. The variation among their conclusions is related to their inclusion criteria, the RCTs available on that date and the outcome variable analyzed. This systematic review and meta-analysis presented similar results, compared to past meta-analyses, associated with the efficacy of preoperative oral amoxicillin for preventing dental implant failures but not postoperative infections. Nevertheless, the present study is the first publication achieving conclusive results over the inefficacy and ineffectiveness of postoperative regimens using oral amoxicillin.

4.2. Limitations

In spite of the fact that the objective of this systematic review and meta-analysis was to assess the effect of overall antibiotics preventing dental implant failures and post-operative infections, only 1 antibiotic type could be assessed. For this reason, the results can only be applied to the use of amoxicillin.

The effect of perioperative amoxicillin should be considered cautiously, due to the imprecision (wide range in the confidence intervals) of statistical analysis results. Moreover, none of the studies included in this meta-analysis showed, on its own, significant benefits of perioperative amoxicillin in the prevention of dental implant failures and postoperative infections, neither considering implants as the experimental unit in the analysis nor considering patients as the experimental unit.

This meta-analysis presented no statistical or graphical heterogeneity among the included studies. However, there are some differences to be considered in the study design, implant placement procedure (flapless, immediate implants, conventional approach, etc.), implant system, type, brand, diameter, length, healing period (immediate, early or conventional loading) and type of restoration among the included studies.

The main differences in the study design are related to the duration of the follow-up period, the antibiotic dose, the antibiotic regimen, and the 2 studies that included only patients who underwent a single implant placement (Anitua et al., 2009; Tan et al., 2014). These 2 studies also included a lower proportion of smokers than the other studies. No great differences were found in relation to the criteria used in the definition of dental implant failure and postoperative infection cases.

In the US only, 3 million people have dental implants, and that number is increasing by 500,000 a year. Additionally, 10 percent of all US dentists place implants, but this is also increasing and the estimated US and European market for dental implants is expected to reach $4.2 billion by 2022 (Hee-Won et al., 2011).

Establishing a protocol for the prophylaxis of dental implant failures and postoperative infections in ordinary conditions and healthy patients has great clinical and economic importance because of the cost for antibiotic prophylaxis in dental practice and the increasing antibiotic prescription frequency of dental practitioners (Lockhart et al., 2013; Marra et al., 2016).

For these reasons, and due to the development of adverse reactions and bacterial resistance (including at the peri-implant sulcus), the use of antibiotics should be measured carefully (Moslemi et al., 2016; Resnik and Misch, 2008; Surapaneni et al., 2016). The risk–benefit equation associated with the use of prophylactic antibiotics should be seriously considered, as the use of preoperative amoxicillin may prevent a moderate percentage of implant failures (approximately 1.30%, data yielded from the NNT).

5. Conclusion

A single preoperative dose of 1 g, 2 g, or 3 g of oral amoxicillin may be efficacious and effective at preventing dental implant failures, while postoperative oral amoxicillin (exclusively postoperative and adjunct with preoperative oral amoxicillin) might not be beneficial in the prophylaxis of dental implant failures in conjunction with dental implant surgery among healthy patients and in ordinary conditions.

However, there is not enough evidence to support the use of perioperative amoxicillin orally in order to prevent the development of postoperative infections.

New clinical trials comparing the efficacy of different antibiotic types, preoperative dosages and regimens are needed to improve clinical application guidelines in preventing dental implant failures and postoperative infections.

Acknowledgements and conflict of interest statement

The authors have nothing to disclose. The authors thank the University of the Basque Country (UPV/EHU) Library Service. The authors would also like to thank Paolo G. Arundo, Alfonso Caiazzo, Wah Ching Tan and Rory Nolan for the extra information given on their articles.

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