J Stomatol Oral Maxillofac Surg 123 (2022) 74–80

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Review

Preventive antibiotic therapy in bone augmentation procedures in oral implantology: A systematic review

Angel-Orión Salgado-Peralvo [a,b,c,*], María-Victoria Mateos-Moreno [d], 'Eugenio Velasco-Ortega [e,f], Juan-Francisco Peña-Cardelles [g], Naresh Kewalramani [h]

[a] Master in Implant Dentistry, University of Seville, Seville, Spain
[b] Master's Degree in Family and Community Dentistry, University of Seville, Seville, Spain
[c] Collaborating Professor of the Master's Degree in Family and Community Dentistry, University of Seville, Seville, Spain
[d] Department of Clinical Dental Specialties, Faculty of Dentistry, Complutense University of Madrid, Madrid, Spain
[e] Professor of Comprehensive Dentistry for Adults and Gerodontology, University of Seville, Seville, Spain
[f] Director of the Master in Implant Dentistry, University of Seville, Seville, Spain
[g] Postgraduate Program in Oral Surgery and Implantology. Rey Juan Carlos University, Madrid, Spain
[h] Postgraduate Program in Oral Surgery, Periodontology and Implantology, Rey Juan Carlos University, Madrid, Spain

ARTICLE INFO

Article history:
Received 7 December 2020
Accepted 11 January 2021
Available online 22 January 2021

Keywords:
Antibiotic prophylaxis
Antibiotics
Guided bone regeneration
Bone augmentation

ABSTRACT

Introduction: Since the beginning of Oral Implantology, preventive antibiotic therapy has been routinely prescribed. However, at present, due to the growing appearance of antimicrobial resistance, its use has been questioned, generating a great debate and an emerging controversy. The present systematic review aims to analyze the scientific literature to determine whether the preventive prescription of antibiotics in augmentation procedures with the insertion of implants in one or two phases decreases the incidence of postoperative infections and/or the survival rate of the implants.
Material and methods: The MEDLINE database was searched (via PubMed) with the following keywords: (bone grafting OR alveolar ridge augmentation OR bone graft augmentation OR guided bone regeneration OR bone block) AND (dental implants OR dental implant OR oral implantology) AND (antibiotic prophylaxis OR antibiotics). The criteria used were those described by the PRISMA® Statement. The search was limited to randomised clinical trials, systematic reviews and meta-analyses published in the last 15 years (2005–2020).
Results: After reading the titles and abstracts of the resulting articles, only one systematic review meeting the described criteria and 4 randomised clinical trials were included.
Conclusions: Prescription of 2 or 3 g of amoxicillin one hour before surgery is recommended to reduce the early failure rate of one-stage implants and to decrease the bacterial load of grafted bone particles in bone augmentation procedures with one or two-stage implants.

1. Introduction

Preventive antibiotic therapy in Oral Implantology or, commonly referred to as "antibiotic prophylaxis", was originally born through its implementation in the first implant therapy protocol described by Branemark et al. [1] These authors routinely prescribed phenoxymethylpenicillin one hour before surgery and for 10 days after to improve the early survival of dental implants. This trend was established due to the presence of more than 300 bacterial species at the oral level in addition to other non-cultivable microorganisms discovered by molecular biological techniques [2] that may contribute to the occurrence of postoperative infections. These practices have now been challenged and oral surgeons are faced with the dilemma of whether or not to prescribe antibiotics preventively in bone augmentation and implant insertion procedures, a controversial issue. The prescription has been accepted to avoid systemic bacteremias [3] but also to reach an adequate antibiotic concentration in the blood to prevent bacterial contamination during the surgical act of the implants or grafted material [4], even though in Oral Implantology

* Corresponding author at: Calle San Salvador 5, bajo (Robles Dental), Vigo, 36204, Pontevedra, Spain.
E-mail addresses: orionsalgado@hotmail.com (A.-O. Salgado-Peralvo), mateosmoreno80@hotmail.com (M.-V. Mateos-Moreno), evelasco@us.es (E. Velasco-Ortega), juanfranciscopenacardelles@gmail.com (J.-F. Peña-Cardelles), k93.naresh@gmail.com (N. Kewalramani).

https://doi.org/10.1016/j.jormas.2021.01.011
2468-7855/

surgical procedures are relatively uncontaminated as they require the elevation of a flap to access the underlying bone in most cases [5]. The *American College of Surgeon*'s [6] (*Committee on Control of Surgical Infections*) developed a classification of surgical wounds and the risk of infection. In this classification, bone and implant procedures would fall into class 2 ("clean-contaminated wound"), which show associated infection rates of 10–15%.

Despite this, the systematic prescription of preventive antibiotics in healthy patients does not have a justified risk-benefit ratio [7–9]. The main reason is the increasing development of bacterial resistance worldwide to virtually all known families of antibiotics, resulting in a growing number of infections that are becoming more difficult to treat due to the loss of efficacy of these drugs [10]. The World Health Organization's (WHO) Global Surveillance System for Antimicrobial Resistance (GLASS) revealed that 500,000 people in 22 countries are suspected of having antibiotic resistance to *Salmonella* spp, *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus* and *Streptococcus pneumonia* [11]. Their consumption also increases the likelihood of idiosyncratic and dose-dependent adverse reactions that can be life-threatening [12].

The objective of this article is to carry out a systematic review of the literature to determine the need for preventive antibiotic therapy in bone augmentation procedures, with or without the simultaneous insertion of dental implants, to reduce the incidence of postoperative infections and, in the favourable case, to determine the most recommendable type and pattern of antibiotics.

2. Material and methods

2.1. Search strategy

An electronic search of the MEDLINE database (via PubMed) was performed using the following MeSH terms (*Medical Subjects Headings*): (bone grafting OR alveolar ridge augmentation OR alveolar bone graft augmentation OR guided bone regeneration OR bone block) AND (dental implants OR dental implant OR oral implantology OR dental implantology) AND (antibiotic prophylaxis OR antibiotics).

The criteria used were those described in the PRISMA® Statement (*Preferred Reporting Items for Systematic Reviews and Meta-analysis*). The primary objective was to answer the following question "PICO" (P = patient/problem/population; I = intervention; C = comparison; O = outcome) (Table 1):

In healthy patients who are going to undergo bone augmentation procedures, with or without the simultaneous insertion of dental implants, does the prescription of preventive antibiotics reduce infectious postoperative complications as opposed to not prescribing them?

Table 1
Components of the PICO question.

P *(participants/population)*	Healthy patients who have undergone bone augmentation surgery with or without the simultaneous insertion of dental implants
I *(intervention/exposure)*	Preventive antibiotic therapy on the day of surgery and/or extended postoperatively
C *(comparison/control)*	Not prescribing antibiotics Prescribing a placebo Other antibiotics or antibiotic regimes Same antibiotic with different dosage/duration
O *(outcome)*	Infection Increased bone gain Rates of implants inserted in one phase

The secondary objective was to determine the type of preventive antibiotic, dose and posology recommended in these cases according to the available scientific evidence. Before starting, inclusion and exclusion criteria were defined for the resulting articles:

2.2. Exclusion criteria

(a) Experimental laboratory studies; (b) animal studies; (c) studies whose main topic was not the prescription of preventive antibiotics in bone augmentation procedures; (d) duplicate articles; (e) books or chapters of books; (f) letters to the Editor; and (g) comments.

2.3. Inclusion criteria

(a) studies conducted in humans; (b) articles published in English or Spanish; (c) meta-analyses; and (d) systematic reviews. Due to the limited results obtained in a first search, (e) randomised clinical trials (RCTs) were incorporated.

At the same time, a Google Scholar search was conducted for articles that met the criteria described above. The bibliographic references of the selected articles were analysed for publications that did not appear in the initial search and might be of interest.

The search was temporarily restricted to the last 15 years (2005–2020), and the search was updated on 07/07/2020.

2.4. Risk of bias

The risk of bias of the included studies was independently assessed by two authors (AOSP, MVMM). In both data extraction and risk of bias assessment, disagreements between the two were resolved through the intervention of a third author (EVO).

3. Results

Systematic reviews and/or meta-analyses were included in the initial search, however, given the small number of articles resulting in MEDLINE (via PubMed) (n = 6), of which only one article met the described criteria, it was decided to include RCTs in the search, resulting in 14 articles. Two independent reviewers read the titles and abstracts, excluding 10 for not meeting the criteria described. After reading the full text of the remaining 4 articles, two related to preventive antibiotic therapy in bone augmentation procedures were included (one systematic review [13] and one RCT [14]). As an complementary measure, after reviewing the references of these articles and after an ancillary search in Google Scholar, 3 RCTs were included [4,15,16] (Fig. 1 and Table 2).

The only systematic review found was the one published by Klinge et al. [13] (2020) whose purpose was to assess whether preventive antibiotic therapy reduces the risk of postoperative infections in one or two-stage bone augmentation and implant insertion procedures. These authors concluded that, due to the small number of included studies, it was not possible to conclude as to the need to prescribe these drugs beyond the day of surgery or whether a single dose is equally effective. This is because the two RCTs with low risk of bias on which it is based, both by Lindeboom et al. (2005 [15], 2006 [16]), studied the effect of a single preoperative antibiotic dose in both the test and control groups. Specifically, the former group [15] studied the treatment with 600 mg of clindamycin one hour before the intervention in both groups and, in the test group, also, 300 mg every 6 h, one-day postoperatively versus placebo, in bone regeneration procedures with blocks covered with collagen membranes. The results showed non-significant postoperative infection rates in the recipient bed,

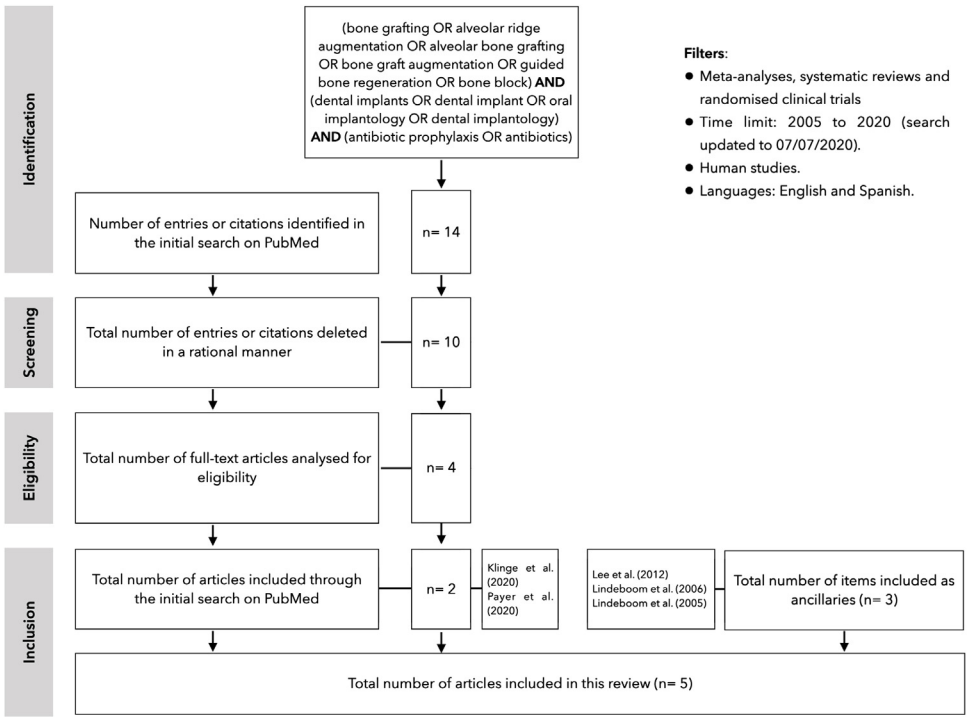

Fig. 1. PRISMA® flow diagram of the search processes and results.

Table 2
Randomised clinical trials (RCTs) that studied antibiotic prophylaxis in GBR procedures simultaneous or not to the insertion of implants (GBR, guided bone regeneration; g., grams; mg., milligrams; h., hour; SDD., statistically significant differences; Post-op., postoperative; Pre-op., preoperative; VAS., visual analogue scale; N., sample size; ATB., antibiotic).

Author(s)/year	Bone augmentation procedure	Sample size/ intervention		Conclusions
		TEST group	CONTROL group	
Payer et al. [14] (2020)	GBR and simultaneous insertion of implants, with submerged or transmucosal healing	N=117 2 g of amoxicillin, 1 h before the operation, followed by 500 mg every 8 h during the 3 days after the operation.	N = 119 Placebo with the same posology	(1) No SDD in terms of pain, swelling, bruising and bleeding during days 1–7 and 14, measured with VAS. (2) No SDD for pain, swelling, peri-implant stability, purulent drainage and opening of stitches. (3) Higher rate of implant success in the control group (99.2%) than in the test (97.4%), without SDD.
Lee et al. [4] (2012)	GBR with or without simultaneous insertion of implants.	N=11 2 g of 1 st generation cephalosporin, followed by 1 g, 3 times/day, 3 days	N=12 2 g of 1 st generation cephalosporin, followed by a placebo with the same dosage as the test group	No SDD in the incidence of post-op infections. These results should be interpreted with caution given the small sample size.
Lindeboom et al. [16] (2006)	Mandibular ascending ramus bone block graft without the simultaneous insertion of implants	N=75 2 g fenetylline 1 h pre-op	N=75 600 mg clindamycin 1 h pre-op	The rate of post-op infections after a single pre-op dose of ATB is low (despite not having achieved SDD and not comparing both groups against placebo or without the administration of antibiotics). The post-op prescription (24 h) did not show SDD against the control group.
Lindeboom et al. [15] (2005)	Ascending ramus or mandibular symphysis bone block graft without simultaneous insertion of implants	N = 62 600 mg clindamycin 1 h pre-op, followed by clindamycin 300 mg/ 6 h/ 1-day post-op	N = 62 600 mg clindamycin 1 h pre-op, followed by 300 mg/ 6 h/ 1-day post-op placebo.	Prescription of a single dose pre-op of clindamycin is effective in preventing post-op infections (despite not having acquired SDD and not having compared both groups against placebo or without administration of antibiotics). The post-op prescription (24 h) did not show SDD versus control.

both in the control (3.2%) and test groups (4.8%), and in the donor area (6.4% and 3.2%, respectively). All the infections appeared after two weeks and in 100% of the cases. As a consequence of these complications, the grafted material was lost. The average time of the surgeries was 67.2 min. (±8.7) in the control group and 65.0 min. (±7.60) in the test. The longer the surgical time, the higher the associated risk. These authors concluded that a single preoperative dose of clindamycin is effective in preventing postoperative infections in augmentation procedures. The second RCT [16] analysed the occurrence of post-surgical infections in the donor and recipient

area of collagen membrane-covered bone block grafts after the administration of a single preoperative dose of 2 g fenethylline or 600 mg clindamycin. These authors estimated the presence of postoperative infections in the recipient bed at 5.3% in the fenethylline group and 2.7% in the clindamycin group, with no significant differences. In all cases of infection, the grafted material was lost. The infection rate in the donor area was 4% in both groups. Most infections appeared after 2–3 weeks. In some cases, the surgical wound opened at 7–8 weeks without clinical signs of infection, causing partial resorption of the graft around the fixation screws of the bone blocks. These authors concluded that a single antibiotic dose is effective in preventing postoperative infections in augmentation procedures.

Lee et al. (2012) [4] conducted a study similar to Lindeboom et al. [15] (2005) in which they studied which dosage generated less postoperative infections in patients undergoing guided bone regeneration (GBR) with simultaneous or no implant insertion. To this end, they administered 2 g of a first-generation cephalosporin to all patients and, post-surgery, in the test group they prescribed 1 g of the same antibiotic, three times a day, three days versus placebo. The results showed a lack of statistical significance in terms of the presence of post-surgical infections in both groups despite being 8% in the control group as only one patient experienced such a complication (the sample size was very small, with 23 participants in total). There were also no differences in pain, inflammation, blood tests (number of white cells, neutrophils, lymphocytes and monocytes), erythrocyte sedimentation rate and C-reactive protein value.

A recent study by the Antibiotic Study Group of the International Team for Implantology (ITI) led by Payer et al. (2020) [14] studied how the administration of 2 g of amoxicillin one hour before surgery, followed by 500 mg of amoxicillin, every 8 h, during the 3 days following surgery and compared to a placebo, affects the occurrence of post-surgical complications and the patient's perception of morbidity secondary to GBR with simultaneous insertion of implants. Both groups received paracetamol every 8 h during the two postoperative days. These authors suggested that systemic antibiotics do not provide any improvement in the patient's subjective perception of postoperative discomfort after these procedures. This was concluded through the Visual Analogical Scale (VAS), which assesses pain, inflammation, the presence of haematomas and bleeding during the period examined (days 1–7 and at 14 days post-surgery). This group of investigation also studied the appearance of complications evaluated by an examiner (objective), such as pain, swelling, implant stability, purulent drainage and closure of the flap at weeks 1, 2, 4 and 12. More specifically, there were no significant differences in the parameters measured by VAS when evaluated at days 4 and 14, but differences were depending on the centre in the first 3 days. Neither did they find significant differences in terms of post-surgical complications in both groups. Despite this, the suppuration in the control group was higher. In the test group, three implants were lost, while in the control group only one, i.e. survival rates were 97.4% versus 99.2% respectively (no significant differences between both groups). They only used an implant system with different lengths (8−12 mm) and diameters (3.30, 4.10 and 4.80 mm). The grafting material was the same in all centres. From an objective point of view, there were no significant differences between the two groups in terms of the parameters studied, but from a clinical point of view, when evaluating the "suppuration" factor, it was higher in the control group, which could influence the prescription of systemic antibiotics in these cases. These authors suggest that there is no evidence to recommend routine antibiotic prescribing for these types of interventions.

4. Discussion

Sometimes, when the amount of residual bone is insufficient, it is necessary to perform bone augmentation procedures before or simultaneous to the insertion of the implants. The appearance of infections in the grafted areas, associated or not with the exposure of the barrier membranes, can negatively affect the vascularization of the graft, jeopardizing the success of regeneration [13]. For this reason, antibiotic prophylaxis is standardized in these cases even though, as has been demonstrated, there is not enough scientific evidence of sufficient depth to support it.

Of the 4 RCTs [4,14–16] included in this review, three of them [4,15,16] prescribed both test and control groups a preoperative dose of antibiotic, without comparing the administration of these drugs with placebo or non-prescription of antibiotics, so the conclusions drawn by these studies should be interpreted with caution. The reason is that they refer to a previous study by Lindeboom et al. (2003) [17] in which they concluded that the prescription of antibiotics in bone augmentation procedures with autologous bone blocks was necessary as the infection rate in the control group (placebo) compared to the test group (which was prescribed 2 g fenethylline) was 40%.

It is worth mentioning that they only included 10 patients in each group, which is an excessively small sample, which was defended by the authors as the high infection rate of the control group did not justify continuing with the study. However, these authors used the "*t*" for Student in the statistical analysis of their primary comparison when, due to the small sample size and the fact that there were no patients in one of the fields of the 2×2 table, Fisher's exact test would have been the appropriate choice. In applying such a test, the data would produce a p-value of 0.09, therefore not significant [18].

The diagnostic criteria for infection in the different studies were the presence of pain, inflammation [14], purulent drainage through the incision line [14–16] or serosanguinous drainage and a positive surgical bed culture for a known pathogen [15,16], spontaneous opening of the stitches [14–16] or deliberate opening by the surgeon if the patient had a fever, pain or localised tenderness and a positive wound culture [15,16] and/or loss of implant stability [14].

The results of the RCTs determined that infection of the grafted material leads to its total loss [15,16] or partial loss (in the case that there is an opening of the mucosa of the surgical area at 7–8 weeks post-surgery without clinical signs of infection) [16] and, it is suggested that, in the case of simultaneous insertion of the implants, it could be a risk factor for the failure of osseointegration because it could cause an increase of the local inflammatory response [19,20]. When early exposure of the barrier membrane occurs, differences in bone healing are significant compared to cases where no exposure occurs [21]. One of the possible etiological agents could be the high bacterial load present at the salivary level reaching values of 109 CFU/mL [20,22–24]. Nowzari and Slots [21] found that the prescription of amoxicillin combined with clavulanic acid (500/ 125 mg) one hour before surgery followed by 500 mg/ 12 h/ 8 days and chlorhexidine rinses at 0.12%, twice a day did not prevent bacterial contamination of the exposed membranes. The reason could be that amoxicillin presents an elimination half-life of 1–1.50 h [25], being effective in reducing the oral flora until 12 h after administration [26]. Azithromycin, on the other hand, presents a greater bioavailability, which makes it interesting as a preventive antibiotic as it is found in concentrations of 224 and 203 mg/l in crevicular and peri-implant fluid respectively, 13 days after surgery after a single preoperative administration of 500 mg. It also has important effects on inflammation and early healing by decreasing levels of granulocyte

colony-stimulating factor (G-CSF), interleukins 6 and 8, macrophage inflammatory protein 1ß (MIP-1ß) and interferon-induced 10 kDa protein, reducing mobilisation of granulocyte precursors and recruitment of immune and inflammatory cells during the healing phase [27]. Furthermore, the scientific literature is unbiased in determining that systemic antibiotics administered to healthy patients do not reduce the risk of infection in implant insertion without anatomical conditions [28,29].

The risk of exposure of the membranes is higher in patients with severe periodontal pockets compared to edentulous or periodontally healthy patients, so it is especially important to remember that all patients who are going to undergo surgical procedures must be controlled at a periodontal level first. For this reason, antibiotic prophylaxis has been suggested through associations commonly used in the treatment of periodontitis. In this regard, a group of experts established a series of recommendations for GBR procedures at a symposium held in Bologna (Italy) in 2016, suggesting the association of amoxicillin with clavulanic acid (2 g/ 125 mg) and metronidazole 500 mg one hour preoperatively, followed by amoxicillin with clavulanic acid (1 g +62.50 mg)/ 8 h/ 7 days and metronidazole 250 mg/ 8 h/ 4 days postoperatively [30]. Despite this, as has been seen, there is no scientific support for this beyond the opinion of this panel of experts.

At present, the use of autologous bone grafts is still the gold standard due to their osteogenic properties, which is why different publications have analysed bacterial counts when extracting this type of graft with various devices. The methods that produce significantly less bacterial contamination are trephine [24], chisels and gouge [23], compared to the bone collector and bone scraper [24]. In the case of combining the bone collectors with another aspirator that collects saliva, bacterial counts decrease by 58 per cent [22]. Various mechanisms for decontamination of bone particles have also been studied. Many of them have shown great effectiveness, although with a negative effect on the preservation of cell vitality. 10% povidone-iodine reduces CFU levels to 79% with an average cell survival per gram of 9.60–105, thus maintaining a viable cell population. To do this, the collected bone is immersed in this compound by mechanically shaking it for 15 s in 5 consecutive washes, waiting 15 min at the end of these washings for the bone to dry out completely. Before implantation, it must be washed in sterile saline. Another method to reduce contamination of the surgical area is the administration of antisialogogues (such as atropine sulphate [31]) to reduce salivary flow and thus offer less possibility for bacteria to colonise bone particles [20], as well as the prescription of chlorhexidine digluconate. This antiseptic has demonstrated its effectiveness in reducing the bacterial load on grafted bone particles by a factor of three (from 3.43-10^5 CFU to 0.72-10^5 CFU) [31] to 10 (from 1.50-10^9 CFU to 1.50-10^8 CFU) [32]. There is no doubt that it is useful, however, it generates some controversy when taking into account the possible effect to the detriment of the osteogenic potential of the collected bone. In this sense, some studies have determined that chlorhexidine is cytotoxic to alveolar bone cells [33] by inhibiting cell growth and proliferation, osteoblastic cell lines and collagen synthesis in a dose-dependent manner. Specifically, 0.005% chlorhexidine constitutes 50% of its inhibitory concentration [34].

Maureci et al. [26] evaluated the effect of the administration of 1 g/62.50 mg amoxicillin/clavulanic acid orally one hour before the intervention, compared to not prescribing antibiotics on bacterial contamination of bone grafts. In both groups, no implants failed or experienced infectious complications during the healing period. Mean values of trypticase soy agar (non-selective solid culture medium useful to isolate facultative and strict microorganisms from samples with mixed flora) were 1.71 (0.78–1.91) in the test group and 2.12 (1.15–3.42) in the control group (p = 0.018), while those of salivary agar mitis were 1.03 (0.60–1.78) and 1.62 (0.82–3.03), respectively (p = 0.201). Isolated samples in both patient groups were also not significant (p = 0.898). These authors suggest that antibiotic prophylaxis reduces bacterial contamination of bone particles collected in these cases.

Topical antibiotic treatment of bone particles is an interesting option as it not only reduces their bacterial load but also provides an antibacterial effect on the surgical site. [35] Petri and Wilson [36] investigated the effect of using a demineralized bone allograft combined in equal parts with a purified powdered gel to which they added 1 mg of cephalothin and 1 mg of tobramycin in the lower chordal filling compared to irrigation with sterile saline in a split-mouth study. These authors found post-surgical infection rates of 0 and 16% respectively, which may be explained by the release of antibiotics during the first 6−8 hours postoperatively, at which time a stable blood clot is formed in which the antimicrobial gel would favour a pathogen-free environment. The concentration of locally released surgical-bed antibiotics is higher than those administered systemically, and significantly reduces the adhesion and penetration of *S. mutans* and *A. actinomycetemcomitans*, bacteria associated with early biofilm formation in barrier membranes [37]. Despite this, further studies are needed on the dose of the drug that can be tolerated at the bone level without influencing the osteogenic process [38].

Another mechanism that can be useful alone or in combination with the preventive measures described is the use of antibacterial barrier membranes incorporating minocycline, [39] tetracyclines [40,41], metronidazole [42] or metal ions (silicon, titanium or silver) [43–46] that modify tissue response and the propensity of bacteria to adhere to and colonise the membranes used in regeneration [39]. Moreover, they can offer additional benefits such as a delay in collagen degradation which helps prolong cell exclusion and repopulation by progenitor cells. Tetracyclines are the most widely used agents because of their broad spectrum of action, efficacy and safety. In addition to their antibacterial activity, tetracyclines have anti-inflammatory effects that promote wound healing, reduce bone resorption by inhibiting osteoclast differentiation and promote bone apoptosis. They also inhibit matrix metalloproteinases (such as collagenases), which play an important role in connective tissue and collagen barrier membrane damage [47]. Besides, in vivo studies, have shown an increase in bone regeneration when using tetracycline-containing membranes, specifically doxycycline, by reducing bacterial overgrowth in contaminated rat tibia defects compared to untreated collagen membranes [41]. Research concerning the study of antibiotic-modified and enriched membranes is showing promising results, especially in extensive bone defects or clinical situations with an increased risk of infectious complications. However, they are in an experimental phase and RCTs are needed to confirm these results in humans [48].

Most of the RCTs included [4,15,16], with the above-mentioned biases, determine that one dose of antibiotic is sufficient to prevent postoperative infections after regeneration with intraoral block bone grafts and that postoperative doses are not justified in these cases. The remaining RCT of adequate methodological design determined that antibiotic prophylaxis was not necessary for the insertion of implants with simultaneous GBR [14]. The study of antibiotic prophylaxis in healthy patients without anatomical conditions is widely studied. In this sense, since in clinical practice a large number of implants require associated GBR in many cases not planned preoperatively, it would be prudent to prescribe, until further studies are performed, the dose recommended by a recent network meta-analysis [28] of 2 or 3 g of amoxicillin one hour before the intervention to prevent early implant failure. In the case of two-stage implant insertion, it could be interesting to adopt the same strategy to reduce bacterial contamination of the grafted

bone particles by decreasing the salivary bacterial load. Other methods designed for this purpose are preoperative chlorhexidine digluconate rinses, administration of antisialogogues, treatment of the grafted bone particles with topical antibiotics or the use of antibacterial membranes.

Future lines of research should aim at performing RCTs comparing infection rates, the level of bone formation achieved after regeneration and, in the case of inserting the implants simultaneously with bone augmentation procedures, their survival rates in patients prescribed preventive antibiotics versus placebo and versus non-prescription of antibiotics in the most aseptic conditions. It is also interesting to know the effects of using topical antibiotics mixed with graft biomaterials and/or antibacterial barrier membranes compared to not using them or not prescribing preventive oral antibiotics.

5. Conclusions

In general, there is a lack of studies on the effect of antibiotic prophylaxis on the prevention of postoperative infections after bone augmentation with or without the simultaneous insertion of dental implants. Given this situation, the authors recommend administering a single dose of 2 or 3 g of amoxicillin one hour preoperatively to reduce the failure rate of implants inserted in one phase, as well as to reduce the degree of bacterial contamination of the grafted bone particles both in these cases and in two phases implants since, in the case of postoperative exposure of the membranes, the prescription of antibiotics does not prevent bacterial contamination of the exposed membranes. The prescription of antibiotics in these cases is done to decrease the bacterial load in a perioperative manner and to reduce the contamination of the surgical bed during the regenerative procedure and the immediate postoperative period.

Conflict of interest

The authors declare the absence of any conflict of interest.

Source of funding

The present investigation has not received any funding.

References

[1] Adell R, Lekholm U, Rockler B, Branemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. Int J Oral Surg 1981;10:387–416.
[2] Smith AJ, Jackson MS, Bagg J. The ecology of Staphylococcus species in the oral cavity. J Med Microbiol 2001;50:940–6.
[3] Canadian Dental Association. CDA position on the prevention of infective endocarditis; 2014.
[4] Lee JW, Lee JY, Kim SM, Kim MJ, Lee JH. Prophylactic antibiotics in intra-oral bone grafting procedures: a prospective, randomized, double-blind clinical trial. J Korean Assoc Oral Maxillofac Surg 2012;38:90–5.
[5] Etcheson AW, Miley DD, Gillespie MJ. Osseous coagulum collected in bone traps: potential for bacterial contamination and methods for decontamination. J Oral Implantol 2007;33:109–15.
[6] Woods RK, Dellinger EP. Current guidelines for antibiotic prophylaxis of surgical wounds. Am Fam Phys J 1998;57:2731–40.
[7] Ahmad N, Saad N. Effects of antibiotics on dental implants: a review. J Clin Med Res 2012;4:1–6.
[8] Chrcanovic BR, Albrektsson T, Wennerberg A. Prophylactic antibiotic regimen and dental implant failure: a meta-analysis. J Oral Rehabil 2014;41:941–56.
[9] Lund B, Hultin M, Tranaeus S, Naimi-Akbar A, Klinge B. Complex systematic review - Perioperative antibiotics in conjunction with dental implant placement. Clin Oral Implants Res 2015;26:1–14.
[10] Organización Mundial de la Salud. Resistencia a los antibióticos; 2017.
[11] World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016–2017. World Health Organization; 2017.
[12] Esposito M, Worthington HV, Loli V, Coulthard P, Grusovin MG. Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. Cochrane Database Syst Rev 2010CD004152.
[13] Klinge A, Khalil D, Klinge B, Lund B, Naimi-Akbar A, Tranaeus S, et al. Prophylactic antibiotics for staged bone augmentation in implant dentistry. Acta Odontol Scand 2020;78:64–73.
[14] Payer M, Tan WC, Han J, Ivanovski S, Mattheos N, Pjetursson BE, et al. The effect of systemic antibiotics on clinical and patient-reported outcome measures of oral implant therapy with simultaneous guided bone regeneration. Clin Oral Implants Res 2020.
[15] Lindeboom JAH, Tuk JGC, Kroon FHM, van den Akker HP. A randomized prospective controlled trial of antibiotic prophylaxis in intraoral bone grafting procedures: single-dose clindamycin versus 24-hour clindamycin prophylaxis. Mund Kiefer Gesichtschir 2005;9:384–8.
[16] Lindeboom JA, Frenken JW, Tuk JG, Kroon FH. A randomized prospective controlled trial of antibiotic prophylaxis in intraoral bone-grafting procedures: preoperative single-dose penicillin versus preoperative single-dose clindamycin. Int J Oral Maxillofac Surg 2006;35:433–6.
[17] Lindeboom JAH, van den Akker HP. A prospective placebo-controlled double-blind trial of antibiotic prophylaxis in intraoral bone grafting procedures: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96:669–72.
[18] Brennan MT, Sasser HC, Fox PC, Lockhart PB. Statistical analysis used in «A prospective placebo-controlled double-blind trial of antibiotic prophylaxis in intraoral bone grafting procedures: a pliot study». Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:664. author reply 664–665.
[19] Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II). Etiopathogenesis. Eur J Oral Sci 1998;106:721–64.
[20] Tezulas E, Dilek OC. Decontamination of autogenous bone grafts collected from dental implant sites via osteotomy: a review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:679–84.
[21] Nowzari H, Slots J. Microbiologic and clinical study of polytetrafluoroethylene membranes for guided bone regeneration around implants. Int J Oral Maxillofac Implants 1995;10:67–73.
[22] Young MP, Carter DH, Worthington H, Korachi M, Drucker DB. Microbial analysis of bone collected during implant surgery: a clinical and laboratory study. Clin Oral Implants Res 2001;12:95–103.
[23] Hashemi HM, Beshkar M. Bacterial contamination of autogenous bone collected by rongeur compared with that collected by bone filter during implant surgery. Br J Oral Maxillofac Surg 2011;49:474–7.
[24] Takamoto M, Takechi M, Ohta K, Ninomiya Y, Ono S, Shigeishi H, et al. Risk of bacterial contamination of bone harvesting devices used for autogenous bone graft in implant surgery. Head Face Med 2013;9:3.
[25] Kaur SP, Rao R, Nanda S. Amoxicillin: a broad spectrum antibiotic. Int J Pharm Pharm Sci 2011;3:30–7.
[26] Maureci R, Campisi G, Matranga D, Maureci N, Pizzo G, Melilli D. The role of antibiotic prophylaxis in reducing bacterial contamination of autologous bone graft collected from implant site. Biomed Res Int 2017;2017. 6 pages.
[27] Escalante MG, Eubank TD, Leblebicioglu B, Walters JD. Comparison of azithromycin and amoxicillin before dental implant placement: an exploratory study of bioavailability and resolution of postoperative inflammation. J Periodontol 2015;86:1190–200.
[28] Romandini M, De Tullio I, Congedi F, Kalemaj Z, D'Ambrosio M, Lafori A, et al. Antibiotic prophylaxis at dental implant placement: which is the best protocol? A systematic review and network meta-analysis. J Clin Periodontol 2019;46:382–95.
[29] Salgado-Peralvo AO, Sanz-Esporrín J, Mateos-Moreno MV, Haidar-Wehbe A, Blanco-Carrión A, Velasco-Ortega E. Profilaxis antibiótica en implantología oral: revisión crítica de la literatura. Rev Esp Cir Oral y Maxilofac 2019;41:80–90.
[30] Cucchi A, Chierico A, Fontana F, Mazzocco F, Cinquegrana C, Belleggia F, et al. Statements and recommendations for guided bone regeneration: consensus report of the guided bone regeneration symposium held in Bologna, October 15 to 16, 2016. Implant Dent 2019;28:388–99.
[31] Young MPJ, Korachi M, Carter DH, Worthington HV, McCord JF, Drucker DB. The effects of an immediately pre-surgical chlorhexidine oral rinse on the bacterial contaminants of bone debris collected during dental implant surgery. Clin Oral Implants Res 2002;13:20–9.
[32] Kürkçü M, Oz IA, Köksal F, Benlidayi ME, Güneşli A. Microbial analysis of the autogenous bone collected by bone filter during oral surgery: a clinical study. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2005;63:1593–8.
[33] Bauer J, Liu RW, Kean TJ, Dennis JE, Petersilge W, Gilmore A. A comparison of five treatment protocols for contaminated bone grafts in reference to sterility and cell viability. J Bone Joint Surg Am 2011;93:439–44.
[34] Lee T-H, Hu C-C, Lee S-S, Chou M-Y, Chang Y-C. Cytotoxicity of chlorhexidine on human osteoblastic cells is related to intracellular glutathione levels. Int Endod J 2010;43:430–5.
[35] Witsø E, Persen L, Løseth K, Benum P, Bergh K. Cancellous bone as an antibiotic carrier. Acta Orthop Scand 2000;71:80–4.
[36] Petri 3rd WH, Wilson TM. Clinical evaluation of antibiotic-supplemented bone allograft. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 1993;51:982–5. discussion 986.
[37] Chen C-F, Wu K-M, Chen Y-T, Hung S-L. Bacterial adhesion to antibiotic-loaded guided tissue regeneration membranes — a scanning electron microscopy study. J Formos Med Assoc 2015;114:35–45.
[38] Sivolella S, Berengo M, Scarin M, Mella F, Martinelli F. Autogenous particulate bone collected with a piezo-electric surgical device and bone trap: a microbiological and histomorphometric study. Arch Oral Biol 2006;51:883–91.

[39] Ma S, Adayi A, Liu Z, Li M, Wu M, Xiao L, et al. Asymmetric Collagen/chitosan membrane containing minocycline- loaded chitosan nanoparticles for guided bone regeneration. Sci Rep 2016;6:31822.
[40] Park YJ, Lee YM, Park SN, Lee JY, Ku Y, Chung CP, et al. Enhanced guided bone regeneration by controlled tetracycline release from poly(L-lactide) barrier membranes. J Biomed Mater Res 2000;51:391–7.
[41] Kütan E, Duygu-Çapar G, Özçakir-Tomruk C, Dilek OC, Özen F, Erdoğan Ö, et al. Efficacy of doxycycline release collagen membrane on surgically created and contaminated defects in rat tibiae: a histopathological and microbiological study. Arch Oral Biol 2016;63:15–21.
[42] Xue J, He M, Niu Y, Liu H, Crawford A, Coates P, et al. Preparation and in vivo efficient anti-infection property of GTR/GBR implant made by metronidazole loaded electrospun polycaprolactone nanofiber membrane. Int J Pharm 2014;475:566–77.
[43] Tokuda S, Obata A, Kasuga T. Preparation of poly(lactic acid)/siloxane/calcium carbonate composite membranes with antibacterial activity. Acta Biomater 2009;5:1163–8.
[44] Ye J, Yao Q, Mo A, Nie J, Liu W, Ye C, et al. Effects of an antibacterial membrane on osteoblast-like cells in vitro. Int J Nanomed 2011;6:1853–61.
[45] Zhang J, Xu Q, Huang C, Mo A, Li J, Zuo Y. Biological properties of an antibacterial membrane for guided bone regeneration: an experimental study in rats. Clin Oral Implants Res 2010;21:321–7.
[46] Li J, Zuo Y, Man Y, Mo A, Huang C, Liu M, et al. Fabrication and biocompatibility of an antimicrobial composite membrane with an asymmetric porous structure. J Biomater Sci Polym Ed 2012;23:81–96.
[47] Florjanski W, Orzeszek S, Olchowy A, Grychowska N, Wieckiewicz W, Malysa A, et al. Modifications of polymeric membranes used in guided tissue and bone regeneration. Polym 2019;11:782.
[48] Lekovic V, Kenney EB, Weinlaender M, Han T, Klokkevold P, Nedic M, et al. A bone regenerative approach to alveolar ridge maintenance following tooth extraction. Report of 10 cases. J Periodontol 1997;68:563–70.