Penicillin Allergy Influence for Early Dental Implant Failure

Subjects: Allergy

Contributor: Angel-Orion Salgado-Peralvo

The prescription of preventive antibiotics (PA) in dental implant treatments reduces the incidence of early failures. The PA used in these patients was clindamycin, showing a significantly high associated risk of implant failure.

Keywords: antibiotic prophylaxis ; preventive antibiotics ; clindamycin ; penicillin allergy ; dental implants ; dental implant failure

1. Introduction

Dental implants are currently the most predictable therapeutic option for total or partial replacement of missing teeth, with high survival rates of around 95% according to different studies, both in pristine bone and in regenerated bone [1]. Despite this, some implant failures occur [2]. Chrcanovic et al. [3] defined implant failure as those signs and symptoms that lead to the explantation of the implant, whereby "failure" is equivalent to implant loss. The failure rate has been estimated to be around 0.7–3.8%. These failures are classified as "early" or "late" depending on whether they take place before or after, respectively, the functional loading of the implants with a prosthetic restoration [4]. This differentiation is important because different etiological factors are associated depending on the time of their occurrence. In this regard, early failures are caused by a failure of osseointegration due to local and/or systemic factors and account for approximately 5% of all failures, affecting more women and younger patients [5][2]. In contrast, late failures are usually due to bacterial infections, parafunctional habits or mechanical factors related to the implant-supported prostheses and affect the 95% of implants that reach osseointegration [5].

To avoid early failures, Branemark et al. [6] originally suggested that protocols for implant placement should include the administration of phenoxymethylpenicillin 1 hour before surgery and for 10 days postoperatively. This approach was introduced due to the presence of more than 500–700 bacterial species in the oral cavity, in addition to other non-culturable microorganisms discovered by molecular biological techniques [7][8] that may contribute to the development of postoperative infections. Therefore, antibiotic therapy in oral implantology can be classified as either prophylactic/preventive (to prevent infections) or therapeutic (as a treatment for infections already established) [9]. Dentists are often faced with the dilemma of whether or not to prescribe antibiotics preventively in dental implant treatments, and this is currently a controversial issue. The prescription has been accepted not only to avoid systemic bacteremia [10] but also to achieve an adequate antibiotic concentration in the blood in order to prevent bacterial contamination during the surgical placement of implants or grafted material [11]. Amoxicillin is the most studied antibiotic for this purpose; however, antibiotics other than beta-lactams in penicillin-allergic patients are not sufficiently studied.

The most common adverse drug reactions associated (≥ 1% of patients) with penicillin use are diarrhea, nausea, rash, neurotoxicity, urticaria and/or superinfection (including candidiasis). Infrequent adverse effects (0.1 to 1% of patients) are fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics) and/or pseudomembranous colitis. Despite this, only 0.01% of patients treated with penicillin have their lives compromised by experiencing true anaphylaxis, i.e., hypersensitivity with hypotension, angioedema, bronchospasm and urticaria [12]. Currently, some organizations such as the American Heart Association [13] (AHA) have stopped recommending clindamycin as an alternative antibiotic for antibiotic prophylaxis against infective endocarditis.

3. Studies regarding PA in penicillin-allergic patients in oral implanvology procedures

3.1. Dental implant placement

Salomó-Coll et al. [14] (2018) described failure rates in patients non-allergic to penicillin of 8.03%, while in the group of patients with SRPA the failure rates were 24.68%, i.e., one in four implants failed (p = 0.032), with a relative risk (RR) of 3.84. Clindamycin was prescribed in 100% of these patients. In patients with SRPA, 21.05% of implants failed late, while 78.95% failed early. The reason for early failure was either a failure of the osseointegration process (80%) or uncontrolled infection (20%). At an individual patient level, failure rates were 5.17% in non-allergic patients and 18.86% in patients with SRPA (p = 0.046) (RR = 3.64).

French et al. [15] (2015) found twice the risk of implant failure in confirmed penicillin-allergic patients who were prescribed clindamycin versus those who were prescribed

French et al. [16] (2016) conducted a similar study in which they described failure rates of implants placed in non-allergic patients of 0.80% (of these, 53.80% were early failures) versus 2.10% in patients with SRPA (80% failed early), these differences being significant (p = 0.002), with an odds ratio (OR) of 3.10. Differences in survival rates measured at 1, 5 and 10 years were also significant (p < 0.002), being 99.50%, 98.90% and 98.40% in non-allergic patients and 98.10%, 97.30% and 97.30% in patients with SRPA, respectively. These authors also studied the occurrence of postoperative infections, which was 0.60% in non-allergic patients and 3.40% in patients with SRPA, i.e., the risk in allergic patients who were prescribed clindamycin was six times higher (p < 0.05). In this study, 12.30% of implants were immediate implants (n = 687), of which 91.7% (n = 630) were placed in non-allergic patients with a failure rate of 1%, while 8.30% were placed in patients with SRPA with a failure rate of 10.50%, which is 10 times higher (p < 0.001). These authors relate these differences between the two groups to a higher infection rate in patients with SRPA.

Wagenberg and Froum **[17]** (2006) carried out an investigation similar to the two studies mentioned above in which they described a 5.70 times higher risk of immediate implant failure secondary to infection in patients with SRPA who were prescribed clindamycin (8.52%) compared to non-allergic patients who were administered amoxicillin (2.95%); these differences were significant (p < 0.001) (RR = 3.34).

Block et al. [18] (2021) conducted a retrospective case-control study on 224 patients who experienced one or more implant failures. The logistic regression model found a significant association between implant failures one year after placement in patients with SRPA (OR = 2.98), but not between the first and fourth year, nor after 4 years. These authors did not specify whether preventive antibiotics were administered and, if so, which ones.

3.2. Other procedures

Khoury et al. [19] (2018) prescribed clindamycin 600 mg 1 h preoperatively followed by 300 mg/8 h/7 days postoperatively in patients with SRPA, while in the non-allergic group they prescribed amoxicillin 2 g preoperatively for antibiotic prophylaxis followed by 10 days of antibiotics postoperatively in sinus lifts with a lateral window approach and a one- or two-stage implant placement. Subantral graft infection occurred in 0.48% of all patients, all of whom were patients with SRPA, which accounted for 6% of all these patients. The infection occurred in the subantral graft and the symptomatology started at 4–8 weeks. None of the patients had a history of sinusitis and there were no surgical complications such as sinus membrane perforation, mucosal dehiscence, graft exposure and/or tissue necrosis.

Basma et al. [20] (2021) studied the incidence of infectious complications on 2,530 socket grafting (SG) and 341 ridge augmentation (RA) procedures performed on 1,814 patients who were prescribed amoxicillin 2 g 1 h before surgery followed by a dose of 500 mg/8 h 7 days postoperatively and, in patients with SRPA, clindamycin 600 mg 1 h before followed by 300 mg/12 h 7 days postoperatively. The results showed postoperative infection rates after SG of 10.7% in the clindamycin group vs. 2.7% in the amoxicillin group (OR = 4.5; p < 0.02) and in RA of 22.5% vs. 4.2%, respectively (OR = 6.9; p < 0.01). Therefore, the described risk of infection in these regenerative procedures after clindamycin administration is 5.5 times higher compared to amoxicillin (p < 0.01).

Two studies evaluated the crestal bone changes after immediate implant placement. Wagenberg et al. [21] (2013) observed that, among patients who were administered penicillin, crestal bone loss was lower (0.52 ± 0.82 mm) compared to the prescription of other antibiotics (0.61 ± 0.86 mm) in patients with SRPA. Although, these differences were not significant. No reference was made to the type of antibiotic prescribed in these patients. The second study conducted by Wagenberg and Froum [22] (2020) had the same objective; however, they compared the administration of amoxicillin 500

mg/6 h one day preoperatively followed by its prescription for 10 days postoperatively, versus azithromycin 250 mg 2 days preoperatively, followed by 6 days postoperatively, with no significant differences at maxillary (p = 0.53) or mandibular level (p = 0.80). These authors also failed to perform specific tests to confirm an allergy.

Finally, Froum et al. [23] (2018) analyzed the results of peri-implantitis treatment in these patients. They were the only authors to observe an improvement in the parameters studied in patients with SRPA. There were a reduction in probing depth, with values of 5.95 ± 1.72 mm in patients with SRPA vs. 5.52 ± 2 mm in non-allergic patients; radiographic bone gain of 2.30 ± 2.13 mm vs. 1.94 ± 1.76 mm; and soft tissue gain/loss of 0.76 ± 1.46 mm vs. 0.56 ± 1.45 mm, respectively, with these differences not being significant. An important bias of this study is that no reference was made to the type of antibiotic prescribed.

4. Possible etiological factors

There are several possible explanations for the presence of an increased risk of implant failure and/or infection in patients who were not prescribed penicillin.

4.1. Suboptimal Efficacy of Alternative Antibiotics, Such as Clindamycin

This drug may favor an increase in the proportions of resistant *Prevotella* species in saliva [24] and some, such as *P. intermedia* and *P. aeruginosa*, are often found in implants with peri-implantitis [25]. In this context, an in vitro study found that one or more pathogenic species found in implants with peri-implantitis, especially *P. intermedia*, *Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*, are resistant at therapeutic concentrations in 46.70% of cases to clindamycin [26]. In addition, several studies have linked the prescription of antibiotics other than beta-lactams to an increase in MRSA [27]. In this regard, *S. aureus* has been found at high concentrations in implants with peri-implantitis, as have other clindamycin-resistant bacteria mentioned above (*A. actinomycetemcomitans*, *P. intermedia* and *T. forsythia*) (p < 0.001) [28]. In addition, if *S. aureus* is part of the early colonizing bacteria of implants, this bacterium will be present one year later [29], thus increasing the risk of future peri-implantitis [29][30][31].

On the other hand, preoperative clindamycin treatment and its continuation for 10 days postoperatively may contribute to sinus colonization with clindamycin-resistant organisms [19]. Zirk et al. [32] studied the type of antibiotic appropriate for the treatment of odontogenic maxillary sinusitis, concluding that clindamycin is the antimicrobial with the most unfavorable results, with 50% of tested pathogens resistant [33]. Pigrau et al. [34] (2009) studied the effect of various antibiotics in the treatment of osteomyelitis in a sample in which 92.48% of patients had previously been exposed to clindamycin for various reasons, including 15.22% for prophylaxis before implant placement. These authors observed that *Streptococci viridans* was susceptible in 81% to penicillin and 96% to fluoroquinolones but only 11.5% to clindamycin. At least one clindamycin-resistant species was present in 92.10% of the samples, indicating the rapid emergence of resistance in patients previously exposed to clindamycin.

4.2. Penicillin Allergy as a Genetic Factor Predisposing to an Increased Risk of Implant Failure

Genetic analysis of more than one million people, more than 100,000 of whom had an adverse response to penicillin, identified a genetic variant in the human leukocyte antigen (HLA) genes associated with penicillin allergy. By comparing the frequencies of thousands of polymorphisms between those showing an adverse response to penicillin and those showing a normal response, two regions of the genome related to the former were detected: one located in the HLA-B major histocompatibility complex gene and the other in the PTPN22 gene. The results of the analysis showed that carriers of the HLA-B*55:01 allele have a 33% higher relative risk of penicillin allergy than the rest of the population, which could point to a lymphocyte-mediated predisposition leading to a delayed penicillin reaction [35]. Recent research suggests a link between polymorphisms in these genes and rheumatoid arthritis [36][37], a systemic autoimmune chronic inflammatory disease that has been identified as a risk factor for dental implant failure [38]. Nevertheless, studies are needed to confirm the hypothesis of a possible link between genetic alterations and increased susceptibility to implant failure.

4.3. Negative Influence of Clindamycin on Osseointegration

In vitro studies have shown that, at high concentrations, clindamycin reduces the activity of alkaline phosphatase (a marker of osteoblastic metabolism and, therefore, of osteogenic differentiation) and the calcification of the extracellular matrix in a dose-dependent manner, while at low concentrations it increases the metabolism of osteoblasts. It is important to note that the concentrations studied (100–500 µg/ml) are not reached after systemic application but are reached after local administration [39]. Other authors have shown that clindamycin produces cytotoxic and cytostatic effects on primary human osteoblasts due to an impairment of mitochondrial energy [40].

Until more studies are conducted, it is recommended that diagnostic tests are performed to confirm SRPA, and, in positive cases, it seems prudent to avoid the use of clindamycin in favor of other drugs. At present, the evidence suggests that prescribing 2–3 g amoxicillin 1 h before implant surgery in healthy patients in ordinary situations, i.e., without the need for associated regenerative surgery [41], or in bone augmentation procedures, with or without the simultaneous insertion of dental implants [42], is the protocol that has been clinically proven to prevent the most implant failures. For many years, clindamycin was the preventive and therapeutic antibiotic of choice in penicillin-allergic patients, which may have resulted in other types of antibiotics not being extensively studied in our field. For this reason, it is not possible to establish solid evidence-based recommendations in penicillin-allergic patients. Nevertheless, from this systematic review, the authors recommend the use of azithromycin 500 mg 1 h before surgery as an alternative until further studies are conducted. In this sense, compared to the preoperative prescription of 2 g amoxicillin 1 h before surgery, it has shown significant effects on inflammation and early healing, with concentrations of 3.4 (0.7) and 2.8 g/mL (0.9) in gingival and peri-implant crevicular fluid on postoperative day 6, respectively, while amoxicillin concentrations were below detectable limits. Likewise, gingival crevicular fluid levels were significantly lower with azithromycin during the initial healing period. These differences are due to decreased levels of granulocyte colony-stimulating factor (G-CSF), interleukins 6 and 8, macrophage inflammatory protein 1 (MIP-1) and interferon (IFN)-gamma-inducible protein 10 kDa (IP-10), reducing the mobilization of granulocyte precursors and the recruitment of immune and inflammatory cells during the healing phase [40].

5. Conclusions

It is not possible to state that penicillin allergy per se constitutes a risk factor for early failure of dental implants because most of the studies included patients with SRPA without specific diagnostic tests. The preventive antibiotic used in these patients was clindamycin, showing a significantly high associated risk of implant failure, mainly related to a failure of osseointegration of the implants as well as an increased risk of infection of up to six times compared to other antibiotics. Immediate implants also have a 5.7- to 10-fold increased risk of failure in these patients. Allergy testing is recommended to confirm the allergy, as well as studies aimed at finding an alternative to penicillin in these patients.

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