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ANTIBIOTIC PROPHYLAXIS IN DENTAL IMPLANT SURGERY: A SYSTEMATIC REVIEW

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Abstract: Introduction: Oral implants rehabilitation has increased in the recent years. In order to reduce failures, some studies have been published pointing the risk factors and using antibiotic prophylaxis as an alternative to prevent infections in patients submitted to implant surgery, despite the fact it is still controvertial in the literature. **Objective:** Answer the following question: "Does antibiotic prophylaxis reduce the rates of postoperative infection or implant loss?" **Methodology:** Only randomized controlled clinical trials which analyzed implant loss or postoperative infection in patients undergoing surgery for single or multiple implants, without graft association, were selected. **Results:** Four randomized controlled trials were included. A total of 827 patients and 1.320 implants were used. The studies had different surgical approaches. Two of them showed multiple implant surgeries and the other two showed single implants. The first parameter assessed was the presence of postoperative complications, which were different between groups. Pain was the parameter present in all of them; The second parameter was implant stability which was evaluated by the studies around the 4th month after surgery, using mobility as the main criteria of implant loss, although other criteria have been used in association. All studies evaluated the administration of amoxicillin 1h prior to the surgery and a placebo group. The most used protocol was 2 g of amoxicillin (3 studies); only one study used 3g of amoxicillin. This review was submitted to a meta-analysis of three parameters: implant survivor after a minimum period of 2 months, rate of postoperative infection per patient and rate of postoperative infection per implant. The results showed that there were no statistically significant differences between the groups. **Conclusion:** There is still no consistent evidence that antibiotic prophylaxis plays a beneficial role in preventing postoperative infections.

Keywords: Dental implantation. Antibiotic prophylaxis.

INTRODUCTION

The study and use of oral implantes has brought, throughout its 60 years of development, clinical evidence of efficacy and predictability[1]. For these reasons, oral rehabilitation with this therapeutic modality has increased significantly[2]. However, failures related to bacterial contamination of the implants after their installation have been observed[3].

In order to assess implant failure rates, as well as infection rates, studies have been published the causes and risk factors that can contribute to this failure. In this context, the infection seems to represent a relevant cause of loss[4].

Antibiotic prophylaxis appears to be an alternative that can contribute to increasing the success rate in the treatments with osseointegrated implants. This pharmacological approach is already used to prevent infections in immunocompromised patients[5] or in patients at risk for bacterial endocarditis[6]. However several studies have evaluated their use and their real importance has not been yet established in this context[7, 8,9].

The present study aims to carry out a systematic review of the literature, in order to compile the most recent data published on antibiotic prophylaxis in oral implant surgeries, providing information on its effectiveness and the most indicated protocols in the literature.

MATERIALS AND METHODS

This review was registered on the PROSPERO platform under number CRD42020198655. To carry out this work, PRISMA guidelines were followed for

systematic reviews (Figure 1). The PICO strategy was also used. The Population was reffered to the clinically healthy patients and the Intervention was the antibiotic prophylaxis (via oral or intravenous) prior to the implant surgery. There is a Control group which received placebo and the Outcome was reffered to the postoperative infection event or failure of the implant.

An electronic search was performed in the PubMed and MEDLINE databases for articles published between the years 2009 and 2019. Only controlled randomized controlled trials that evaluated the rate of postoperative infection and / or the rate of survival / failure of single and multiple implants, immediate or not, performed in clinically healthy patients (ASA I or II classification) were included, as well as studies that used, in addition to antibiotic prophylaxis, antibiotic therapy. The following keywords used were: dental implant; antibiotic prophylaxis; using the Boolean operator "AND".

Case reports, case series, literature reviews, pilot studies, non-randomized clinical trials, uncontrolled clinical trials, laboratory studies, studies that did not inform the surgical approach and studies that did not standardize the use of antibiotics were excluded (used several regimens), as well as studies that did not exclude patients with comorbidities, smokers or uncontrolled periodontal disease. Duplicate studies between the bases were also excluded.

For this review, the meta-analysis was performed using the parameter implant survival rate after the osseointegration period (average of 3 months in the studies), postoperative infection rate per patient and postoperative infection rate per implant. Each study determined specific parameters for implant survival. The Mantel-Haenszel method was used to calculate the weighted summary of the Relative Risk (RR) in the fixed and random effects model and, after the heterogeneity test, the calculation of the Relative Risk summary was made in the random effects model.

RESULTS

Four hundred and four articles were found in the initial search and after exclusion, according to the criteria, 400 were excluded. Thus, four manuscripts were included in this review, totaling 827 patients and 1.320 implants. All studies were categorized as randomized controlled clinical trials, involving patients undergoing implant surgery. Two described in details the protocols and the results evaluated (Anitua et al., 2009[7]; Tan et al., 2014[11]), and the other two do not adequately described the evaluated parameters (Esposito et al., 2010a[8]; Nolan et al., 2014[9]). The analysis of the risk of bias is described in figure 2.

The most used dosage regimen was 2g of amoxicillin 1h before surgery. One study involved only single implants with no association with graft (Tan et al., 2014[11]), another involved single implants, but with graft association in one of the cases in each group (Anitua et al., 2009[7]), and two manuscripts involved surgeries of different types such as single and multiple implants, without graft association. (Esposito et al. 2010a[8]; Nolan et al. 2014[9]).

The Mantel-Haenszel method was used to calculate the weighted summary of the Relative Risk (RR) in the fixed effects model. However, as the tests did not demonstrate sufficient homogeneity (0.0341), the heterogeneity statistic was incorporated to calculate the summary of the Relative Risk in the random effects model. The statistical meta-analysis demonstrated that there were no statistical differences for the question of interest, that is, antibiotic prophylaxis did not have a statistically significant protective effect (Relative Risk: 1,010) on implant survival

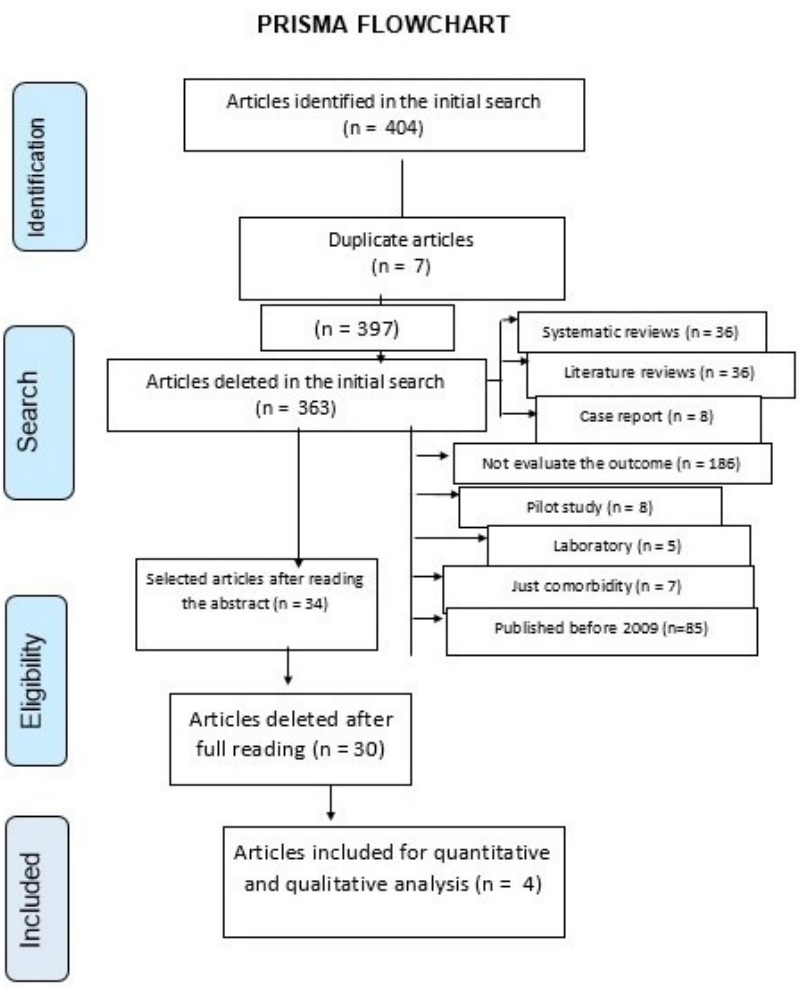


Figure 1 – PRISMA flowchart

	Anitua et al. 2009	Esposito et al. 2010a	Nolan et al. 2014	Tan et al. 2014
Randomized	1	1	1	1
Has randomization been described and is it adequate?	1	1	1	1
Double blind	1	1	1	1
Has blinding been described and is it adequate?	1	1	1	1
Describes losses	1	1	1	0
Did it standardize the surgical size?	1	0	0	1
Define the evaluation criteria well?	0	1	1	0
Score total	6	6	6	5

Figure 2 – Analysis of the risk of bias – Adapted from Jadad et al. 1996

after the minimum period of osseointegration (3 months) (Graphic 1).

The results of the individual studies included in the meta-analysis are listed: event occurrence, total by groups and the relative risk with a 95% Confidence Interval. (Table 1).

Regarding the infection rates, the meta-analysis also revealed the absence of statistical differences between the groups when compiling the data (Relative Risk: 0.827) (Graphic 2).

The results of the individual studies included in the meta-analysis are listed: occurrence of the postoperative infection event per implant, total by groups and the relative risk with confidence interval (Table 2).

The third meta-analysis was performed listing the occurrence of postoperative infection per implants. One of the studies (Nolan et al., 2014[9]) did not show this data, therefore, it was excluded from this meta-analysis. With the inclusion of 3 studies, there were no statistically significant differences when the data were compilled (Relative Risk: 0.863).

The results of the individual studies included in the meta-analysis are listed: occurrence of the event post-operative infection per implant, total by groups and the relative risk with a 95% Confidence Interval.

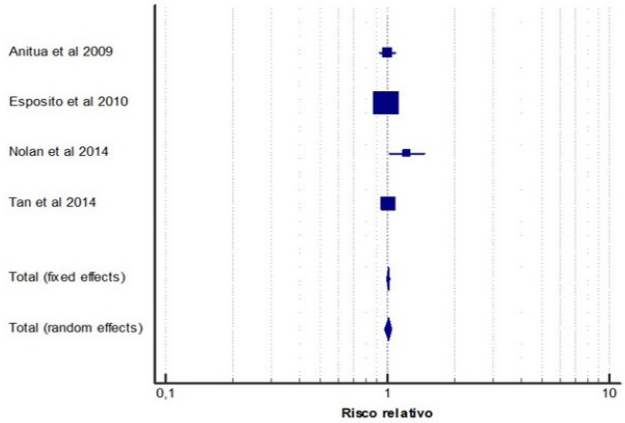
DISCUSSION

Antibiotic prophylaxis is a widely recognized alternative in the literature for preventing infections in clinically compromised patients or for those at risk of developing bacterial endocarditis.[5,12] Regarding surgical treatment with oral implants, this is still not well established.[13]

Some systematic reviews have been published on the topic[8, 13-17] and what is known so far is the statistics are favorable ($p < 0.05$) to the usage of the 2g regimen of amoxicillin for the survival of the implants in a follow-up, on average, of 3 months. However, most of these reviews are limited to assessing implant failure in general, and not just related to infection, as Asenjo-Lobos et al.[13] (2015), which, when relating implant failures due to infection, found no statistically significant association ($p = 0.249$).

In this systematic review, it was not possible to identify implant failures in isolation, which means, associated exclusively with the infection. The calculation was made based on the results of the studies with regard to the survival of the implants, according to the criteria mentioned above, in the methodology section. Inevitably, this is a limitation of this study, which was due to the lack of this data - the association of implant loss exclusively due to infection - in all included studies. It is known that implant failure is a multifactorial experience and is not always associated with infection[7].

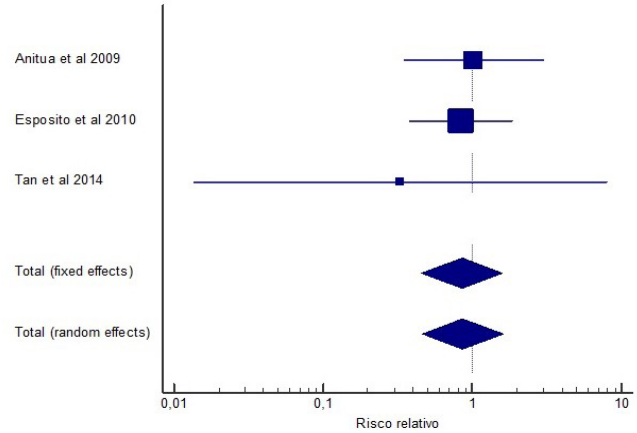
Randomized clinical studies differ in their methodology, which limits the interpretation of their results by systematic reviews. The study published in 2009 by Anitua et al.[7], for example, which was a clinical trial (double-blind, randomized, controlled and multicentric) involving 105 patients who needed single implants placement with or without a graft. The association with biomaterial in implant surgeries modifies the surgical approach and alters the tissue inflammatory response, requiring an adequate response from the body for the graft osseointegration process. Lindeboom et al.[18] (2003) performed an RCT (Randomized Clinical Trial) comparing the use of antibiotics in patients undergoing a membrane-covered bone graft in implant surgery. The results showed that there was a significant increase in the risk of infection for patients who were treated without the administration of antibiotics ($p < 0.05$). Thus, the use of a graft can be a confounding factor



Graphic 1 – Meta-analysis of implants survival after minimum 2 months of osseointegration for included articles

Study	Intervention	Control	Relative Risk	95% CI	z	P
Anitua et al 2009	50/52	51/53	0,999	0,926 to 1,078		
Esposito et al 2010a	482/489	479/483	0,994	0,981 to 1,007		
Nolan et al 2014	54/54	23/28	1,223	1,024 to 1,461		
Tan et al 2014	81/81	79/80	1,013	0,978 to 1,048		
Total (fixed effects)	667/676	632/644	1,008	0,992 to 1,023	0,957	0,339
Total (random effects)	667/676	632/644	**1,010**	0,972 to 1,050	0,510	**0,610**

Table 1 – Results of meta-analysis by studies and by fixed and random models for implant survival after minimum of 2 months



Graphic 2 – Meta-analysis of post-operative infection rates by implant for included articles

Study	Intervention	Controls	Relative risk	95% CI	z	P
Anitua et al 2009	6/52	6/53	1,019	0,351 to 2,957		
Esposito et al 2010	11/489	13/483	0,836	0,378 to 1,847		
Tan et al 2014	0/81	1/80	0,329	0,0136 to 7,965		
Total (fixed effects)	17/622	20/616	**0,852**	0,458 to 1,584	-0,507	0,612
Total (random effects)	17/622	20/616	**0,863**	0,463 to 1,611	-0,462	0,644

Table 2 – Results of meta-analysis by studies and by fixed and random models for the occurrence of post-operative infection by implant

in the analysis of the results, although Anitua et al.[7] (2009), despite the fact that did not exclude patients who underwent bone graft, included only 1 patient who underwent graft in both groups (placebo and antibiotic).

In the study of Anitua et al.[7] (2009), patients were followed up on the 3rd day, 10th day, 1 month and 3 months after surgery. The results showed that there was no statistically significant difference between the two groups for the parameter postoperative infection ($p = 0.960$), characteristics of the oral microbiota ($p = 0.362$) and implant loss (2 implants lost in the Test Group and 2 lost implants in the Control Group). According to the authors, 6 cases of postoperative infection were reported in the Test Group, with one case associated to bone graft. These data were repeated in the Control Group, with 6 cases of infection, with also one case associated to bone graft. However, the authors concluded that antibiotic prophylaxis can be supressed in surgeries for single implant placement, with and without a graft.

The lack of standardization of studies remains the main cause of the lack of consensus on the use of antibiotics in implant surgery. For this reason, systematic reviews are not able to cover many studies, involving about 4 or 6 studies. (Esposito et al.[8] 2010a, Esposito et al.[15] 2013, Ata Ali et al.[16] 2014). The dosage regimen is variable in the literature, although the most used for antibiotic prophylaxis in implant surgery is similar to the AHA (American Heart Association), 2g of amoxicillin; however, there are studies using other types of drugs, and in several other concentrations. (Chracnovic et al.[17] 2014; Asenjo-Lobos et al.[13] 2015).

In this sense, the use of indiscriminate prescription of antibiotics can favor bacterial resistance and increase the adverse events that may occur with its administration. In this regard, Deeb[19] et al. (2015) conducted a survey evaluating antibiotic prescription practices by oral and maxillofacial surgeons at the American College of Oral and Maxillofacial Surgery. The survey results showed that about half (51.6%) of surgeons prescribed antibiotics preoperatively and more than half (71.4%) prescribe antibiotics postoperatively. Regarding the regimen, these were the most variables. According to the authors, the most common regimen is 2 g of amoxicillin 1 hour before the procedure and 500 mg 3 times daily in the postoperative period.

In addition to the dose, the class of antibiotics also varies between clinical trials. Although most studies have administered amoxicillin, some have not specified the antibiotics used[3,20], which makes it difficult to compare, since each class of antibiotic has its own spectrum of action and particular pharmacological profile, which can influence the analysis of results. Therefore, this review disagrees with other systematic reviews published on the topic, which included studies with a high risk of bias or studies that did not define properly the surgical approach (Esposito et al.[21] 2010b; Ata-Ali et al.[16] 2014), while it included only one study which presented a medium risk of bias.

According to Figueiredo et al.[4] (2015), in their retrospective cohort study, patients who develop infection after implant surgery were 80 times prone to present implant loss. Therefore, there is a concern to avoid infection in a treatment that involves many expectations by the patient and often an important financial cost. Regarding failures in treatment with implants, Asenjo-lobos et al.[13] (2015) stated that the implant loss is due to a complex and multifactorial process. And, the lack of standardization in surgical approach can be one of the causes of conflicting results in the studies.[13,17]

The study by Esposito et al.[8] (2010a) demonstrated, after comparing implant loss

rates between immediate implants and healed sites, that immediate implants represented a higher failure rate compared to the two stages implant placement, 9% versus 2% of failure, respectively. In addition, the study by Camps-Font et al.[22] 2018, associated the loss of implants with a longer duration of surgery. Procedures involving bone grafting also require more surgical time and the risk of infection is greater. Peterson[12] in 1990 recommended the use of antibiotic prophylaxis, specially in situations which there is systemic compromise of the patient and in surgeries with prolonged duration, which means after 3 or more hours of surgery.

In this systematic review, the parameters of implant loss and postoperative infection were evaluated. The definition criteria for the infection parameter that have been evaluated in the literature are varied. According to the studies, postoperative infection is commonly associated with suppuration and pain[7-9,11], although some studies also include dehiscence of suture (Esposito et al.[8] 2010a; Nolan et al.[9] 2014), edema (Nolan et al.[9] 2014) and bleeding (Tan et al.[11] 2014). For the parameter failure / loss of implant, there is a much greater variation for the evaluation of implant stability, although the loss of the implant was considered basically by removal of the device by mobility, in most studies. The average assessment time in the studies was 3 months after surgery, a slightly shorter period than that initially recommended for osseointegration.[1] Only one study (Tan et al.[11] 2014) evaluated patients in a shorter period, 1, 2, 4 and 8 weeks after surgery, which allowed an early assessment of the signs of infection, and probably more associated with the immediate effects of the antibiotic, given its half-life and bioavailability.[23]

Regarding the discussion between choosing to administer antibiotics only preoperatively as opposed to pre and post administration, the systematic review by Sharaf et al.[14] (2011) found similar results among antibiotic prophylaxis when compared to administration for longer. According to these authors, there is evidence available to suggest that a single preoperative dose can reduce early implant failure, but there is no additional benefit in using postoperative antibiotics with regard to the implant survival rate.

Similarly, Arduino et al.[24] in 2015 published a clinical trial that compared two groups: group 1 that received only antibiotic prophylaxis with 2g of oral amoxicillin 1 hour before the procedure and no antibiotics in the post, and group 2 that also received prophylatic antibiotic, but also used antibiotic therapy, with 1 g of amoxicillin twice a day for 2 days. No statistically significant differences were found between the groups although adverse events were reported only in group 2. According to the authors, prophylaxis is more recommended than antibiotic therapy. This study corroborates the latest findings in the literature.

Thus, in order to prevent a bacterial resistance, assuming the time in which microorganisms are exposed to antibiotics is shorter in prophylaxis than in therapy, which means, it is restricted to the drug's half-life as opposed to exposure in the institution of a therapy of 7 to 10 days, [23] it may be preferable to choose the preoperative administration, avoiding overtreatment and unnecessary financial costs to the patient.

Due to the limitations and lack of proper evidence, good clinical sense points towards the antibiotic prophylaxis restricted to surgeries that involve greater complexity, such as multiple implant placements, grafts association and maxillary sinus lifting.[12] According to this review, the studies showed that the most consistent protocol is 2 g amoxicillin preoperatively.

CONCLUSION

There is still no consistent evidence that antibiotic prophylaxis plays any beneficial role in preventing postoperative infections.

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