EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

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MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

INFLUENCE OF LOCAL AND SYSTEMIC ANTIBIOTICS IN PERI-IMPLANTITIS TREATMENT: A SYSTEMATIC REVIEW

Trabalho submetido por
Catarina Batista Pires da Costa Estácio
para a obtenção do grau de Mestre em Medicina Dentária

Outubro de 2023

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Trabalho orientado por
Prof. Doutor Alexandre Miguel Santos

Mestre Catarina Izidoro

Outubro de 2023

’The more I learn, the more I realize how much I don't know, yet the more I yearn to seek knowledge because in it, I find the beauty of understanding, and in understanding, I find the essence of love’’

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ABSTRACT

Background: This systematic review (SR) aimed to synthesize what is known about local and systemic antibiotics effectiveness in treating peri-implantitis. (Page et al., 2021)

Material and methods: This SR is reported in compliance with the PRISMA statement. The review protocol was registered into the PROSPERO database (CRD4202238040) (Page et al., 2021)

Results: The analysis included ten randomized controlled trials (RCTs) with follow-ups ranging from 3 to 12 months. No implant loss occurred during the study's follow-up periods. Probing pocket depth (PPD) reduction across the studies varied from 0.00 to 3.82 mm, while bleeding on probing (BOP) resolution ranged from 1.02% to 51.0%. Interestingly, certain trends emerged when the effects of local antibiotics were compared to those of systemic antibiotics. Compared to local antibiotics, systemic antibiotics appeared to result in greater reductions in probing pocket depth (PPD) and bleeding on probing (BOP), suggesting that systemic antibiotics may significantly improve peri-implant tissue health and lower inflammation.

Conclusions: Non-surgical antibiotic treatment (both systemic and local) improves peri-implant tissue health, lowering PPD and BOP. Complete pocket resolution, on the other hand, is not guaranteed. While systemic antibiotics are useful, they must be used with caution due to various patient circumstances.

Keywords: Dental implants, peri-implantitis, periodontitis, peri-implantitis therapy and treatment.

RESUMO

Objetivos: Esta revisão sistemática (RS) teve como principal objetivo sintetizar o conhecimento atual sobre a eficácia dos antibióticos locais e sistémicos no tratamento da peri-implantite. (Page et al., 2021)

Material e Métodos: Esta revisão sistemática (RS) foi conduzida de acordo com as diretrizes estabelecidas no PRISMA. O protocolo desta revisão foi previamente registado na base de dados PROSPERO sob o número de registo CRD4202238040.

Resultados: A presente análise abrangeu um conjunto de dez ensaios clínicos randomizados (ECRs), com períodos de acompanhamento variando de 3 a 12 meses. Importa salientar que não foi registada qualquer perda de implantes ao longo dos períodos de acompanhamento destes estudos. Observou-se que a redução da profundidade de sondagem (PPD) apresentou uma variação que se estendeu de 0,00 a 3,82 mm, ao passo que a resolução de sangramento à sondagem (BOP) oscilou entre 1,02% e 51,0%. Um aspeto particularmente intrigante foi a emergência de tendências específicas quando se procedeu à comparação dos efeitos dos antibióticos locais com os antibióticos sistémicos. Nesta comparação, os antibióticos sistémicos pareceram induzir reduções mais substanciais tanto na profundidade de sondagem (PPD) como na resolução do sangramento à sondagem (BOP), sugerindo, assim, que os antibióticos sistémicos podem ter um impacto significativamente benéfico na saúde dos tecidos peri-implantares, promovendo a redução da inflamação.

Conclusões: O tratamento não cirúrgico com antibióticos (seja local ou sistémico) melhora a saúde dos tecidos peri-implantares, reduzindo a PPD e o BOP. No entanto, a resolução completa da bolsa não é garantida. Quanto aos antibióticos sistémicos, embora sejam benéficos, a sua utilização deve ser cuidadosamente ponderada face às diversas circunstâncias dos pacientes.

Palavras-chave: Implantes dentários, peri-implantite, periodontite, terapia e tratamento da peri-implantite.

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LIST OF ABBREVIATIONS

SR = Systematic Review

RCT = Randomized Clinical Trial

PPD = Pocket Probing Depth

BOP = Bleeding On Probing

SOP = Suppuration On Probing

ROB = Risk of Bias

WMD = Weighted Mean Differences

CI = Confidence Intervals

SD = Standard Deviation

OR = Odds Ratios

P = Placebo

CHX = Chlorhexidine

MD = Mechanical Debridement

Atb = Antibiotic

DOX = Doxycycline

MIN = Minocycline

MINm = Minocycline Microspheres

Serrap = Serrapeptidase

MTZ = Metronidazole

AMX = Amoxicillin

NST = Non-Surgical Treatment

I. INTRODUCTION

Dental implants are now an important and well-established therapeutic solution, addressing tooth loss in various clinical settings. Long-term success rates have been found to be an outstanding 82.9%, as indicated by studies with up to 16 years of follow-up (Simonis et al., 2010). Dental implantation is a reasonably secure treatment method due to carefully studied reasons, consideration of anatomical and individual constraints, and precise implant placement (Simonis et al., 2010).

Nevertheless, the scenario is evolving as more evidence points to the advent of peri-implant inflammations, a prevalent issue affecting adjacent soft and hard tissues. The consequences of such inflammations can be severe, potentially leading to the loss of the implant. As a result, the emphasis has switched to ways for preventing and effectively treating peri-implant disorders that are smoothly integrated into modern dental rehabilitation paradigms. (Smeets et al., 2014)

Peri-implant diseases are inflammatory pathological conditions that specifically target peri-implant tissues and are caused mostly by the presence of microbial biofilms in the peri-implant environment. These types of conditions can be divided into two distinct groups: peri-implant mucositis and peri-implantitis (Herrera et al., 2023).

Peri-implant mucositis is an inflammatory lesion that impacts the peri-implant mucosal tissues without causing any immediate marginal bone loss (Heitz-Mayfield & Salvi, 2018). Its clinical manifestation is primarily distinguished by the presence of bleeding on probing. Furthermore, visible clinical signs of inflammation may include erythema, swelling, suppuration, and an increase in probing depth, which is frequently attributed to causes such as edema or a reduction in probing resistance (Berglundh et al., 2018). The primary cause of peri-implant mucositis is a disruption in the balance between the host and microbial communities at the interface of the implant and the mucosal tissues. Importantly, it is a treatable condition, especially when detected indirectly through host biomarkers (Heitz-Mayfield & Salvi, 2018). The accumulation of biofilm, as well as habits like as smoking and exposure to

radiation therapy, are significant contributors to the onset and progression of peri-implant mucositis (Berglundh et al., 2018).

The term "peri-implantitis" (or "Periimplantitis") emerged over two decades ago to describe infectious pathological diseases affecting peri-implant tissues (Levignac 1965; Mombelli et al. 1987). During the First European Workshop on Periodontology in 1993, it was agreed that this word should be used primarily to characterize damaging inflammatory responses around functioning osseointegrated implants.

Peri-implantitis is a pathological condition that is closely connected with peri-implant biofilm formation, mostly affecting the tissues surrounding dental implants. The condition in question is defined by substantial inflammation within the peri-implant mucosa, which leads to the gradual loss of supportive bone structure. Symptoms of peri-implantitis include inflammation, bleeding on probing, and possible suppuration. In addition, greater probing depths and mucosal margin recession, as well as radiographic evidence of bone loss compared to earlier examinations, are characteristic indications of this illness. (Berglundh et al., 2018) The primary etiological component underlying the onset and progression of peri-implantitis is the formation of a biofilm in the surrounding region of the implant. Several substantial risk factors and indicators have been identified, including a documented history of severe periodontitis, inadequate plaque control, and the absence of frequent supportive peri-implant care following implant placement. While there is less conclusive evidence with regards to associations with smoking and diabetes, or local variables such as the presence of submucosal cement post-prosthetic implant restoration, or implant placing that restricts access to oral hygiene and upkeep practices, these factors require further investigation. (Berglundh et al., 2018) Several other potential contributing factors have been proposed, including the absence of peri-implant keratinized mucosa, occlusal overload, the presence of titanium particles within peri-implant tissues, bone compression necrosis, overheating, micromotion, or biocorrosion. Yet greater study is required to get a thorough understanding of their precise involvement in the beginning and progression of peri-implant disorders. (Schwarz et al., 2018)

Based on the evidence shown thus far and the increasing use of dental implants in routine clinical settings, it is fair to expect an increase in the prevalence of peri-implantitis. This increased prevalence emphasizes the importance of developing a dependable and consistent therapy approach. As a result, decisions addressing the management and treatment of peri-implantitis should be reasonable and evidence-based. (Prathapachandran & Suresh, 2012)

The prevalence of peri-implant diseases is still an object of dispute in the field (Tarnow, 2016). Derks and Tomasi (2015) performed a systematic review with a meta-analysis to shed light on this issue. They presented patient-based average prevalence rates and the corresponding ranges for both peri-implant mucositis and peri-implantitis. Peri-implant mucositis was reported to have a prevalence of 43% (with a range of 19% to 65%), whereas peri-implantitis had a prevalence of 22% (with a range of 1% to 47%) (Derks & Tomasi, 2015). Furthermore, recent cross-sectional studies that were not included in the comprehensive review found peri-implantitis prevalence within the ranges described by Derks and Tomasi (2015). The prevalence rates in these studies were 20% (Rokn et al., 2017) , 15.1% (Aguirre-Zorzano et al., 2015), 13.9% (Schwarz et al., 2017) , 26% (Daubert et al., 2015) , 16.4% (Dalago et al., 2017), 12.9% (Konstantinidis et al., 2015) , and 28% (Schuldt Filho et al., 2014).

A majority of documented peri-implantitis therapeutic approaches are periodontitis-based. The mechanism guiding bacterial colonization of dental and implant surfaces is comparable, and it is well-recognized that microbial biofilms play an equal role in developing peri-implant inflammation. Peri-implantitis can be treated with both conservative (non-surgical) and surgical methods (Smeets et al., 2014). Aside from medication and manual treatment (such as using curettes, ultrasonic, and air polishing systems), new therapies, such as laser-supported and photodynamic therapy, have recently been characterized as conservative therapy choices (Smeets et al., 2014).

An extensive variety of treatment techniques, including implant surface scaling with plastic or titanium curettes (Renvert et al. 2009), laser therapy (Schwarz et al. 2005), and low-abrasive powders (Sahm et al. 2011), have been presented. However, the information supplied thus far is insufficient to offer clinical practitioners

unambiguous treatment recommendations regarding which type of peri-implantitis treatment would be the most successful. (Faggion et al., 2014)

As previously stated, numerous non-surgical and surgical procedures are indicated while treating peri-implantitis. However, the treatment should begin with infection control techniques. Decontaminating the implant surface is more difficult and unpredictable than treating normal teeth, the main difficulty is the implant's surface roughness, which promotes bacterial adherence and colonisation (Mellado-Valero et al., 2013) . As a result, the supplementary use of lasers, systemic or local antibiotics, and antimicrobial photodynamic therapy has been proposed and examined in both pre-clinical and clinical investigations to promote implant surface cleaning. (Barbato et al., 2023; Barootchi & Wang, 2021; Heitz-Mayfield et al., 2011; Wong et al., 2017; Schwarz et al., 2006; Romanos & Nentwig, 2008)

Mombelli and Lang pioneered the use of antibiotics as supplemental therapies in the treatment of peri-implantitis in 1992. As a result, various studies have been conducted to evaluate the potential benefits of administering antibiotics via systemic and localized methods in conjunction with other therapeutic options. Nonetheless, there is some debate about the efficacy of combining antibiotics, whether systemically or locally, with traditional peri-implantitis therapy techniques. (Mombelli & Lang, 1992; Jan van Winkelhoff, 2012; D'Ambrosio et al., 2022; Sukumar et al., 2020; Busa et al., 2014)

1.1.Main goal of this review

As a result, within the context of non-surgical treatment, this systematic review (SR) aimed to assess the efficacy of local and systemic antibiotics in the treatment of peri-implantitis. (Page et al., 2021)

II. MATERIALS AND METHODS

The protocol of this review was registered in PROSPERO database (CRD4202238040). The review design adhered to the comprehensive and transparent reporting of research findings guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. (Page et al., 2021)

2.1.Information sources and search strategy

Two reviewers (CE and JB) performed a thorough and comprehensive electronic search technique to discover appropriate studies for inclusion in the review across six well-known online databases: COCHRANE, EMBASE, LILACS, Open Grey, PubMed, and Web of Science.

The search algorithm included precise keywords and search terms relating to the issue of interest: (Additional file 1)

a) (′′peri-implantitis'' [mh] OR ''peri implantitis'' [mh] OR ''periimplantitis [mh])
b) (′′peri-implantitis'' [mh] AND ''antibiotic'' [mh])
c) (′′peri-implantitis'' [mh] AND ''antibiotic'' [mh] OR ''antibiotic agent''[mh])
d) (''peri-implantitis'' [mh] AND ''non-surgical treatment'' [mh])
e) (''peri-implantitis'' [mh] AND ''non-surgical treatment'' [mh] OR ''non-surgical therapy''[mh])

The aim was to collect all randomized controlled trials (RCTs) investigating the clinical outcomes of using local or systemic antibiotics to treat periimplantitis within the context of non-surgical treatment. The primary outcomes of interest, or the principal measurements used to assess the success of the therapies, were reductions in probing pocket depth (PPD) and bleeding on probing (BOP). Pocket probing depth refers to the distance from the gingival margin to the apical portion of the sulcus, indicating the severity of inflammation and probable infection. A decrease in probing pocket depth indicates that the disease has improved. In contrast, bleeding on probing

indicates inflammation and can also reflect the general health of the peri-implant tissue. (Monje et al., 2021)

For the evaluation of pocket probing depth and bleeding on probing, around implants, it is important to gently insert a periodontal probe into the sulcus. To avoid unintentional damage to the soft tissue around the implant, the utmost care is taken. The probe should be inserted parallel to the long axis of the implant being examined. PPD is carefully assessed by referring to the millimeter marks on the probe, with the usual range for a healthy sulcus being between 1 and 4 millimeters. Each tooth is thoroughly examined, and pocket depths are properly noted. Observations are done in parallel to identify the presence of bleeding following probing. These dual examinations, when performed precisely and thoroughly, provide critical insights into the patient's periodontal health. (Gerber et al., 2009)

2.2.Focus question

The research approach used for this study followed the PICO (Patient/Population, Intervention, Comparison, Outcome) framework and the protocols established by the Centre for Evidence-Based Medicine at the University of Oxford in the United Kingdom (Miller & Forest, 2021) to answer a well-defined question: How do local and systemic antibiotics influence the treatment of periimplantitis, within the context of non-surgical treatment?

2.3. Population

Adults with peri-implantitis (a diagnosis of peri-implantitis in accordance with the 2017 classification) (Schwarz et al., 2018) and adults with peri-implantitis who are being treated for their condition.

2.4. Intervention

Implant surface debridement (mechanical debridement) without the need for surgery.

Mechanical debridement is the process of gently removing biofilm, plaque, calculus, and any inflammatory tissue from the implant surface and surrounding peri-implant tissues . This procedure aims to generate a clean and biocompatible implant surface, reduce inflammation, and encourage tissue repair.

2.5. Outcome

The primary outcomes were pocket probing depth (PPD) and bleeding on probing (BOP). Secondary outcomes were the depth of bone lesion (BDL) and treatment success.

The definition of success in peri-implantitis therapy encompass the implant's continued survival, the absence of peri-implant probing depths (PD) greater than or equal to 5 millimetres, the absence of bleeding on probing (BOP) under light pressure, and the absence of suppuration. This success is further emphasized by the prevention of additional bone loss (Heitz-Mayfield & Mombelli, 2014).

2.6. Eligibily criteria

1. Randomized controlled trials (RCTs) or systematic reviews of RCTs;
2. Each patient had at least one dental implant with peri-implantitis, which was treated with non-surgical debridement plus administering local or systemic antibiotics;
3. Diagnoses of peri-implantitis were made in accordance with the 2017 classification (Schwartz et al., 2018). Studies conducted or published before 2017 were included if they utilized the same diagnostic criteria as outlined in the 2017 classification;
4. The minimum period of follow up was 3 months;
5. Only articles written in English were examined.

2.7. Study selection

We conducted a comprehensive search of the following 6 electronic databases: COCHRANE, EMBASE, LILACS, Open Grey, PubMed, and Web of Science.

Two reviewers (CE and JB) independently selected potentially suitable research based on their titles and abstracts. The full articles of the initially chosen studies were read. Additionally, the references of the selected papers, or the RCTs included in relevant systematic reviews related to the topic, were carefully examined to identify any additional pertinent primary studies.
Any discrepancies or differences between the two reviewers were resolved through a meeting and discussion with a third reviewer (PM) to reach a consensus.

2.8. Data collection process and data items

Information such as authors and year of publication, follow up duration, type of antibiotic therapy, treatment harms and success, classification system, number of subjects (and implants), location of the study, and reported clinical measures (BOP, PPD, DBL) were all extracted and recorded in a predetermined data extraction table. (Additional file 2)

2.9. Risk of bias assessment

The risk of bias for the studies included in the analysis was assessed using the Cochrane Collaboration's Tool RoB 2.0 (Sterne et al., 2019)
Five domains were used to appraise potential bias in each study: risk of bias arising from the randomization process**,** risk of bias due to deviations from the intended interventions**,** risk of bias due to missing outcome data, risk of bias in the measurement of the outcome**,** risk of bias in the selection of the reported result.
Each study was rated based on the evaluation in these domains:

a. Low risk of bias: This suggests that plausible bias is unlikely to impact the results significantly, and all applicable criteria were met.

b. Some concerns risk of bias: This indicates that plausible bias exists, casting some doubts about the results, and one or more criteria were partly met.

c. High risk of bias: This indicates that plausible bias is present and severely undermines confidence in the results, with one or more applicable criteria failing to be met.

2.10. Effects measures and synthesis methods

The studies were initially categorized based on their characteristics and the type of antibiotic administered. In cases where the standard deviation (SD) was not provided, it was calculated using a formula that allows the derivation of SD from a given confidence interval. (Kragten et al., 1994) Further, SD from data resulting from arithmetic operations was estimated following error propagation rules formulas.

$$\mathrm{SD} = \frac{\mathrm{LS} - \mathrm{LI}}{2 \times 1{,}96} \times \sqrt{\mathrm{n}}$$

$$SD\bar{x}A \pm SD\ \bar{x}B = \sqrt{(DP\ xA)^2 + (DP\ xB)^2}$$

We conducted a meta-analysis using the metafor R package (Viechtbauer, 2010). Pocket depth recovery data from baseline to follow-up for each antibiotic were pooled in a random-effects multivariate model adjusted for the initial pocket depth (PDi), the follow-up period and the mode of antibiotic administration (local or systemic). The covariance shared by different antibiotic data from within the same studies was handled by adding a random term (treatment | study) to the model. The final adjusted results and associated 95% confidence intervals were obtained having as a reference the mechanical debridement treatment and presented for comparison in a forest plot produced by the OpenMeta Analyst for Windows 8 (64-bit) software (Wallace et al., 2012). Significance was admitted for $p<0.05$ in all statistical procedures.

III. RESULTS

3.1. Study selection

The search approach yielded 365 potentially eligible articles. After reviewing the titles and abstracts, 114 publications were chosen for full-text examination. Consequently, 16 articles underwent the eligibility process. Finally, 10 articles were included in the review. [Fig.1] (Büchter et al., 2004; Renvert et al., 2006; Renvert et al., 2008; Passariello et al., 2012; Shibli et al., 2019; De Waal et al., 2021; Park et al., 2021; Blanco et al., 2022; Polymeri et al., 2022; Alhumaidan et al., 2022) [Figure 1]

During the extensive screening process of 16 potentially relevant papers, it was necessary to reject six of them from our study based on predefined inclusion criteria. A thorough review indicated that two studies were disqualified due to their primary focus on periodontitis, a different condition from peri-implantitis (Cosgarea et al., 2021; Cosgarea et al., 2022). Also, one article was removed since it mostly addressed prophylactic measures rather than the specific therapy methods that we wished to study (Tan et al., 2014). Two other papers did not match our inclusion criteria since they largely dealt with surgical interventions, which were outside the focus of our study (Carcuac et al., 2016; Payer et al., 2020) . Finally, one publication was excluded from consideration because it did not include any references to the use of either local or systemic antibiotics in the context of peri-implantitis treatment, which was an important feature of our study (Wagner et al., 2021). These rigorous standards were used to ensure that the studies included in our analysis were directly related to our study objectives and kept a clear focus on antibiotic therapy of peri-implantitis. [Table 1]

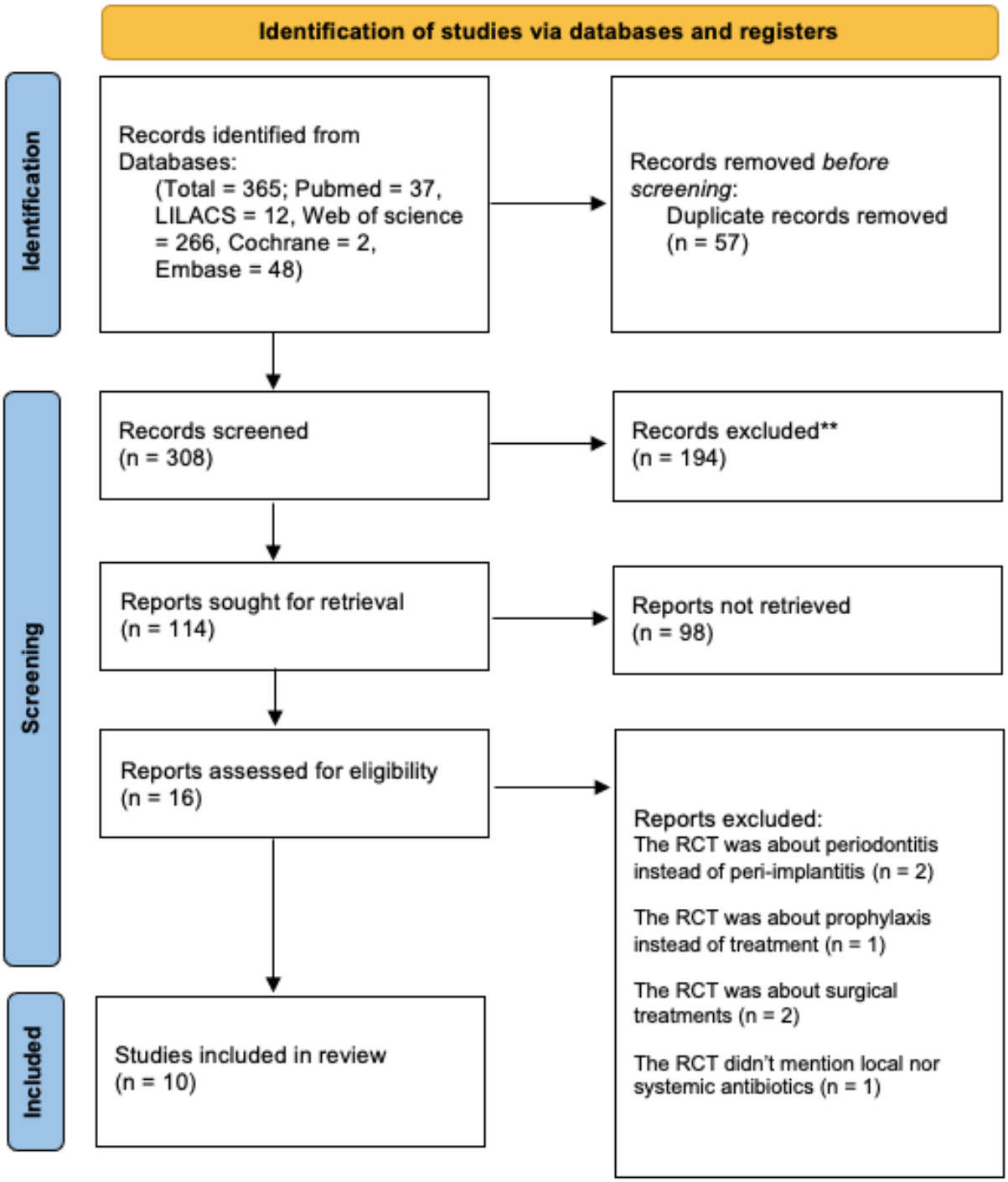

Figure 1. Search results according to PRISMA (RCT, randomized clinical trial)

Table 1. Reasons of exclusion (RCT, randomized clinical trial)

Article	**Reason of exclusion**
(Cosgarea et al., 2021)	The RCT was about periodontitis instead of peri-implantitis
(Cosgarea et al., 2022)	The RCT was about periodontitis instead of peri-implantitis
(Tan et al., 2014)	The RCT was about prophylaxis instead of treatment
(Carcuac et al., 2016)	The RCT was about surgical treatments
(Payer et al., 2020)	The RCT was about surgical treatments
(Wagner et al., 2021)	The RCT didn't mention local or systemic antibiotics

3.2. Study characteristics and results of individual studies

This systematic review (SR) covered randomized controlled trials (RCTs) that were published from 2004 to 2022 [Fig. 6, 7 and 8].

The follow-up duration varied across the included studies: three studies had a follow-up period of 3 months (De Waal et al., 2021; Park et al., 2021; Polymeri et al., 2022) one study had a follow-up of 4 months (Büchter et al.,2004), two studies had a follow-up of 6 months (Passariello, et al., 2012; Alhumanaidan et al., 2022) and four studies had a follow-up of 12 months. (Renvert et al., 2006; Renvert et al., 2008; Shibli et al., 2019; Blanco et al., 2022) [Table 2].

In each study, mechanical debridement was conducted before initiating the treatment. Furthermore, all the papers explicitly stated that patients received comprehensive instructions regarding self-plaque control measures before commencing the treatment.

Five more studies examined the supplementary impact of local antibiotics, employing various drugs and dosages as follows: a single-unit dose of topical doxycycline. (''AtridoxTM'' is a solution containing 8.5% doxycycline by weight and 37% poly d,l-lactide by weight, incorporated in a biocompatible carrier known as N-methyl-2-pyrrolidone. ''Atridox'' is administered in two separate syringes that are linked immediately before usage and well mixed for 100 cycles. After mixing, it is allowed to sit at room temperature for 15 minutes before going through another 10 mixing cycles before application. A 23-gauge blunt cannula on the delivery syringe is used to inject ''Atridox'' into the peri-implant pocket) (Butcher et al., 2004), a single-unit dose of minocycline 1mg (''Arestin'' in microspheres)(Renvert et al., 2006; Renvert et al., 2008; Alhumanaidan et al., 2022), minocycline 500mg once a week for 3 weeks (Park et al.,

2021), and a combination of minocycline plus metronidazole 500 mg once a week for 3 weeks (Park et al., 2021). [Table 3, 4 and 5].

Five studies evaluated the adjunctive effect of systemic antibiotics; however, each used a different medication and dosage: metronidazole 500mg plus amoxicillin 500mg three times a day for fourteen days (Shibli et al., 2019), metronidazole 500mg plus amoxicillin 500mg three times a day for seven days (De Waal et al., 2021), metronidazole 250mg three times a day for seven days (Blanco et al., 2022), amoxicillin 375mg plus metronidazole 250mg every 8h for seven days (Polymeri et al., 2022) and amoxicillin or clindamycin plus serrapeptidase 5mg twice a day for fifteen days (Passariello et al., 2012). Serratiopeptidase is a bacterial protease that is accessible commercially as an anti-inflammatory drug and has the unique capacity to enhance the action of several antibiotics against bacterial biofilms by boosting their penetration at infected locations

None of the implants with peri-implantitis treated in the studies were lost during the follow-up period. A reduction in Probing Pocket Depth (PPD) was reported in all the groups that underwent testing, with variations ranging from 0.00 to 3.82 mm. Eight of the 10 studies provided data on Bleeding on Probing (BOP) changes, ranging from 0.13 to 51.0% (Büchter et al., 2004; Renvert et al., 2006; Renvert et al., 2008; Passariello et al., 2012; Shibli et al., 2019; De Waal et al., 2021; Park et al., 2021; Blanco et al., 2022). Only four studies reported a depth of bone lesions (DBL), showing reductions of up to 2.33 mm (Renvert et al., 2008; Passariello et al., 2012; De Waal et al., 2021; Polymeri et al., 2022). Out of the total studies, only five provided information on treatment success, and none recorded a success rate of 100% (Passariello et al., 2012; Shibli et al., 2019; Park et al., 2021; Blanco et al., 2022; Polymeri et al., 2022).

The treatment success rates varied greatly, ranging from 2.7% to 96.9%.

The key findings are succinctly presented in Figures 2, 3 and 4.

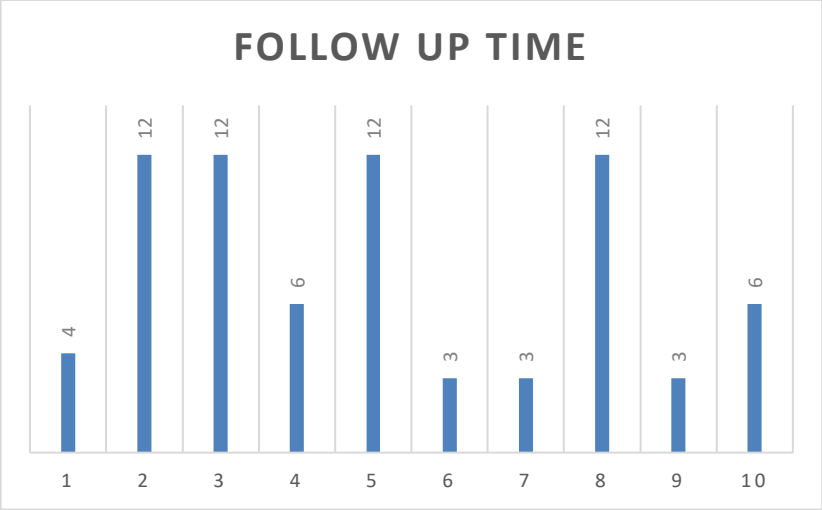

Figure 2. Follow up time (months) in studies

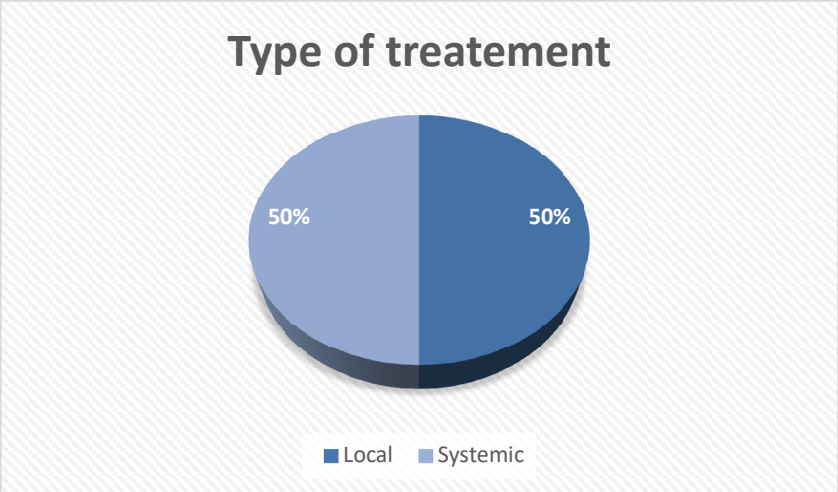

Figure 3. Type of treatment in studies

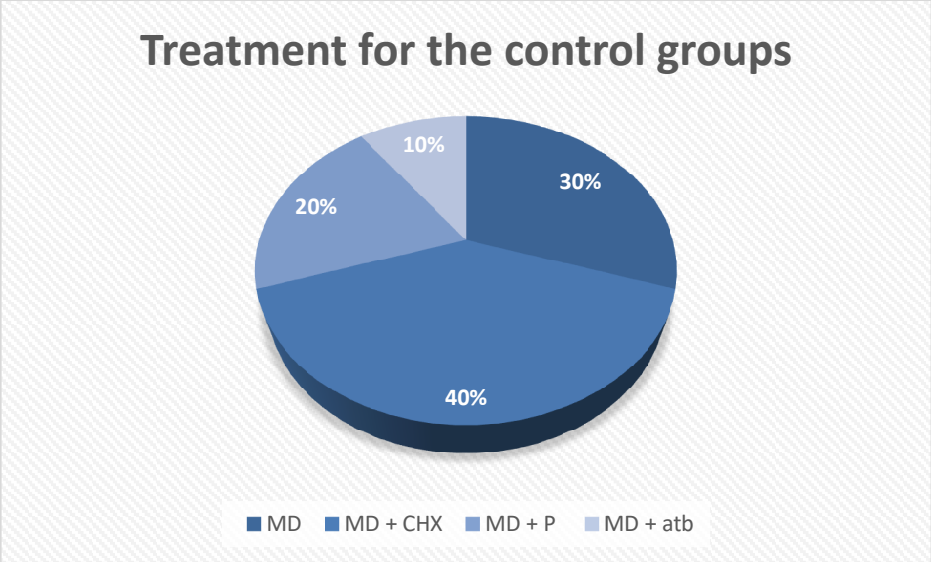

Figure 4. Treatment for the control groups

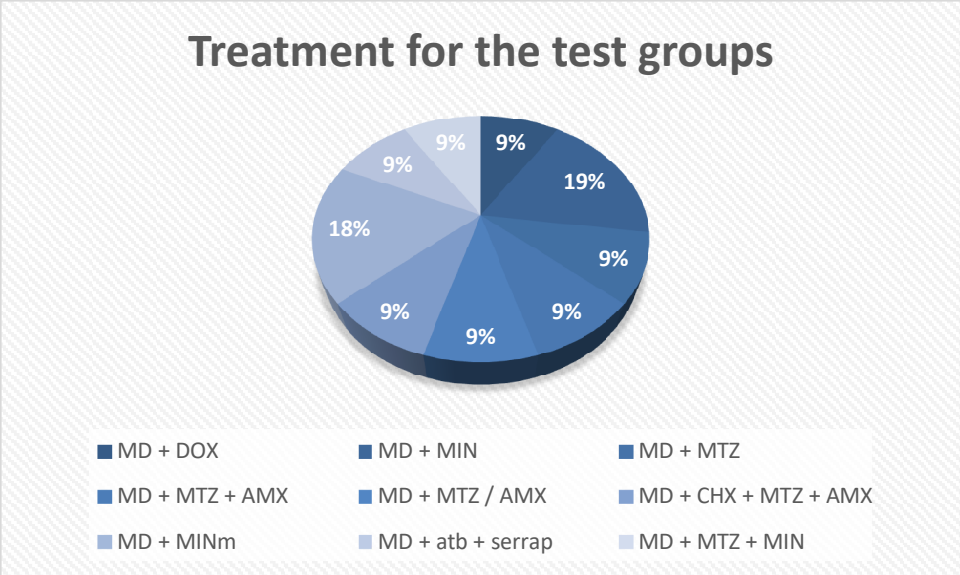

Figure 5. Treatment for the test groups

	Authors	Nº of Patients / implants		F. up (months)	Tretament		Treatement sucess (%)	
		Control	Test		Control	Test	Control	Test
1	André Büchte	14	14	4	MD	MD + DOX	-	-
2	Stefan Renve	14	16	12	MD + CHX	MD + MINm	-	-
3	Stefan Renve	15 (57)	15 (38)	12	MD + CHX	MD + MINm	-	-
4	C. PASSARIEL	64 (64)	64 (64)	6	MD + atb	MD + atb + serrap	78,1	96,9
7	Jamil Awad Sl	20	20	12	MD + P	MD + MTZ + AMX	50	65
10	Yvonne C M D	29 (64)	28 (68)	3	MD + CHX	MD + MTZ/AMX	-	-
11	Seung-Hyun F	37 (37)	38 (38) 39 (39)	3	MD	MD + MTZ + MIN MD + MIN	2,7	31,6 20,5
12	Carlota Blanc	16 (34)	16 (28)	12	MD + P	MD + MTZ	25	56,3
13	Angeliki Polyr	19	18	3	MD + CHX	MD + CHX + MTZ + AMX	5,26	5,56
16	A A Alhumaid	12 (12) 12(!2)	12(12) 12 (!2)	6	MD	MD + MIN	-	-

Table 2. Results of individual studies (MD, mechanical debridement; atb, antibiotic; serrap, serrapeptidase; MIN, minocycline; MTZ, metronidazole; AMX, amoxicillin; DOX, doxycycline; CHX, chlorhexidine; MINm, minocycline microspheres; P, placebo)

PPD reduction (mm)		PPD (INICIAL)		PPD (FINAL)		BOP reduction (%)		DBL (mm)	
Control	Test	Control	Test	Control	Test	Control	Test	Control	Test
0,28 (0,44)	1,15 (0,43)	5,68 (0,28)	5,64 (0,32)	5,40 (0,34)	4,49 (0,29)	50 (7)	27 (6)	-	-
0,00 (0,50)	0,30 (0,92)	3,90 (0,30)	3,90 (0,70)	3,90 (0,40)	3,60 (0,60)	8 (19)	17 (25)	-	-
0,15 (1,54)	0,30 (1,43)	3,87 (1,16)	3,85 (1,04)	3,72 (1,02)	3,55 (0,98)	25,7 (25,8)	38,4 (28,8)	_0,05 (1,03)	0,07 (1,20)
3,30 (1,86)	3,82 (1,20)	6,55 (0,87)	6,30 (0,95)	3,25 (1,64)	2,48 (0,73)	1,02 (0,80)	1,50 (0,81)	1,19 (1,71)	1,96 (1,42)
1,7 (1,7)	3,1 (2,7)	5,50 (1,30)	7,0 (2,6)	3,80 (1,10)	3,9 (0,8)	44,7 (35,4)	51,0 (41,5)	-	-
1,40 (0,80)	1,67 (0,82)	5,82 (1,42)	5,63 (1,24)	4,42 (1,38)	3,96 (1,21)	39,20 (32,31)	38,59 (29,60)	_ 0,04 (0,20)	_ 0,06 (0,17)
	1,95 (1,28)		5,71 (1,33)				51 (32)		
1,28 (1,15)	1,88 (1,50)	5,82 (1,39)	6,22 (1,92)	-	-	33 (41)	50 (34)	-	-
0,89 (2,63)	2,44 (2,73)	5,89 (1,45)	7,29 (2,24)	4,87 (1,78)	5,16 (1,38)	20,50%	39,10%	-	-
1,47 (1,95)	2,28 (1,49)	8,00 (1,41)	7,44 (1,38)	6,53 (2,59)	5,17 (1,92)	-	-	_ 1,33	_ 2,33
1,6 (0,31)	1,7 (0,45)								
2,72 (0,31)	2,1(0,41)	6,02 (0,30)	5,60 (0,40)	3,30 (0,08)	3,50 (0,10)	-	-	-	-

Table 3. Results of the individual studies (PPD, Pocket probing depth; BOP, bleeding on probing; DBL, depth of bone lesion)

Mean age			Latitude	Region	Average time in funciton (years)			Type of treatment (local or systemic)
Control	Test	Total			Control	Test	Total	
56	54	55	51° 57' 44.50"	Munster, Gern	-	-	5,2 (2,1)	Local
61,1 (8,6)	65,6 (8,6)	-	56° 01' 52.64"	Kristianstad, S\	-	-	11	Local
62,40 (7,72)	60,82 (12,72)	-	57° 42' 25.78"	Goterbord, Sw	-	-	11	Local
36,6 (6,6)	38,2 (7,4)	37,4 (7,0)	45° 32' 8.09" N	Brescia, Italy	-	-	-	Systemic
-	-	58,5 (11,1)	_23° 32' 51.00	São Paulo, Bra	-	-	60,5 (6,3)	Systemic
53,5 (11,2)	60,0 (10,4)	-	53° 13' 9.01" N	Groningen, Th	8,9 (5,9)	8,0 (4,3)	-	Systemic
61,2	60,7 61,2	61,1	37° 33' 57.60"	Seoul, Republic	9	8,7 9,0	9	Local
60,74	58,31	-	42° 52' 49.87"	Santiago de Cc	-	-	-	Systemic
60,8 (14,8)	58,3 (13,9)	-	52° 22' 26.51"	Amesterdam, '	-	-	>1	Systemic
52,2	56,1	-	40° 42' 59.99"	New York, USA	3,8 (0,4)	4,1 (0,6)	-	Local
55,1	52,8				4,2 (0,6)	4,7 (0,2)		

Table 4. Results of the individual studies

3.3. Definition of peri-implantitis

The randomised controlled trials (RCTs) included in our study classified peri-implantitis based on specific factors such as probing pocket depth (PPD), bleeding on probing (BOP), and the existence of radiographic evidence showing peri-implant bone loss. While all these studies provided criteria of peri-implantitis that were consistent with the 2017 categorization (Schwarz et al., 2018) there were small differences between them. In order to maintain transparency and offer readers with reliable information, we have collated the distinct definitions used by each study for the diagnosis of peri-implantitis and presented them thoroughly in a separate table. This improves the clarity and dependability of the data offered in our review. [Table 6]

Table 5. Definition of peri-implantitis according to the studies (PPD, pocket probing depth; MBL, marginal bone loss; BOP, bleeding on probing; SOP, suppuration on probing)

Authors	PPD	MBL	BOP	SOP
(Park et al., 2021)	≥ 5 mm	≥ 2 mm	Yes	Yes
(Park et al., 2021)	≥ 5 mm	≥ 5 mm	Yes	Yes
(Blanco et al., 2022)	≥ 6 mm	≥ 3 mm	Yes	Yes
(Alhumaidan et al., 2022)	≥ 4 mm	≥ 2 mm	Yes	Yes

3.4. Risk of bias in studies

Among the 10 included studies (Büchter et al., 2004; Renvert et al., 2006; Renvert et al., 2008; Passariello et al., 2012; Shibli et al., 2019; De Waal et al., 2021; Park et al., 2021; Blanco et al., 2022; Polymeri et al., 2022; Alhumaidan et al., 2022), 2 were categorized as having a high risk of bias (Renvert et al., 2006; Renvert et al., 2008), 3 were considered to some concerns (Shibli et al., 2019; Polymeri et al., 2022; Alhumaidan et al., 2022), and 5 were rated as having a low risk of bias (Büchter et al., 2004; Passariello et al., 2012; De Waal et al., 2021; Park et al., 2021; Blanco et al., 2022). [Fig. 5 and 6]

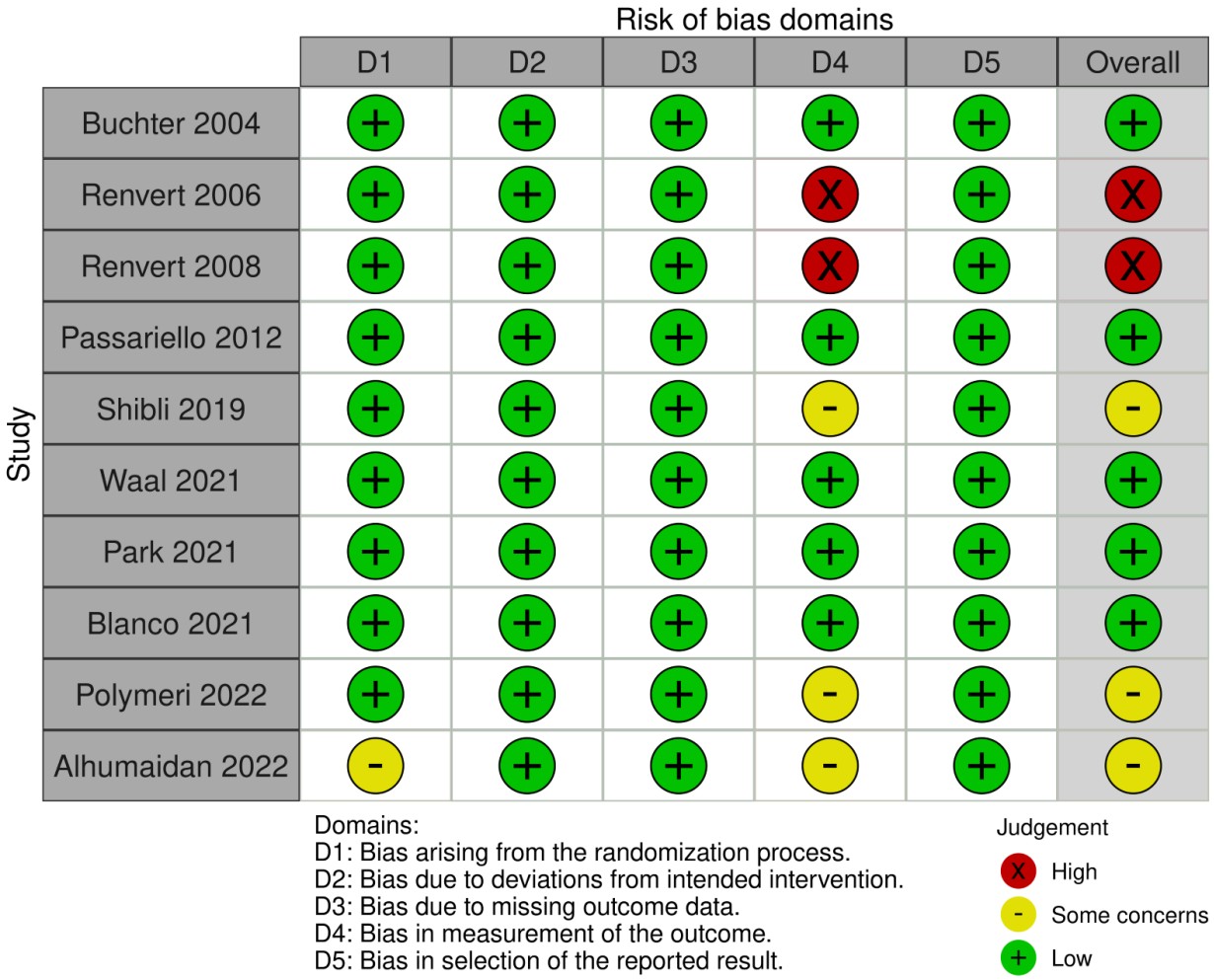

Figure 6. Risk of bias of the included studies (RoB 2 tool according to Sterne et al., 2019)

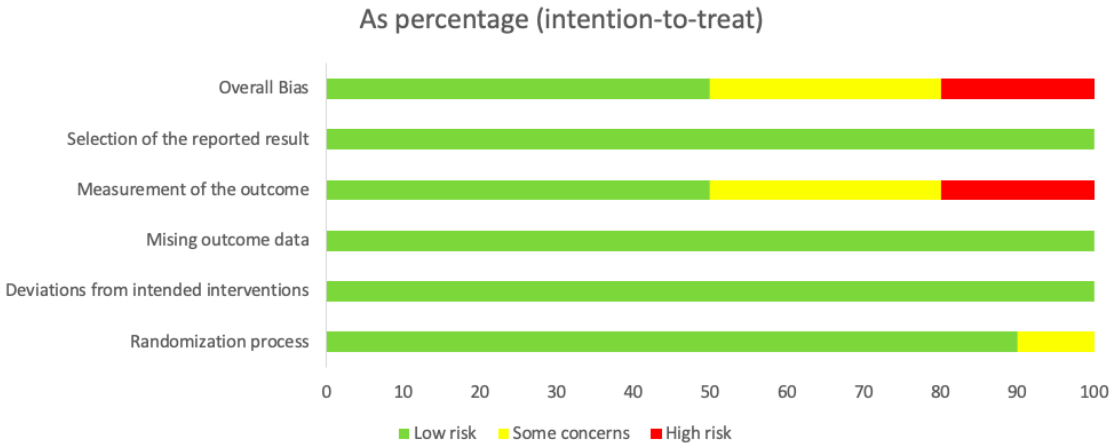

Figure 7. Risk of bias of the included studies (RoB 2 tool according to Sterne et al., 2019)

3.5. Results of synthesis

Ten randomized controlled trials (RCTs) were incorporated into the meta-analyses, forming two distinct meta-analytical studies. [Fig. 7 and 8]

Regarding the relative effect (standardized: MD), the meta-analysis revealed that among the various treatment groups studied, one group exhibited relatively more favourable outcomes on average than the other groups. However, it is important to note that these observed outcome differences did not reach statistical significance. Therefore, while a trend may suggest better results with this particular treatment, further investigation is required to establish whether this tendency holds across a larger population or could be due to chance.

The findings of the meta-analysis also provided insight into the potential benefits of using antibiotics. Specifically, concerning the measure of MD (as indicated by the representation of a blue diamond labelled "OVERALL", in Figure 7), there seems to be a notable improvement linked to the use of antibiotics. This improvement could potentially have clinical implications, emphasizing the value of antibiotic intervention in managing or addressing the condition under study.

However, it is crucial to exercise caution when interpreting these results. While the reported improvement in MD (mechanical debridement) associated with antibiotic usage is intriguing, it is imperative to acknowledge the study's limitations. The lack of statistical significance underscores the need for more robust evidence to substantiate these findings, and therefore, the call for additional studies comes into play.

The significance of these findings resides in the necessity for further research to improve the accuracy and reliability of the observed outcomes for each treatment modality. More thorough and rigorous studies involving larger sample sizes and possibly different study designs can assist in validating and improving our understanding of the effects of various treatments. Future studies can provide a more comprehensive and detailed perspective on the efficacy of different treatments by addressing potential confounding variables, increasing the diversity of participants, and employing rigorous statistical analyses.

In essence, while the initial results indicate a promising direction in terms of treatment outcomes, the uncertainties surrounding statistical significance and potential biases emphasize the need for a more comprehensive and in-depth exploration. This will ultimately contribute to a more informed and evidence-based approach to treatment

decisions, ensuring the best possible outcomes for individuals seeking medical interventions.

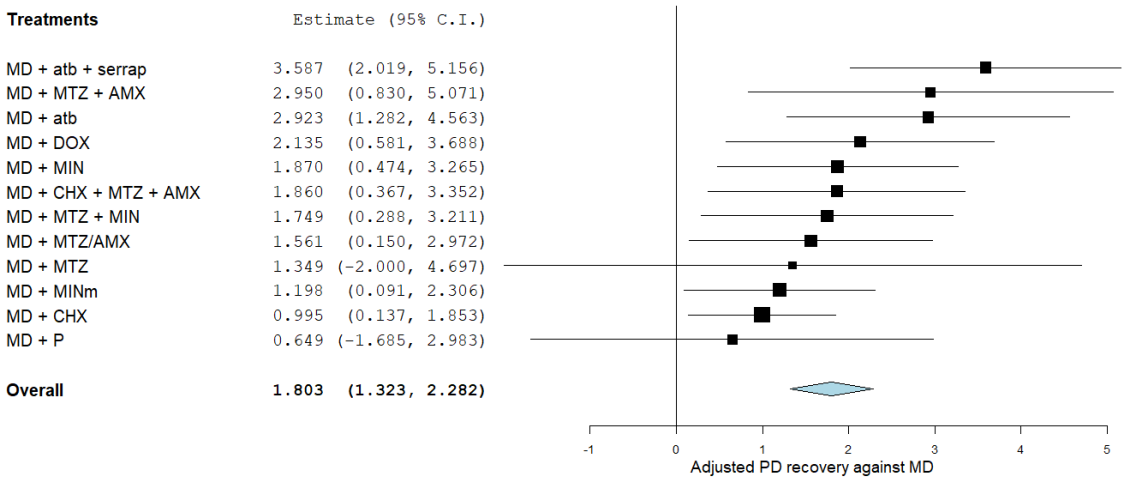

Figure 8. Meta-analysis of the included studies (MD, mechanical debiredment; atb, antibiotic; serrap, serrapeptidase; MIN, minocycline; MTZ, metronidazole; AMX, amoxicillin; DOX, doxycycline; CHX, chlorhexidine; MINm, minocycline microspheres; P, placebo)

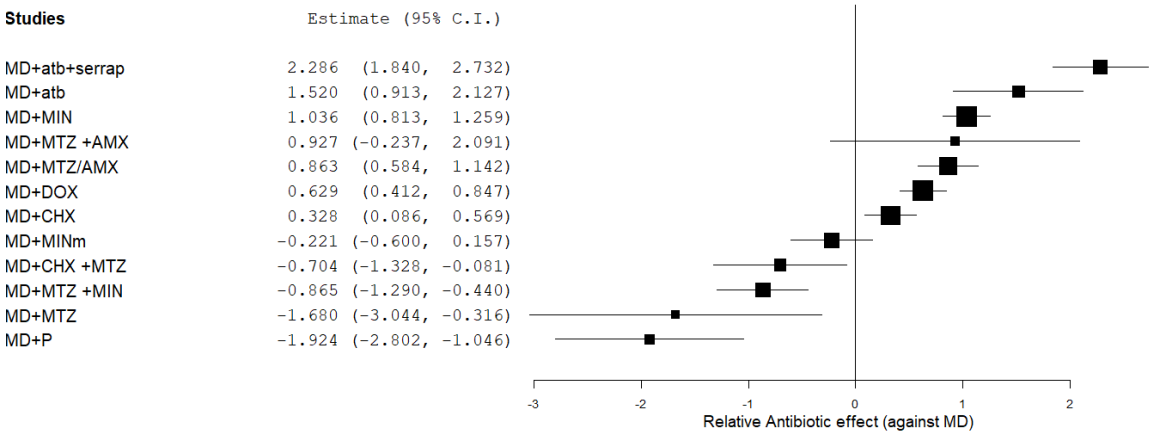

Figure 9. Meta-analysis of the included studies regarding the type of application (MD, mechanical debridement; atb, antibiotic; serrap, serrapeptidase; MIN, minocycline; MTZ, metronidazole; AMX, amoxicillin; DOX, doxycycline; CHX, chlorhexidine; MINm, minocycline microspheres; P, placebo)

IV. DISCUSSION

4.1 Summary of main findings

Peri-implantitis, is defined by substantial inflammation within the peri-implant mucosa, which leads to the gradual loss of supportive bone structure (Berglundh et al., 2018). As the prevalence of dental implantation grows, appropriate peri-implantitis management options become increasingly important. Among the treatment options considered, locally and systemically, antibiotics have emerged as a viable option (Passarelli et al., 2021). In this systematic review, we tried to look into the consequences, benefits, controversies, and issues surrounding the use of local and systemic antibiotics in treating peri-implantitis.

This systematic review (SR) revealed a noteworthy observation: none of the implants were reported as lost throughout the follow-up period, which ranged from 3 to 12 months. While this study suggests a promising outlook, final conclusions must be handled with caution. Short-term follow-up data, often covering 3-6 months, provides vital insights into early treatment responses and safety considerations. They fail to make long-term predictions about the efficiency of antibiotic therapies in peri-implantitis. This situation may be explained by the limited efficacy of non-surgical therapies in reaching resolution, necessitating additional surgical treatments. As a result, gathering medium and long-term data on implant survival via non-surgical procedures becomes a challenging task filled with complexity. (Barbato et al., 2023)

It is critical to understand that assessing peri-implant health is a complex assessment. This assessment includes examining criteria such as the absence of inflammation, the absence of bleeding on probing (BOP), and the absence of any indicators pointing to increased probing pocket depth (PPD) or bone loss post-initial healing, in addition to the absence of implant loss. The evaluation of peri-implant health entails a complex review of numerous parameters other than the absence of implant loss. While a high survival rate suggests that implants are still in place, it falls short of creating a comprehensive rate of success. Consider the following scenario: all implants are retained within the patient's oral cavity, resulting in a faultless 100% survival rate. Despite this, a closer look may indicate that these implants have suffered significant bone loss, jeopardizing their long-term stability and overall success. In such cases, the survival rate remains excellent, but

the success rate, which considers a variety of factors that contribute to the overall health and stability of the implant and its surrounding tissues, may show an alarming decline. (Renvert et al., 2018)

Adopting a composite outcome (containing minimal probing pocket depth (PPD), absence of bleeding on probing (BOP), and prevention of progressive bone loss) offered complications for evaluating treatment success after non-surgical therapies. The rates of reaching this composite outcome showed great variability, ranging from 2.7% to 96.9%.

It is worth noting that the observed fluctuations were erratic and unpredictable. These disparities show the difficulty in obtaining a consistent success rate for such composite outcomes. Furthermore, the follow-up period in the studies evaluated ranged from 3 to 12 months, limiting the availability of long-term data.

This scarcity of long-term data could be attributed to the lower success rates observed after non-surgical treatments. In instances where non-surgical interventions did not lead to the desired resolution, necessitating subsequent surgical procedures, it posed a challenge in obtaining medium to long-term data on implant survival with non-surgical methodologies. In summary, using composite outcomes to determine treatment success after non-surgical therapies found significant diversity in resolution rates among studies. The relatively short duration of follow-up and the probable necessity for surgical treatments exacerbated the difficulty in acquiring long-term data, emphasizing the complexities of evaluating implant survival through non-surgical paths. Hence, it can be concluded that non-surgical treatment, whether accompanied by adjunctive methods or not, lacks predictability when it comes to achieving long-term resolution of peri-implantitis and preventing implant loss.

However, it is important to note that non-surgical treatment was associated with a reduction in peri-implant pocket depth. A recurring result across all of the studies included in this systematic review (SR) was a reduction in probing pocket depth (PPD) following implant debridement (done independently). The documented extent of PPD reduction ranged from 0.00 mm to 3.82 mm. This indicates that non-surgical therapies may assist in reducing the depth of peri-implant pockets.

The disparity in outcomes can be attributed to several reasons, including the variety of baseline conditions and the various proficiency levels of the operators involved.

Several factors contribute to the variation in baseline circumstances among the selected studies. These include fluctuations in the number of patients and implants, with sample

sizes ranging from 12 to 64. Also, there were significant differences in the follow-up intervals, which ranged from 3 to 12 months. A further significant divergence was the initial pocket probing depth, which ranged from 3.85 to 8.00 millimetres and is a key metric in peri-implantitis assessment. Furthermore, the mean age of research participants varied significantly, with values ranging from 36.6 to 62.4 years. When analysing and comparing the results of these research, it is critical to acknowledge and account for these discrepancies in baseline circumstances.

Notably, at the start of this systematic review, the baseline mean probing pocket depth (PPD) values ranged from 3.85 mm to 8.00 mm. Despite this variation, it is important to note that no significant inter-group differences were found within the individual investigations, which highlights the potential role of factors other than baseline PPD values in contributing to the observed outcome variability.

To summarise, using local and systemic antibiotics in treating peri-implantitis offers a viable avenue for disease control. While encouraging results have been recorded, getting consistent and predictable outcomes remains challenging. Antibiotic cautious usage, informed by evidence-based practices, patient concerns, and a thorough understanding of microbial dynamics, will be critical in optimizing treatment regimens and improving patient outcomes in the arena of peri-implantitis. While antibiotics can be useful tools in combating infections, their arbitrary or excessive use can lead to the emergence of antibiotic resistance, a serious worldwide health concern. Antibiotic resistance develops when bacteria adapt and become less receptive to the medications targeted to eradicate them, making antibiotics less effective. This event emphasizes the importance of taking a thorough and personalized strategy to antibiotic therapy in peri-implantitis cases. By optimizing treatment regimens and tailoring antibiotic therapies to individual patient needs, healthcare practitioners can improve treatment outcomes while also playing a critical role in preventing antibiotic resistance and ensuring the long-term effectiveness of these critical medications in the context of implant dentistry (Thompson et al., 2021).

4.2. Agreements and disagreements with other SR and studies

Barbato et al. (2023) conducted a systematic review with a meta-analysis, encompassing 16 studies. Their primary objective was to assess the clinical effectiveness of various adjunctive therapies employed in non-surgical treatment for peri-implantitis (Barbato et al., 2023). Their findings revealed that non-surgical treatment (NST), whether

administered in isolation or conjunction with additional therapies (local antibacterial agents, systemic antibiotics, lasers, antimicrobial photodynamic therapy, probiotics, and a desiccant agent), demonstrated the capacity to reduce probing pocket depth (PPD) and bleeding on probing (BoP). Nevertheless, it was underscored that achieving complete resolution of the peri-implant pocket remained an unpredictable outcome. Among the adjunctive approaches, systemic antibiotics emerged as a potential avenue for additional benefits. However, the use of systemic antibiotics warranted a cautious approach, considering factors such as antibiotic resistance and potential side effects. Notably, within the scope of adjunctive therapies, the combination of mechanical debridement and antibiotics yielded a significant estimated mean difference of 0.34 mm in PPD reduction when compared to debridement alone (Barbato et al., 2023).

In this systematic review (SR) context, our findings align with those of Barbato et al. (2023) specifically, our study's use of systemic antibiotics resulted in a significant reduction in PPD, with a substantial difference of 0.91mm compared to the control group. Furthermore, our results are consistent with the outcomes reported in other systematic reviews (Ramanauskaite et al., 2021; Barbato et al., 2023), which also indicated favourable effects in favour of adjunctive systemic antibiotics, with differences in PPD reduction measuring 1.46 mm and 1.56 mm, respectively.

The use of local antibiotics applications (doxycycline, minocycline, minocycline microspheres and minocycline plus metronidazole) did not yield a statistically significant difference in PPD reduction (1.3414 (0.89) compared to the control group (1.005 (0.86)). These findings closely reflect the results of previous systematic reviews addressing peri-implantitis (et al., 2023; Toledano-Osorio et al., 2022) and a more recent systematic review that specifically focused on peri-implant mucositis (Barootchi et al., 2020).

4.3. Quality of the evidence and potential limitations in the review process

This systematic review (SR) does have some limitations that require consideration. A notable constraint arises from the inclusion of studies that employed different control groups, even though all of them utilized mechanical debridement as a common baseline control. It is important to emphasize that, within this shared control group of mechanical

debridement, there are variations in terms of additional components utilized in certain studies, such as the incorporation of chlorhexidine. The presence of these disparities across control groups provides a degree of variability in the study designs, potentially impacting the ability to compare outcomes across the included studies. As a result, while the primary objective of this SR is to provide significant insights into the efficacy of peri-implantitis therapies, it is critical to recognise and account for these differences in control groups when interpreting the data and assessing their wider implications.

Another noteworthy issue of this systematic review (SR) is the definition of peri-implantitis used in the included studies. It is important to note that only four of the ten studies included in this SR gave a clear and unambiguous description of peri-implantitis. This disparity in definition and diagnosis criteria among studies raises issues about the consistency of the diagnostic standards used. Given the potential for heterogeneity in diagnostic criteria, ensuring consistency in the examination and categorization of peri-implantitis cases becomes increasingly difficult. This variation in defining the condition among studies highlights the importance of exercising caution when comparing and synthesising the data, as it adds another layer of complexity to interpreting and generalising the findings. The implementation of the updated peri-implantitis classification is expected to ease the mitigation of classification differences, hence promoting standardization, and eliminating inherent biases found in scientific articles. As a result, this development has the potential to improve the overall resilience and reliability of the research outputs.

Bias is an important concern while performing a systematic review (SR), as it can significantly affect the validity and reliability of the review's conclusions. Despite our thorough attempts to include high-quality papers in our SR, we discovered that only 5 of the RCTs analyse had a low risk of bias. This topic requires thorough consideration and critical thought to improve the credibility and utility of systematic reviews in the future. The adequacy of the randomization process is one of the key factors of bias in RCTs. Randomization is a key component of experimental study design because it ensures that treatment allocation is not influenced by outside factors, hence decreasing systematic variations between treatment groups. Unfortunately, our research indicated that some of the trials in our SR did not give enough clarity or transparency about their randomization techniques. This lack of critical information creates confusion and may jeopardize the

internal validity of these investigations. Allocation concealment, which is crucial for decreasing selection bias, was either underreported or absent in some of the studies assessed. This lack of transparency makes it difficult to assess bias risk and raises questions about the integrity of participant group assignments.

Transparent reporting must be prioritized by researchers in order to increase research quality and eliminate bias in systematic reviews. RCT authors should include extensive details of randomization and allocation concealment. Journals and institutions should adhere to strict reporting criteria such as CONSORT (Schulz et al., 2010). These efforts will increase the credibility of research and support decision-making processes. Addressing these limitations is critical for maintaining the integrity of systematic reviews and increasing knowledge.

V. CONCLUSIONS

The current systematic review included ten randomized control trials, five of which were classified as having a low risk of bias, three of which had some concerns and two of which were classified as having a high risk of bias, according to the RoB2 tool.

Non-surgical therapeutic approaches, which include the use of both local and systemic antibiotics, have shown significant promise, particularly in terms of improving probing pocket depth (PPD) and lowering bleeding on probing (BOP) within peri-implant tissues. These developments highlight their potential to improve the overall health of peri-implant tissues. Nonetheless, it is critical to recognize that achieving complete disease resolution is a complex and unpredictable task.

Additional investigation is needed to determine the most effective antibiotics, routes of administration, therapy regimens, and treatment protocols for the treatment of peri-implantitis, whether used alone or in combination with other techniques. This research should focus on distinguishing case-specific and site-specific indications to identify the most effective antibiotic therapy while also reducing the dangers associated with inappropriate antibiotic use.

VI. IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

Further research is required in the complex realm of antibiotic treatments for peri-implantitis. The forthcoming research studies ought to dive deeper into the specifics, including an in-depth review of antibiotic types, routes of administration, and most suitable therapy regimens. Furthermore, there is an urgent need to develop standardized treatment procedures that account for the peculiarities of this condition. This research effort should broaden its scope to investigate the viability of using antibiotics as standalone therapies or in conjunction with alternative therapeutic techniques in the context of peri-implantitis therapy. The precise identification of indications that are inherently linked to unique clinical cases and implant sites is a critical component of this research program. The ultimate goal of this research effort is to uncover the most effective antibiotic therapy for peri-implantitis while simultaneously exercising cautiousness to reduce the potential risks associated with unnecessary or indiscriminate antibiotic use.

Additionally, this research emphasizes the critical need of reducing the inherent hazards associated with antibiotic treatment in peri-implantitis care. The prudent selection of antibiotics adapted to the unique clinical circumstance is critical, with special attention paid to the potential harm of antibiotic resistance. Furthermore, the inquiry should broaden its scope to include the interaction of antibiotics and complementary therapy methodologies. This comprehensive strategy aims to maximize therapeutic efficacy while protecting patient well-being. Finally, the study hopes to provide doctors with a complete and evidence-based framework for navigating the complex landscape of peri-implantitis treatment, with a focus on antibiotic therapy that is both effective and ethical.

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VIII. APPENDICES

Additional file 1

Search strategy in PubMed on March 1, 2023

1. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
2. ''peri-implantitis'' AND ''antibiotic''
3. ''peri-implantitis'' AND ''non-surgical treatment''
4. ''peri-implantitis'' AND ''non-surgical therapy''
5. ''peri-implantitis'' AND ''antibiotic agent''

Limits
- Type of article: Randomized clinical trial
- Dates: until 01.03.2023
- Human or animals: humans

Search strategy in Cochrane Library on March 2, 2023

1. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
2. ''peri-implantitis'' AND ''antibiotic''
3. ''peri-implantitis'' AND ''non-surgical treatment''
4. ''peri-implantitis'' AND ''non-surgical therapy''

Limits:
- Type of article: Randomized clinical trial
- Dates: until 02.03.2023
- Human or animals: humans

Search strategy in Web of Science on March 6, 2023

5. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
6. ''peri-implantitis'' AND ''antibiotic''
7. ''peri-implantitis'' AND ''non-surgical treatment''
8. ''peri-implantitis'' AND ''non-surgical therapy''

Limits:
- Type of article: Randomized clinical trial
- Dates: until 06.03.2023
- Human or animals: humans

Search strategy in Cochrane Library on March 7, 2023

1. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
2. ''peri-implantitis'' AND ''antibiotic''
3. ''peri-implantitis'' AND ''non-surgical treatment''
4. ''peri-implantitis'' AND ''non-surgical therapy''

Limits:
- Type of article: Randomized clinical trial
- Dates: until 07.03.2023
- Human or animals: humans

Search strategy in Open Grey on March 7, 2023

5. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
6. ''peri-implantitis'' AND ''antibiotic''
7. ''peri-implantitis'' AND ''non-surgical treatment''
8. ''peri-implantitis'' AND ''non-surgical therapy''

Limits:

- Type of article: Randomized clinical trial
- Dates: until 07.03.2023
- Human or animals: humans

Search strategy in Cochrane Library on March 9, 2023

6. ''peri-implantitis'' OR '''peri implantitis'' OR ''periimplantitis''
7. ''peri-implantitis'' AND ''antibiotic''
8. ''peri-implantitis'' AND ''non-surgical treatment''
9. ''peri-implantitis'' AND ''non-surgical therapy''
10. ''peri-implantitis'' AND ''antibiotic agent''

Limits

- Type of article: Randomized clinical trial
- Dates: until 09.03.2023
- Human or animals: humans

Additional file 2

Title	Round 1	Reason	Round 2	Reason	Authors	Publication Year
Surgical and non-surgical debridement for the treatment of peri-implantitis: a two-center 12	Included		Included		Wagner TP, Pires PR, Reis FS, da	2021
A New Strategy Against Peri-Implantitis: Antibacterial Internal Coating	Excluded	Antibacterial internal coating			Calinci F, Lauritano D, Bignozzi C	2019
Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical t	Excluded	Surgical treatment			Carcuac O, Derks J, Abrahamsso	2017
Systemic antibiotic therapy as an adjunct to non-surgical peri-implantitis treatment: A sing	Included		Included		De Waal YCM, Vangsted TE, Van	2021
Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis	Included		Included		Bianco C, Pico A, Dopico J, Gánc	2021
Non-surgical peri-implantitis treatment with or without systemic antibiotics: a randomized c	Included		Included		Polymeri A, van der Horst J, Ana	2022
Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clii	Excluded	Surgical treatment			Derks J, Ortiz-Vigón A, Guerrero	2022
Open flap debridement of peri-implantitis with or without adjunctive systemic antibiotics: A	Excluded	Surgical treatment			Hallström H, Persson GR, Lindgre	2017
Efficacy of adjunct subgingival minocycline delivery for treatment of peri-implantitis in mic	Included		Included	Smokers and non-smokers	Alhunaidan AA, Alabdah M, Al-Au	2022
Surgical Therapy of Peri-Implantitis with Local Minocycline: A 6-Month Randomized Contro	Excluded	Surgical treatment			Cha JK, Lee JS, Kim CS	2019
Microbiological and clinical effects of adjunctive systemic metronidazole and amoxicillin in	Included		Included		Shibli JA, Ferrari DS, Sicoma RS,	2019
Systemic antibiotics and debridement of peri-implant mucositis. A randomized clinical trial	Included		Excluded	Mucositis	Hallström H, Persson GR, Lindgre	2012
The effectiveness of photodynamic and antibiotic gel therapy as an adjunct to mechanical	Excluded	Photodynamic therapy			Ahmed P, Bukhari IA, Albaijan R,	2020
Assessment of safety and efficacy of antimicrobial photodynamic therapy for peri-implant	Excluded	Photodynamic therapy			Ohba S, Sato M, Noda S, Yamam	2020
Clinical and microbiological outcomes of photodynamic and systemic antimicrobial therapy	Excluded	Photodynamic therapy			Deeb RMA, Alsahhaf A, Mubaraki S	2019
Adjunctive use of metronidazole-minocycline ointment in the nonsurgical treatment of peri-	Included		Included		Park SH, Sieng YW, Cha JK, Lee	2021
Adjunctive Systemic and Local Antimicrobial Therapy in the Surgical Treatment of Peri-imp	Included		Included		Carcuac O, Derks J, Charalampal	2015
Mechanical and repeated antimicrobial therapy using a local drug delivery system in the tr	Included		Included		Renvert S, Lessem J, Dahlén G,	2006
Clinical observation of minocycline hydrochloride ointment in the treatment of early perim	Included		Excluded	Clinical observation	Tian B.	2019
The effects of Lactobacillus reuteri probiotics combined with azithromycin on peri-implantiti	Excluded	Probiotics combined with antibiotics			Tada H, Masaki C, Tsuka S, Muk	2017
Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynami	Excluded	Photodynamic therapy			Bassetti M, Schär D, Wicki B, Eic	2014
Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynami	Excluded	Photodynamic therapy			Schär D, Ramseier CA, Eick S, A	2013
D-PLEX300: a local biodegradable prolonged release doxycycline-formulated bone graft to	Excluded	Surgical treatment			Emanuel N, Machtei EE, Reichart	2020
The adjunctive use of light-activated disinfection (LAD) with FotoSan is ineffective in the t	Excluded	Light-activated disinfection (LAD)			Esposito M, Grusovin MG, De An	2013
Effects of non-surgical treatment modalities on peri-implantitis	Included		Excluded	Clinical trial	Tang Z, Cao C, Sha Y, Lin Y, Ma	2002
The effectiveness of adjunctive light-activated disinfection (LAD) in the treatment of perii	Excluded	Light-activated disinfection (LAD)			De Angelis N, Felice P, Grusovin	2012
Long-term stability of surgical bone regenerative procedures of peri-implantitis lesions in a	Excluded	Surgical treatment			Roos-Jansåker AM, Lindahl C, Pe	2011
Sustained release of doxycycline for the treatment of peri-implantitis: randomised controlli	Included		Included		Büchter A, Meyer U, Kruse-Lösler	2004
Effect of prophylactic application of doxycycline at the implant-abutment interface on the	Excluded	Prophylaxis			Arshad M, Mahgoli H, Akhoundzac	2022
Role of antimicrobial photodynamic therapy in reducing subgingival oral yeasts colonizatio	Excluded	Mucositis			Shetty B, Ali D, Ahmed S, Ibrahe	2022
Reconstruction of Peri-Implant Osseous Defects: A Multicenter Randomized Trial	Excluded	Surgical treatment			Jepsen K, Jepsen S, Laine ML, A	2015
Efficacy of Antibiotic Versus Probiotics As Adjuncts to Mechanical Debridement for the Tr	Excluded	Probiotics			Alqahtani F, Alshaikh M, Mehmoo	2022
Effects of Topical Antibiotic Prophylaxis on Wound Healing After Rapless Implant Surgery	Excluded	Prophylaxis			Ku L, Wang Y, Nguyen VT, Chen	2015
Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot ran	Excluded	Microimplant			Łyczek J, Kawala B, Antoszewsk	2018
A single-centre randomized controlled clinical trial on the adjunct treatment of intra-bony d	Excluded	Surgical treatment			Aghazadeh A, Rutger Persson G,	2012
Efficacy of antibacterial sealing gel and O-ring to prevent microleakage at the implant abu	Excluded	In vitro			Nayak AG, Fernandes A, Kulkarni	2014
Topical minocycline microspheres versus topical chlorhexidine gel as an adjunct to mecha	Included		Included		Renvert S, Lessem J, Dahlén G,	2006

Título	Round 1	Reason	Round 2	Reason	Duplicado
Peri-implant mucositis associated to corrective orthodontics	Excluded	Mucositis			
Etiology and treatment of perimplantites: integrative review	Included		Excluded	Integrative review	
A clinical practice guideline for the prevention and treatment of peri-implant diseas	Included		Excluded	Clinical practice guideline	
Microbiological and clinical effects of adjunctive systemic metronidazole and amo	Included				X
Peri-implantite: tratamentos e manutenção peri-implantar - parte 2ª / Peri-implantit	Included		Excluded	Clinical practice guideline	
Peri-implantite: etiologia e tratamento / Perimplantitis: etiology and treatment	Included		Excluded	Integrative review	
Antibioticoterapia no tratamento da peri-implante / Antibioticotherapy in the treatm	Included		Excluded	Integrative review	
A terapia fotodinâmica antimicrobiana como opção de tratamento não invasivo da	Excluded	Photodynamic therapy			
Análise microbiológica comparativa da ação de diferentes agentes descontaminan	Excluded	Decontaminant agents			
Tratamento das doenças peri-implantares: experiências passadas e perspectivas	Included		Excluded	Clinical practice guideline	
Utilização de biomateriais e de tecido conjuntivo subepitelial no tratamento de per	Excluded	Surgical treatment			
Perimplantitis infecciosa: propuesta de un plan preventivo / Infectious peri-implar	Excluded	Preventive plan			

Autor	Publication year
Díaz-Caballero, Antonio; Lozada-Martínez, Ariana; Almar	2021
Oliveira, Yasmin Caldas de Macêdo Abrantes Rodrigues	2021
Marín-Jaramillo, Rubiel Antonio; Villegas-Giraldo, Alejand	2019
Gulinelli, Jéssica Lemos; Santos, Pâmela Letícia dos; M	2016
Oliveira, Mariano Craveiro de; Corrêa, Débora Freire Mar	2015
Rodrigues, Fábio; Smanio, Júlia Almeida; Smanio Neto, I	2014
Corrêa, Ricardo de Oliveira; Rettore Júnior, Ronaldo; Sou	2012
Biagitz, Renata Rodrigues de Freitas.	2011
Casado, Priscila Ladeira; Guerra, Rafael Rangel; Fonsec	2011
Casarin, Renato Corrêa Viana; Ribeiro, Fernanda Veiras;	2007
Negroni de Bonvehi, Marta Beatriz; Domenech, María del	1996

Title	Round 1	Reason	Round 2	Reason	Duplicado	Authors
Antibiotic resistance in human peri-implantitis microbiota	Excluded	Antibiotic resistance				Rams, TE; Dege
Clinical efficacy of antibiotics in the treatment of peri-implantitis	Included		Excluded	Systematic review		Javed, F; AlGha
Antibiotics in the treatment of peri-implantitis	Included		Excluded	Review		van Winkelhoff, .
Biomaterial and Antibiotic Strategies for Peri-implantitis	Included		Excluded	Review		Norowski, PA an
STUDY REGARDING ANTIBIOTIC RESISTANCE OF PREVOTELLA SPECIES IN PERI-IMPLA	Excluded	Antibiotic resistance				Ciprian, BF; Aur
Open flap debridement of peri-implantitis with or without adjunctive systemic antibiotics: A ran	Excluded				X	
Local and Systemic Antibiotics in Peri-Implantitis Management: An Umbrella Review	Included		Excluded	Umbrela review		Boccia, G; Di Sp
Antimicrobial photodynamic therapy versus antibiotics as an adjunct in the treatment of perio	Excluded	Photodynamic therapy				Zhao, YX; Pu, R
Surgical therapy for the control of peri-implantitis	Excluded	Surgical treatment				Renvert, S; Poly
A Systematic Review and Meta-Analysis of Systemic Antibiotic Therapy in the Treatment of P	Included		Excluded	Systematic review		Toledano-Osorio
The efficacy of systemic antibiotics as an adjunct to surgical treatment of peri-implantitis: a s	Excluded	Surgical treatment				Oen, M; Leknes,
Photodynamic Therapy in Peri-implantitis	Excluded	Photodynamic therapy				Lenetter, M; Gan
Emphysema following air-powder abrasive treatment for peri-implantitis	Excluded	Out of context				Lee, ST; Sulku, F
Apical Peri-Implantitis: Etiology, Prevention, Diagnosis, Treatment: Literature Review and Cas	Excluded	Apical peri-implantitis				Zarenti, S; Tsom
Peri-Implantitis Associated With a Pre-Existing Pathology	Excluded	Pre-Existing Pathology				Oh, SL
Radiographic bone fill of peri-implantitis defects following nonsurgical therapy: Report of three	Excluded	Surgical treatment				Nibali, L and Dor
Development of a peri-implantitis model in the rat	Excluded	Animal subject				Sun, JQ; Eberhe
Management of Peri-Implantitis Lesions without the Use of Systemic Antibiotics: A Systematic	Excluded	Without the use of antibiotics				Khan, A; Goyal,
Metabolic Conditions and Peri-Implantitis	Excluded	Metabolic conditions				Benahmed, AG;
A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis	Excluded	Anti-infective therapy				Klinge, B; Gusta
Systemic antibiotics and the risk of superinfection in peri-implantitis	Included		Excluded	Systematic review		Verdugo, F; Lak
Assessment of periodontal and opportunistic flora in patients with peri-implantitis	Excluded	Out of context				Albertini, M; Lop
Local/Topical Antibiotics for Peri-Implantitis Treatment: A Systematic Review	Included		Excluded	Systematic review		Passarelli, PC; F
Efficacy of Local Minocycline Agents in Treating Peri-Implantitis: An Experimental In Vivo Stu	Included		Excluded	Animal subject		Yoon, SW; Kim,
A follow-up study of peri-implantitis cases after treatment	Excluded	After treatment				Charalampakis,
Clinical Evaluation of Three Surgical Modalities in the Treatment of Peri-Implantitis: A Random	Excluded	Surgical treatment				Tonsa, S; Bracx,
Microbiologic effect of two topical anti-infective treatments on ligature-induced peri-implantitis	Excluded	Animal subject				Ramos, UD; Sua
Non-surgical peri-implantitis treatment with or without systemic antibiotics: a randomized cont	Included				X	
Transcriptome-wide Gene Expression Analysis in Peri-implantitis Reveals Candidate Cellular P	Excluded	Gene expression analysis				Martin, A; Zhou,
The effectiveness of photodynamic and antibiotic gel therapy as an adjunct to mechanical del	Excluded				X	
Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A	Included				X	

Vancomycin and tobramycin impregnated mineralized allograft for the surgical regenerative tre	Excluded	Surgical treatment				Nart, J; Tapia, B
Implantoplasty associated with the regenerative treatment of peri-implantitis	Excluded	Implantoplasty				Austoni, C; Azzi
Systemic antibiotic therapy as an adjunct to non-surgical peri-implantitis treatment: A single-b	Included				X	
Adjunctive use of metronidazole-minocycline ointment in the nonsurgical treatment of peri-imp	Included				X	
Antibiotics as Adjunctive Therapy in the Non-Surgical Treatment of Peri-Implantitis: A System	Included		Excluded	Systematic review		Grusovin, MG; F
Surgical treatments of peri-implantitis	Excluded	Surgical treatment				Mombelli, A; Mo
Efficacy of adjunct subgingival minocycline delivery for treatment of peri-implantitis in modera	Included				X	
Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinica	Excluded				X	
The efficacy of interventions to treat peri-implantitis: a Cochrane systematic review of randor	Included		Excluded	Systematic review		Esposito, M; Gr
The effects of Lactobacillus reuteri probiotics combined with azithromycin on peri-implantitis:	Excluded				X	
Microbial Etiology and Antimicrobial Therapy of Peri-Implantitis: A Comprehensive Review	Included		Excluded	Comprehensive review		Hussain, MW; Al
Prevalence, Etiology and Treatment of Peri-Implant Mucositis and Peri-Implantitis: A Survey o	Included		Excluded	Survey of periodontists + out of c		Papathanasiou,
Antibiotic Resistance in Patients with Peri-Implantitis: A Systematic Scoping Review	Excluded	Antibiotic resistance				Ardila, CM and V
SUPPORTIVE THERAPY (SPT) CAN POTENTIALLY IMPROVE IMPLANT SURVIVAL RATE (SF	Excluded	Supportive therapy				Farsai, OS
Nonsurgical Treatment of Peri-Implantitis: Case Series	Included		Excluded	Case series		Dachkova, E; C
Electromagnetic irradiation may be a new approach to therapy for peri-implantitis	Excluded	Electromagnetic irradiation				Cao, ZS; Chen, '
Re-osseointegration after treatment of peri-implantitis at different implant surfaces - An experi	Excluded	Surgical treatment				Persson, LG; Be
The adjunctive use of light-activated disinfection (LAD) with FotoSan is ineffective in the treat	Excluded				X	
Efficacy of local antibiotic therapy in the treatment of peri-implantitis: A systematic review an	Included		Excluded	Systematic review		Toledano, M; Os
Definition, etiology, prevention and treatment of peri-implantitis - a review	Included		Excluded	Review		Smeets, R; Henr
The effectiveness of adjunctive light-activated disinfection (LAD) in the treatment of peri-impl	Excluded				X	
Isoeugenol-functionalized nanogels inhibit peri-implantitis associated bacteria in vitro	Excluded	In vitro				Shi, YT; Berga,
Brain abscess caused by dental peri-implantitis	Excluded	Brain abscess caused by peri-implantitis				Steiner, C; Battis
Nonsurgical Treatment of Peri-Implantitis Using the Biofilm Decontamination Approach: A Case	Excluded	Case report				Pini-Prato, G; Mi
Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review	Included		Excluded	Literature review		Renvert, S; Roo
Adjunctive local antibiotic therapy in the treatment of peri-implantitis - II: clinical and radiogra	Included		Excluded	Article		Salvi, GE; Pers
Management of peri-implantitis: a systematic review, 2010-2015	Included		Excluded	Systematic review		Mahato, N; Wu,
Current state-of-the-art and future perspectives of the three main modern implant-dentistry co	Excluded	Out of context				Lopez-Piriz, R; C
Maxillary Sinusitis Associated With Peri-implantitis at Sinus Floor Augmented Sites: Case Seri	Excluded	Maxillary sinusitis				Park, WB; Han,
Surgical treatment of peri-implantitis using enamel matrix derivative, an RCT: 3-and 5-year foll	Excluded	Surgical treatmet				Isehed, C; Sven
Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic th	Included				X	
Preparation and characterization of antibacterial and anti-inflammatory hyaluronic acid-chitosa	Excluded	Antibacterial and anti-inflammatory hyaluronic acid-chitosan-dexa				Zhou, Z; Zhang,

Prevalence and treatment of retrograde peri-implantitis: a retrospective cohort study covering	Included		Excluded	Its about radiolucency around the		Di Murro, B; Can
Therapy of peri-implantitis: a systematic review	Included		Excluded	Systematic review		Kotsovilis, S; Ku
Non surgical mechanical/pharmacological therapy of peri-implantitis: one year results	Included		Excluded	Article		Latronico, M; Ca
Surgical approach combining implantoplasty and reconstructive therapy with locally delivered	Excluded	Surgical treatment				Regueiro, IG; Ric
Implant surface characteristics influence the outcome of treatment of peri-implantitis: an expe	Excluded	Animal subject				Albouy, JP; Abri
Non-surgical therapy for the management of peri-implantitis: a systematic review	Included		Excluded	Systematic review		Muthukuru, M; Z
Peri-implantitis prevalence, incidence rate, and risk factors: A study of electronic health reco	Excluded	Prevalence, incidence rate, and risk factors				Changi, KK; Finl
Innovative Regeneration Technology to Solve Peri-implantitis by Er:YAG Laser Based on the I	Excluded	Out of context				Yoshino, T; Yam
Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial	Excluded	Out of context				Kotsakis, GA an
Adjunctive Systemic and Local Antimicrobial Therapy in the Surgical Treatment of Peri-implant	Included		Included			Carcuac, O; Der
Clinical, Microbiological, and Biochemical Impact of the Surgical Treatment of Peri-Implantitis	Excluded	Surgical treatment				Luenga, F; Solor
The Importance of Histopathological Diagnosis in the Management of Lesions Presenting as P	Excluded	Diagnosis				Kaplan, I; Hirshb
Resolution of peri-implantitis following treatment - An experimental study in the dog	Excluded	Animal subject				Persson, LG; Ar
Non-surgical therapeutic outcomes of peri-implantitis: 12-month results	Included		Excluded	Article		Nart, J; Pons, R
Peri-Implantitis: A New Definition Proposal Based on Unnatural Spatial Arrangement and Late	Excluded	Out of context			X	Ihde, S; Ihde, A
Microbiological and clinical effects of adjunctive systemic metronidazole and amoxicillin in the	Included		Excluded	Article		Shibli, JA; Ferra
Antibiotic Susceptibility of Cocultures in Polymicrobial Infections Such as Peri-Implantitis or P	Excluded	In vitro				Mouratidou, A; K
Primary prevention of peri-implantitis: Managing peri-implant mucositis	Excluded	Prevention				Jepsen, S; Berg
Efficacy of Antibiotics Used as an Adjunct in the Treatment of Peri-Implant Mucositis and Peri	Included		Excluded	Systematic review		Wang, Y; Chen,
Risk factors, diagnosis, and treatment of peri-implantitis: A cross-cultural comparison of US a	Included		Excluded	Survey of periodontists + out of c		Polymeri, A; Loo
A doxycycline-treated hydroxyapatite implant surface attenuates the progression of peri-implc	Excluded	Animal subject				Ding, L; Zhang, I
The Effect of Nonaugmentative Approaches in the Surgical Treatment of Peri-implantitis: A Sy	Excluded	Surgical treatment				Li, ZB; Li, K; (...
Hybrid system with stable structure of hard/soft tissue substitutes induces re-osseointegratio	Excluded	Animal subject				Xu, LY; Qin, X; ...
Surgical treatment of peri-implantitis intrabony lesions by means of deproteinized bovine bone	Excluded	Surgical treatment				Roccuzzo, M; Pi
Surgical reconstructive treatment for infraosseous peri-implantitis defects with a submerged h	Excluded	Surgical treatment				Wen, SC; Barsor
A systematic review and Bayesian network meta-analysis of randomized clinical trials on non-	Included		Excluded	Systematic review		Faggion, CM; Lis
Mechanical and repeated antimicrobial therapy using a local drug delivery system in the treatr	Included				X	
Antimicrobial therapy using a local drug delivery system (Arestin (R)) in the treatment of peri-i	Included		Excluded	Article		Persson, GR; Sa
Risk of Superinfection in Peri-Implantitis After Systemic Broad Spectrum Antibiotics	Excluded	Risk of superinfection after systematic broad spectrum antibiotic				Verdugo, F
Non-submerged reconstructive approach for peri-implantitis osseous defect, with removal of ir	Excluded	Surgical treatment				Wen, SC; Barsor
Combination of ultrasonic decontamination, soft tissue curettage, and submucosal air polishin	Excluded	Ultrasonic decontamination				Stein, JM; Hamm
Therapeutic use of antibiotics A review on local and systemic antibiotic therapy of peri-implan	Included		Excluded	Review		Begic, A; Obreja

Peri-Implantitis Management: Surgical versus Non-Surgical Approach Using Photodynamic The	Excluded	Photodynamic Therapy				Caccianiga, G; F
Osseointegration following treatment of peri-implantitis and replacement of implant components	Excluded	Animal subject				Persson, LG; Er
Shift in antibiotic prescription at a University Dental Clinic in Norway 2013-2017	Excluded	Shift in antibiotic prescription				Bolstad, AI; Sae
Long-term stability of surgical bone regenerative procedures of peri-implantitis lesions in a pre	Excluded				X	
Bioactive Healing Abutment as a Potential Tool for the Treatment of Peri-Implant Disease-in V	Excluded	In vitro				Iwanczyk, B; Wy
Peri-implantitis-like medication-related osteonecrosis of the jaw: Clinical considerations and hi	Excluded	Medication-related osteonecrosis				Tempesta, A; Co
The Application of Antimicrobial Photodynamic Therapy (aPDT) in the Treatment of Peri-Implar	Excluded	Photodynamic therapy				Zhao, TY; Song,
Specialists' management decisions and attitudes towards mucositis and peri-implantitis	Included		Excluded	Out of context		Matthaeos, N; Co
Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical trial	Excluded				X	
Implant survival after surgical treatment of peri-implantitis lesions by means of deproteinized I	Excluded	Surgical treatment				Roccuzzo, M; Pi
Identification of microbiota in peri-implantitis pockets by matrix-assisted laser desorption/ioniz	Excluded	Matrix-assisted laser desorption/ionization				Yeh, HC; Lu, JJ;
Treatment of peri-implantitis: what interventions are effective? A Cochrane systematic review	Included		Excluded	Cochrane systematic review		Esposito, M; Gn
Pneumocephalus as result of nonsurgical peri-implantitis treatment with an air-polishing device	Excluded	Pneumocephalus				Bruckmann, C; E
Two-year clinical outcomes following non-surgical mechanical therapy of peri-implantitis with a	Included	Adjunctive diode	Excluded	Diode laser application		Meltraux, GR; S
Five-year clinical, microbiological, and radiological outcome following treatment of peri-implanti	Included		Excluded	Its a surgical treatment + system		Leonhardt, A; Di
Complete regeneration of peri-implantitis-induced bony defects using guided bone regeneratio	Excluded	Surgical treatment				Elangovan, S
Therapeutic options in the treatment of peri-implant diseases	Included		Excluded	Article		Neuschl, M; Bec
Clinical, host-derived immune biomarkers and microbiological outcomes with adjunctive photoc	Included		Excluded	Diode laser + smokers		Al-Khureif, AA; M
INSUFFICIENT EVIDENCE ABOUT THE BENEFITS OF USING SYSTEMIC AZITHROMYCIN AS	Excluded	Open flap debriement				Brignardello-Petr
Electrophoretic-deposited MXene titanium coatings in regulating bacteria and cell response fo	Excluded	Electrophoretic-deposited MXene titanium coatings				Huang, S; Fu, Y
The impact of antimicrobial photodynamic therapy on peri-implant disease: What mechanisms	Excluded	Photodynamic therapy				Tavares, LJ; Par
Efficacy of alternative or adjunctive measures to conventional non-surgical and surgical treati	Included		Excluded	Systematic review		Ramenauskaite,
Surface decontamination protocols for surgical treatment of peri-implantitis: A systematic revi	Excluded	Surgical treatment				Baima, G; Citteri
An 11-Year Retrospective Research Study of the Predictive Factors of Peri-Implantitis and Im	Included		Excluded	Implant failure - out of context		Mayta-Tovalino,
A Two-Stage Surgical Approach to the Treatment of Severe Peri-Implant Defect: A 30-Month C	Excluded	Surgical treatment				Kim, JE; Kim, HY
Nonsurgical Treatment of Retrograde Peri-Implantitis: A Case Report	Included		Excluded	Case report - out of context		Waasdorp, J and
D-PLEX500: a local biodegradable prolonged release doxycycline-formulated bone graft for the	Excluded				X	
A review of dental implants and infection	Excluded	Dental implants and infection				Pye, AD; Lockh
In vitro Interactions between Streptococcus intermedius and Streptococcus salivarius K12 on	Excluded	In vitro				Vaccia, C; Contu
Using the Best Available Evidence to Support Clinical Decisions in Implant Dentistry	Excluded	Decisions in Implant Dentistry				Faggion, CM and
Microbiological Aspects of Human Mandibular Subperiosteal Dental Implants	Excluded	Microbiological Aspects of Human Mandibular Subperiosteal Dent				Rams, TE; Balkis
Peri-Implant Diseases: Diagnosis, Clinical, Histological, Microbiological Characteristics and Th	Included		Excluded	Narrative review		Komas, I; Peda

Evaluating the Knowledge of General Dentist Towards the Management of Peri-Implant Diseas	Included		Excluded	Survey of periodontists + out of c	Algahtani, AR; G
Management of Peri-Implant Diseases: A Survey of Australian Periodontists	Included		Excluded	Survey of periodontists + out of c	Khan, A and Shi
Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology	Included	Peri-implant dise	Excluded	Report	Lindhe, J and M
Peri-implant squamous cell carcinoma	Excluded	Squamous cell carcinoma			Ito, K; Takahasl
Effects of a novel gel containing 5-aminolevulinic acid and red LED against bacteria involved	Excluded	LED			Radunovic, M; P
The Antibacterial Activity of Hydroxyapatite-Tryptophan Complex with Gray Titania by Photoca	Excluded	LED			Leelanarathiwat,
Antibacterial efficacy of hubballi propolis against aggregatibacter actinomycetemcomitans one	Excluded	In vitro			Srinivas, S; Rav
Current treatment strategies for peri-implant diseases with antimicrobial photodynamic therapy	Excluded	Photodynamic therapy			Neugebauer, J; I
A single-centre randomized controlled clinical trial on the adjunct treatment of intra-bony defe	Excluded			X	
The patient undergoing implant therapy. Summary and consensus statements. The 4th EAO C	Included		Excluded	Review	Klinge, B; Flemn
Acute Prevertebral Abscesses Caused by Bacterial-Infected Traumatic Tooth Fractures	Excluded	Abscesses Caused by Bacterial-infected Traumatic Tooth Fractur			Matsunaga, K; T
Adhesive durability of bone cements containing gentamicin or gentamicin/clindamycin-based a	Excluded	Adhesive durability of bone cements			Muller, N; Schmi
Photodynamic Therapy for Peri-Implant Diseases	Excluded	Photodynamic therapy			Rahman, B; Ach
Long-term results after treatment of periodontitis in patients with Papillon-Lefevre syndrome: t	Excluded	Periodontitis			Nickles, K; Schu
Efficacy of air polishing for the non-surgical treatment of peri-implant diseases: a systematic	Excluded	Air polishing			Schwarz, F; Bec
Disinfection and Biocompatibility of Titanium Surfaces Treated with Glycine Powder Airflow an	Excluded	In vitro			Alovisi, M; Caro
5-aminolevulinic acid and LED against peri-implant disease	Excluded	LED			Petrini, M; Manc
Magnetic drug-loaded osteoinductive Fe3O4/CaCO3 hybrid microspheres system: efficient for	Included		Excluded	In vitro	Xue, JY; Li, XL;
EFFICACY OF A NEW CHEMICAL DEVICE TO MINIMIZE MICROBIAL CONTAMINATION ALON	Excluded	In vitro			Oberti, L; Gabric
Antibacterial effect of doxycycline-coated dental abutment surfaces	Included		Excluded	Not a RCT	Xing, R; Witos, I
Tetracycline impregnated bone grafts in the management of peri-implantitis and guided bone r	Excluded	Bone graft			Shrivastava, PK
Cost-effectiveness of non-surgical peri-implantitis treatments	Excluded	Cost-effectiveness			Listl, S; Fruehau
Antimicrobial Potential of Strontium Hydroxide on Bacteria Associated with Peri-Implantitis	Included		Excluded	In vitro	Alsharmani, H; I
Photodynamic Therapy by Mean of 5-Aminolevulinic Acid for the Management of Periodontitis	Excluded	Photodynamic therapy			Rossi, R; Rispoli
Laser Cleaning Improves Stem Cell Adhesion on the Dental Implant Surface during Peri-Implar	Excluded	Laser Cleaning			Furtsev, TV; Kot
Antibacterial Effects of Modified Implant Abutment Surfaces for the Prevention of Peri-Implant	Excluded	Prevention			Jennes, ME; Nic
The Treatment of Peri-implant Diseases: A New Approach Using HYBENX(R) as a Decontamin	Included		Excluded	Decontamination with Excluded -	Lopez, MA; Pas
Antibacterial Properties of Nano-Ag Coating on Healing Abutment: An In Vitro and Clinical Stu	Excluded	In vitro			Odatsu, T; Kuro
SUCCESSFUL BONE FILL IN LATE PERI-IMPLANT DEFECTS USING GUIDED TISSUE REGEI	Excluded	Surgical treatment			HAMMERLE, CH
Biofilm-mediated Antibiotic-resistant Oral Bacterial Infections: Mechanism and Combat Strateg	Included		Excluded	Article - out of context too	Kanwar, I; Sah,
Hydrogel-based therapeutic coatings for dental implants	Excluded	Hydrogel-based therapeutic			Alavi, SE; Panal
Microbiological Profiles of Dental Implants in Metabolic Syndrome Patients: A Case-Control St	Excluded	Out of context			Di Murro, B; Mor

Attitude in Radiographic Post-Operative Assessment of Dental Implants among Italian Dentist	Excluded	Out of context			Di Murro, B; Pap
Reconstruction of Peri-implant Osseous Defects: A Multicenter Randomized Trial	Excluded	Surgical treatment		X	
Topical minocycline microspheres versus topical chlorhexidine gel as an adjunct to mechanica	Included			X	
Design of Cefotaxime Sodium-Loaded Polydopamine Coatings with Controlled Surface Roughn	Included		Excluded	Article	He, F; Li, J; (...)
Microcalorimetric Determination of the Effects of Amoxicillin, Metronidazole, and Their Combin	Excluded	In vitro			Astasov-Frauent
Mechanical, chemical and laser treatments of the implant surface in the presence of marginal	Included		Excluded	Review	Meyle, J
The Effectiveness of Chlorhexidine and Air Polishing System in the Treatment of Candida albi	Excluded	In vitro			Passarelli, PC; D
COMBINATION THERAPY INCLUDING SERRATIOPEPTIDASE IMPROVES OUTCOMES OF MI	Included		Excluded	Not a RCT	Sannino, G; Gig
Antimicrobial mouthrinse use as an adjunct method in peri-implant biofilm control	Included		Excluded	Review	Pedrazzi, V; Esv
The use of antibiotics: data analysis of a survey among a sample of italian dentists	Included		Excluded	Survey of periodontists + out of c	Giargia, M; Scot
Efficacy of 0.05% Chlorhexidine and 0.05% Cetylpyridinium Chloride Mouthwash to Eliminate L	Excluded	In vitro			Becker, K; Brun
Managing Oral Health in the Context of Antimicrobial Resistance	Excluded	Out of context			Bessa, LJ; Bote
Physicochemical and Antibacterial Characterization of a Novel Fluorapatite Coating	Excluded	Out of context			Alhilou, A; Do, T
Systematic review on diabetes mellitus and dental implants: an update	Excluded	Diabetes			Wagner, J; Spill
Effects of Topical Antibiotic Prophylaxis on Wound Healing After Flapless Implant Surgery: A	Included			X	
Single-Dose Bioavailability for Prophylactic Coverage in Patients Undergoing Dental Implant S	Excluded	Prophylactic			Aravena, PC; Oj
Indications for Extraction before Implant Therapy: Focus on Endodontic Status	Excluded	Endodontic status			Sebring, D; Kvis
The overview of antimicrobial peptide-coated implants against oral bacterial infections Special	Included		Excluded	Review	Sun, Z; Ma, L; (.
Treatment of severe peri-implant bone loss using autogenous bone and a bioabsorbable polym	Excluded	Surgical treatment			Buchter, A; Klein
A novel histopathological classification of implant periapical lesion: A systematic review and t	Included		Excluded	Systematic review	Gong, JM; Zhao,
Development of Antibacterial Ti-Cu-x Alloys for Dental Applications: Effects of Ageing for Alloy	Included		Excluded	Out of context	Fevler, L; Mesia
Prevalence of antibiotic resistance genes in the oral cavity and mobile genetic elements that	Included		Excluded	Systematic review	Brooks, L; Narv
Interventions for replacing missing teeth: treatment of perlimplantitis	Included		Excluded	Systematic review	Esposito, M; Gn
Methods of Topical Administration of Drugs and Biological Active Substances for Dental Impla	Included		Excluded	Narrative review	Wychowanski, P
Osteomyelitis and pathological mandibular fracture related to a late implant failure: A clinical r	Excluded	Surgical treatment			O'Sullivan, D; Ki
Periodontists' Trends in the Management of Peri-Implant Diseases	Included		Excluded	Survey of periodontists + out of c	Dell'Olmo, F; Bla
In Vitro Invasion and Survival of Porphyromonas gingivalis in Gingival Fibroblasts; Role of the	Excluded	In vitro			Inshad, M; van d
Antibacterial and Anti-Inflammatory Properties of a Novel Antimicrobial Peptide Derived from L	Excluded	Out of context			Zhuo, HW; Zhan
Antibiotics in implant dentistry	Included		Excluded	Not a RCT	Al-Nawas, B and
Salt impregnation of implant materials	Excluded	Salt impregnation			Ewald, A and Ha
Implant Placement in Failed Endodontic Sites: A Review	Excluded	Endodontic study			Flanagan, D
A New Horizon in the Antibacterial Treatment of Oral Pathogens	Included		Excluded	Not a RCT + out of context	Shlezinger, M; K

Peri-implant Infection Concomitant with a Flare-up Episode of Chronic Periodontitis: An Unusu	Excluded	Out of context				Tewil, G and Tav
Antibacterial Properties of Charged TiN Surfaces for Dental Implant Application	Included		Excluded	Out of context (+ in vitro?)		Carey, PH; Ren,
Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot random	Excluded	Prophylaxis			X	
Microbial Composition of Oral Biofilms after Visible Light and Water-Filtered Infrared a Radiatic	Excluded	VIS plus wIRA				Burchard, T; Kar
Novel materials and therapeutic strategies against the infection of implants	Included		Excluded	Review		Agarwalla, SV; S
Biological factors contributing to failures of osseointegrated oral implants - (II). Etiopathogene	Excluded	Failures of osseointegrated				Esposito, M; Hir
Mandibular Osteomyelitis Following Implant Placement	Excluded	Mandibular osteomyelitis				Schlund, M; Rao
Osteogenic response and osteoprotective effects in vivo of a nanostructured titanium surfac	Excluded	Osteogenic response				Ravenetti, F; Ch
In vitro study of the effect of titanium on Porphyromonas gingivalis in the presence of metron	Excluded	In vitro				Bunetel, L; Guer
In Vitro antibacterial efficacy of tetracycline hydrochloride adsorbed onto Bio-Oss (R) bone gr	Excluded	In vitro				Dashti, A; Ready
Photodynamic therapy for periodontal diseases: State of the art	Excluded	Photodynamic therapy			X	
ORAL AND DENTAL INFECTIONS WITH ANAEROBIC-BACTERIA - CLINICAL-FEATURES, PRE	Included		Excluded	Not a RCT and its not about atb		TANNER, A and
Antibiotic resistance testing of the total implant-associated micro-flora and its pure isolates	Included		Excluded	In vitro		Karbach, J; Calli
Dental implant procedures in immunosuppressed organ transplant patients: a systematic revie	Excluded	Immunosuppressed organ transplant				Burtscher, D and
Antibacterial Property and Biocompatibility of Silver, Copper, and Zinc in Titanium Dioxide Lay	Excluded	Out of context				Shimabukuro, M
A systematic review of latest evidence for antibiotic prophylaxis and therapy in oral and maxil	Excluded	Prophylaxis				Blatt, S and Al-A
A decomposable silica-based antibacterial coating for percutaneous titanium implant	Included		Excluded	In vitro		Wang, J; Wu, Gl
Emerging Applications of Drug Delivery Systems in Oral Infectious Diseases Prevention and T	Included		Excluded	Not a RCT		Liang, JO; Peng
Effectiveness of Different Chemotherapeutic Agents for Decontamination of Infected Dental Ir	Excluded	Chemotherapeutic Agents for Decontamination of Infected Dental				Patil, C; Agrawal
An implantable antibacterial drug-carrier: Mesoporous silica coatings with size-tunable vertical	Included		Excluded	Not a RCT + very specific study,		Liu, ML; Huang,
Prevention of biofilm formation on titanium surfaces modified with conjugated molecules comp	Excluded	Prevention treatment				Yoshinari, M; Ka
Evaluation of biofilm colonization on multi-part dental implants in a rat model	Excluded	Animal subject				Blank, E; Grisch
Inflammatory Implant Periapical Lesion: Etiology, Diagnosis, and Treatment-Presentation of 7	Included		Excluded	Not a RCT + surgical treatment		Penarrocha-Diag
Improvements on biological and antimicrobial properties of titanium modified by AgNPs-loaded	Excluded	properties of titanium modified by AgNPs-loaded chitosan-heparin				Li, W; Yang, YW
Effect of systemic antibiotics on clinical and patient-reported outcomes of implant therapy - a	Included		Included	RCT but its a prophylactic study		Tan, WC; Ong, M
Antibacterial Effects of Curcumin Nanocrystals against Porphyromonas gingivalis Isolated fro	Included		Excluded	Not a RCT + in vitro		Dizaj, SM; Shoku
A Topical Desiccant Agent in Association with Manual Debridement in the Initial Treatment of I	Excluded	Mucositis			X	
What is the Role of Biofilms in Severe Head and Neck Infections?	Excluded	Head and neck infections				Ray, JM and Tri
Medication-Related Osteonecrosis of the Jaw with Spontaneous Hemimaxilla Exfoliation: Repc	Excluded	Medication-Related Osteonecrosis				Bennardo, F; Bu
Niche Specific Microbiota-Dependent and Independent Bone Loss around Dental Implants and	Excluded	Bone loss				Heyman, O; Hon
Biocompatible and Biomaterials Application in Drug Delivery System in Oral Cavity	Included		Excluded	Not a RCT + its about biomaterial		Hakim, LK; Yaco
A New Controlled-Release Material Containing Metronidazole and Doxycycline for the Treatmer	Excluded	In vitro				Nastri, L; De Ro

The In-Vitro Activity of a Cold Atmospheric Plasma Device Utilizing Ambient Air against Bacte	Excluded	In vitro				Jungbauer, G; F
Antibacterial investigation of titanium-copper alloys using luminescent Staphylococcus epiden	Excluded	Luminescent Staphylococcus epidermidi				Fowler, L; Jamso
Strategies to Reduce Biofilm Formation in PEEK Materials Applied to Implant Dentistry-A Com	Excluded	Prevention treatment				Brum, RS; Labe
Controlled release of metronidazole from composite poly-epsilon-caprolactone/alginate (PCL/a	Included		Excluded	In vitro		Lan, SF; Kehind
The effect of systemic antibiotics on clinical and patient-reported outcome measures of oral ir	Included		Included			Payer, M; Tan, V
Oral fungal-bacterial biofilm models in vitro: a review	Excluded	In vitro				Chevalier, M; Ra
Is Penicillin Allergy a Risk Factor for Early Dental Implant Failure? A Systematic Review	Included		Excluded	Systematic review		Salgado-Peralvo
Enzyme-Responsive Nanoparticles and Coatings Made from Alginate/Peptide Ciprofloxacin Co	Included		Excluded	Not a RCT		Bourgat, Y; Mikc
Long-term results of a three arms prospective cohort study on implants in periodontally comp	Excluded	Out of context				Roccuzzo, M; Bi
Implant Surface Detoxification: A Comprehensive Review	Excluded	Detoxification				Suarez, F; Monje
Ten-year results of a three arms prospective cohort study on implants in periodontally compr	Excluded	Out of context				Roccuzzo, M; Bi
Hydrophobicity of graphene as a driving force for inhibiting biofilm formation of pathogenic bac	Excluded					Agarwalla, SV; E
Antimicrobial treatment of peri-implant diseases	Included				X	
Antimicrobial Photodynamic Therapy of S. mutans Biofilms Attached to Relevant Dental Mater	Excluded	Photodynamic therapy				Zoccolillo, ML; R
Persistent inhibition of Candida albicans biofilm and hyphae growth on titanium by graphene n	Excluded	graphene nanocoating				Agarwalla, SV; E
Extracellular biofilm matrix leads to microbial dysbiosis and reduces biofilm susceptibility to a	Excluded	In vitro				Costa, RC; Souz
Antimicrobial photodynamic therapy alone or in combination with antibiotic local administration	Included		Excluded	In vitro		Tavares, LJ; de
Odontogenic sinusitis in immunosuppressed patient: a clinical case and literature review	Excluded	Odontogenic sinusitis				Bacci, C; Prosse
Guided bone regeneration in the treatment of periimplantitis	Excluded	Surgical treatment				Persson, LG; Er
The effect of antimicrobial therapy on periimplantitis lesions - An experimental study in the do	Excluded	Animal subject				Ericsson, I; Pers
In vitro activity of the antiasthmatic drug zafirlukast against the oral pathogens Porphyromon	Excluded	In vitro				Gerits, E; Van d
Interventions for replacing missing teeth: treatment of periimplantitis	Included				X	
The Impact of Incorporating Antimicrobials into Implant Surfaces	Included		Excluded	In vitro		Hickok, NJ; Sha
Antimicrobial and Antibiofilm Coating of Dental Implants-Past and New Perspectives	Included		Excluded	Review		Esteves, GM; Es
Effects of systemic administration of staffaxacin on subgingival microflora and antimicrobial s	Included		Excluded	Not a RCT		Tomita, S; Kasai
CLINICAL, MICROBIOLOGICAL AND INFLAMMATORY EVIDENCE OF THE EFFICACY OF COI	Included		Included			Passanello, C; L
In Vitro Evaluation of Antimicrobial Activity of Minocycline Formulations for Topical Applicatior	Excluded	In vitro				Schmid, JL; Kirs
Clindamycin in dentistry: More than just effective prophylaxis for endocarditis?	Excluded	Prophylaxis				Brook, I; Lewis,
Immediate placement of dental implants into debrided infected periodontal sockets	Excluded	Out of context				Casap, N; Zeltsi
An ionic silver coating prevents implant-associated infection by anaerobic bacteria in vitro an	Excluded	In vitro				Soma, T; Iwasak
Immediate Placement of Implants into Infected Sites: A Systematic Review	Excluded	Out of context				Chrcanovic, BR;
Photodynamic Therapy has no Adverse Effects In Vitro on Human Gingival Fibroblasts and Or	Excluded	In vitro				Azarpour, A; Az

Immediate Placement of Implants Into Infected Sites: A Systematic Review of the Literature	Excluded	Out of context				Waasdorp, JA; E
Effect of Copper Ion Concentration on Bacteria and Cells	Excluded	Out of context				Fowler, L; Engov
Radiolucent Inflammatory Implant Periapical Lesions: A Review of the Literature	Excluded	Radiolucent Inflammatory Implant Periapical Lesions				Feller, L; Jadwat
Chitosan Coatings Deliver Antimicrobials From Titanium Implants: A Preliminary Study	Excluded	Out of context				Norowski, PA; C
Effect of PRF and Allograft Use on Immediate Implants at Extraction Sockets with Periapical I	Excluded	PRF and allograft				Medikeri, RS; Mi
Clinical and Microbiological Evaluation of Local Doxycycline and Antimicrobial Photodynamic T	Included		Included			Cosgarea, R; Ex
One-Year Clinical, Microbiological and Immunological Results of Local Doxycycline or Antimicr	Included		Included			Cosgarea, R; Ra
The Antimicrobial Effect of Cold Atmospheric Plasma against Dental Pathogens-A Systematic	Excluded	In vitro				Jungbauer, G; M
In vivo evaluation of an antibacterial coating containing halogenated furanone compound-load	Excluded	Out of context				Cheng, YC; Gao
New approaches to combat Porphyromonas gingivalis biofilms	Excluded	Gingivalis				Gerits, E; Verst
Infections associated with implantable biomaterials	Excluded	Out of context				Pokrowiecki, R;

Additional file 3

	Authors	Nº of Patients / implants		F. up (months)	Tretament		Treatement sucess (%)		PPD reduction (mm)	
		Control	Test		Control	Test	Control	Test	Control	Test
1	André Büchte	14	14	4	MD	MD + DOX	-	-	0,28 (0,44)	1,15 (0,43)
2	Stefan Renve	14	16	12	MD + CHX	MD + MINm	-	-	0,00 (0,50)	0,30 (0,92)
3	Stefan Renve	15 (57)	15 (38)	12	MD + CHX	MD + MINm	-	-	0,15 (1,54)	0,30 (1,43)
4	C. PASSARIEL	64 (64)	64 (64)	6	MD + atb	MD + atb + serrap	78,1	96,9	3,30 (1,86)	3,82 (1,20)
7	Jamil Awad Sl	20	20	12	MD + P	MD + MTZ + AMX	50	65	1,7 (1,7)	3,1 (2,7)
10	Yvonne C M D	29 (64)	28 (68)	3	MD + CHX	MD + MTZ/AMX	-	-	1,40 (0,80)	1,67 (0,82)
11	Seung-Hyun F	37 (37)	38 (38) 39 (39)	3	MD	MD + MTZ + MIN MD + MIN	2,7	31,6 20,5	1,28 (1,15)	1,95 (1,28) 1,88 (1,50)
12	Carlota Blanc	16 (34)	16 (28)	12	MD + P	MD + MTZ	25	56,3	0,89 (2,63)	2,44 (2,73)
13	Angeliki Polyr	19	18	3	MD + CHX	MD + CHX + MTZ + AMX	5,26	5,56	1,47 (1,95)	2,28 (1,49)
16	A A Alhumaid	12 (12) 12(I2)	12(12) 12 (I2)	6	MD	MD + MIN	-	-	1,6 (0,31) 2,72 (0,31)	1,7 (0,45) 2,1(0,41)

PPD reduction (mm)		PPD (INICIAL)		PPD (FINAL)		BOP reduction (%)		DBL (mm)	
Control	Test	Control	Test	Control	Test	Control	Test	Control	Test
0,28 (0,44)	1,15 (0,43)	5,68 (0,28)	5,64 (0,32)	5,40 (0,34)	4,49 (0,29)	50 (7)	27 (6)	-	-
0,00 (0,50)	0,30 (0,92)	3,90 (0,30)	3,90 (0,70)	3,90 (0,40)	3,60 (0,60)	8 (19)	17 (25)	-	-
0,15 (1,54)	0,30 (1,43)	3,87 (1,16)	3,85 (1,04)	3,72 (1,02)	3,55 (0,98)	25,7 (25,8)	38,4 (28,8)	_0,05 (1,03)	0,07 (1,20)
3,30 (1,86)	3,82 (1,20)	6,55 (0,87)	6,30 (0,95)	3,25 (1,64)	2,48 (0,73)	1,02 (0,80)	1,50 (0,81)	1,19 (1,71)	1,96 (1,42)
1,7 (1,7)	3,1 (2,7)	5,50 (1,30)	7,0 (2,6)	3,80 (1,10)	3,9 (0,8)	44,7 (35,4)	51,0 (41,5)	-	-
1,40 (0,80)	1,67 (0,82)	5,82 (1,42)	5,63 (1,24)	4,42 (1,38)	3,96 (1,21)	39,20 (32,31)	38,59 (29,60)	_ 0,04 (0,20)	_ 0,06 (0,17)
1,28 (1,15)	1,95 (1,28) 1,88 (1,50)	5,82 (1,39)	5,71 (1,33) 6,22 (1,92)	-	-	33 (41)	51 (32) 50 (34)	-	-
0,89 (2,63)	2,44 (2,73)	5,89 (1,45)	7,29 (2,24)	4,87 (1,78)	5,16 (1,38)	20,50%	39,10%	-	-
1,47 (1,95)	2,28 (1,49)	8,00 (1,41)	7,44 (1,38)	6,53 (2,59)	5,17 (1,92)	-	-	_ 1,33	_ 2,33
1,6 (0,31) 2,72 (0,31)	1,7 (0,45) 2,1(0,41)	6,02 (0,30)	5,60 (0,40)	3,30 (0,08)	3,50 (0,10)	-	-	-	-

Mean age			Latitude	Region	Average time in funciton (years)			Type of treatment (local or systemic)
Control	Test	Total			Control	Test	Total	
56	54	55	51° 57' 44.50"	Munster, Gern	-	-	5,2 (2,1)	Local
61,1 (8,6)	65,6 (8,6)	-	56° 01' 52.64"	Kristianstad, S	-	-	11	Local
62,40 (7,72)	60,82 (12,72)	-	57° 42' 25.78"	Goterbord, Sw	-	-	11	Local
36,6 (6,6)	38,2 (7,4)	37,4 (7,0)	45° 32' 8.09" N	Brescia, Italy	-	-	-	Systemic
-	-	58,5 (11,1)	_23° 32' 51.00	São Paulo, Bra	-	-	60,5 (6,3)	Systemic
53,5 (11,2)	60,0 (10,4)	-	53° 13' 9.01" N	Groningen, Th	8,9 (5,9)	8,0 (4,3)	-	Systemic
61,2	60,7 61,2	61,1	37° 33' 57.60"	Seoul, Republi	9	8,7 9,0	9	Local
60,74	58,31	-	42° 52' 49.87"	Santiago de Cc	-	-	-	Systemic
60,8 (14,8)	58,3 (13,9)	-	52° 22' 26.51"	Amesterdam,	-	-	>1	Systemic
52,2 55,1	56,1 52,8	-	40° 42' 59.99"	New York, USA	3,8 (0,4) 4,2 (0,6)	4,1 (0,6) 4,7 (0,2)	-	Local