Journal of Dentistry 113 (2021) 103790

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent

Review article

Efficacy of local antibiotic therapy in the treatment of peri-implantitis: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Anti-bacterial agents
Bleeding on probing
Peri-implantitis
Probing pocket depth

ABSTRACT

Objectives: The aim of this systematic review and meta-analysis was to state the efficacy of local administration of antibiotics in the treatment of peri-implantitis in terms of peri-implant probing depth (PPD) and bleeding on probing (BoP) reduction.

Data, sources and study selection: Electronic and manual literature searches were conducted. Screening process was done using the National Library of Medicine (MEDLINE by PubMed), Embase and the Cochrane Oral Health. Included articles were randomized controlled trials and observational studies. Weighted means were calculated. Heterogeneity was determined using Higgins (I2). Due to the encountered heterogeneity between the studies being combined, random-effects models were applied in order to analyze effect sizes. Twelve studies (365 patients and 463 implants) were included in the systematic review. After peri-implantitis treatment with local antibiotics, PPD was reduced 1.40 mm (95% confidence interval: 0.82-1.98). When local antibiotics were applied, a 0.30 mm higher reduction of PPD was obtained than in the control group (95% confidence interval: 0.07-0.53). BoP attained an odds ratio value of 1.82 (95% confidence interval: 1.09-3.04), indicating that the likehood of bleeding is almost two-fold when antibiotics are not locally administrated. Adverse effects were not found after applying local antibiotics.

Conclusions: The local antibiotic administration does reduce, without adverse effects, both peri-implant probing depths and bleeding on probing in patients affected by peri-implantitis, if compared to control groups without local antibiotic application.

Clinical significance: Patients with dental implants frequently suffer from peri-implantitis. Clinical features of peri-implantitis lesions include the presence of bleeding on probing and increased peri-implant probing depths. Both BoP and PPD have become reduced after local administration of antibiotics.

1. Introduction

Dental implants have been widely used as rehabilitation therapy for fully or partially edentulous ridges. However, the inflammatory conditions of tissue around implants often leads to peri-implant diseases, including peri-implant mucositis and peri-implantitis (PI) [1,2]. With the increasing popularity of dental implants, PI has been considered as a worldwide health challenge. PI is expected to affect 63.4% of all patients and 30.7% of all functional dental implants [3]. It is expected that the cases of PI will highly increase in the future due to the growing tendency to replace lost teeth with implants as a common clinical alternative [4].

PI has been defined as "a plaque-associated pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone" [5,6], which can lead to the implant loss [7]. Thereby, PI has been characterized as irreversible infectious pathological condition [2]. The causes of PI are multi-factorial. Poor oral hygiene, history of periodontal disease, and smoking are known to be the risk factors contributing to PI [4]. Those risk factors are generally gathered under four categories: excessive mechanical stress, lesions of peri-implant attachment, corrosion and presence of aggressive bacteria. PI is considered as a disease with an important infectious component which affects the tissues around of the dental implant. Titanium in combination with bacteria products can aggravate inflammation, by foreign body

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https://doi.org/10.1016/j.jdent.2021.103790
Received 26 April 2021; Received in revised form 1 August 2021; Accepted 20 August 2021
Available online 27 August 2021

response [7]. Clinical characteristics of peri-implantitis involve the increase in peri-implant probing depths (PPD) and/or mucosal recession; bleeding on probing (BoP) and/or suppuration on probing and, if compared to previous examinations, radiographic marginal bone loss [5]. BoP and PPD have been the two clinical features of PI more widely reported.

The re-osseointegration with newly formed bone at the exposed implant surface is considered the ultimate target of PI treatment [8]. From a therapeutic viewpoint, decontamination of implants surface and resolution of inflammation represent the main goals in the treatment of PI [9]. Non-surgical therapy has not been to be effective, and surgical treatment protocols that include bone grafting have also shown limited predictability [4]. There is a wide variety of current biomaterials, different in nature, to prevent or treat PI. All of them pursue to develop antibacterial properties and bone regeneration [10]. Various approaches have been suggested for the treatment of PI diseases, but not consensus on clinical protocols has been achieved [2]. In accordance with the cause-related concept of therapy, plaque removal administered by a professional is considered a key strategy to prevent and manage peri-implant diseases [11,12]. In previous years, it has been proposed several alternative or adjunctive measures (*e.g.* air-abrasive systems [13], dental laser application [14] or local antibiotics [15] have been proposed to improve the effectiveness of nonsurgical treatment approaches [16–18], but some of them have demonstrated scarce evidence in clinical efficacy [8,19].

Antibiotics have been regarded beneficial in clinical management, intra-oral biofilm control and radiographic bone fill in PI as an adjuvant. Nevertheless, systemic antibiotics are commonly associated with undesirable side effects such as dysbacteriosis, antibiotic-resistance [2] and gastrointestinal problems [20]. Clinical and microbiological improvements of PI lesions were observed after adjunctive delivery of local resorbable antibiotics and chlorhexidine gel [9,21], but severe allergic reactions such as sensitivity or oral pain appeared within the use of chlorhexidine [22]. Local application of antibiotics and other antimicrobials (metal and hydroxyapatite nanoparticles) is effective at short-term [19,23]. Minocycline hydrochloride-loaded graphene oxide films have been applied on implant abutment surfaces in order to prevent PI; they have shown excellent antibacterial activity, but results about bone gain are absent [24]. In general terms, the antibacterial agents to prevent the biofilm formation may jeopardize the osteogenic role of osteoblasts [25].

Due to the pivotal role of bacterial plaque accumulation in the pathogenesis of PI, it becomes obvious the need for implant debridement and/or decontamination to remove pathogenic bacterial flora [26]. The adjunctive treatment with antibiotics may have a positive effect on treatment outcomes, but it confounds the efficacy of any given therapy. The advantages of local administration of antibiotics have been investigated, which permit high concentrations to be maintained in a peri-implant bone defect, having reduced both PPD and BoP [8]. Hence, the aim of this systematic review was therefore to address the following focused question: In patients requiring peri-implantitis treatment, what efficacy of local antibiotic administration, in terms of probing pocket depth and bleeding on probing reduction, could be expected?

2. Material and methods

2.1. Protocol and registration

The study protocol was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The developed protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO), database hosted by the National Institute for Health Research, University of York, Center for Reviews and Dissemination (www.crd.york.ac.uk/PROSPERO) (ID: CRD42021241395).

2.2. Focused question

The focused question was carried out according with the PICO format: In patients requiring peri-implantitis treatment, what efficacy of local antibiotic administration, in terms of probing pocket depth and bleeding on probing reduction, could be expected?

The PICOs elements were as follows:

Population (P): Inclusion: Healthy patients, older than 18 years, with at least one implant with a probing pocket depth higher than 4 mm and bleeding on probing that needs peri-implantitis treatment with a clinical follow-up above 4 months post-operative.

Intervention (I): Peri-implantitis treatment performed without local antibiotic therapy with pre and post-operative clinical evaluation.

Comparison (C): Pocket probing depth and bleeding on probing, at implant site, before and after (at least 4 months) peri-implantitis treatment.

Outcome (O): Outcomes measuring changes in clinical parameters including PPD and BoP.

Study (S): randomized controlled trials (-RCTs-) and observational studies (cohort and case-control studies and case series).

2.3. Search strategy

PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for eligible articles published between January 2001 and March 2021. Only studies published in English were considered. Reference lists of the previous reviews and included studies were analyzed trying to search for relevant manuscripts that were missing after the electronic screening. Bibliographies of eligible articles were manually searched.

The following search terms were used: ((“periimplantitis” OR “peri-implantitis” [MeSH Terms] OR “peri-implant infection” OR “peri-implant disease*” OR “peri-implant bone loss” OR “periimplant mucositis” OR “peri-implant mucositis” OR “periimplant” OR “peri-implant” OR “dental implant inflammation”) OR “bone loss” OR “bone resorption” OR “attachment loss” OR “bone defect”)) AND (“drug delivery” OR “drug compounding” OR “drug implants” OR “local drug treatment” OR “drug release” OR “drug treatment” OR “medication” OR “local drug administration” OR “antibacterial agents” OR “bactericides” OR “antimicrobial” OR “antibiotics” OR” anti-infective agents” OR “antibiotic prophylaxis” OR dental implant” OR “anti-microbial” OR “anti-infective”)).

2.4. Eligibility: inclusion and exclusion criteria for studies

Inclusion of an article was based on the following inclusion criteria:

- For clinical studies, publications of adult subjects in good general health and at least four-month follow-up period.
- Studies performing an explicit diagnosis of peri-implantitis.
- Studies assessing the effectiveness by comparing changes in clinical parameters including PPD reduction and BoP reduction.

2.5. Study selection

Electronic and manual literature searches were conducted by 2 independent reviewers (RO, MT), who selected eligible studies by reviewing the list of titles and abstracts and considering the inclusion and exclusion criteria. The complete articles sourced *via* eligible titles and abstracts were obtained and examined independently to determine eligibility. Discrepancies between these reviewers pertaining to the selection and inclusion of any specific paper were discussed until either a consensus was reached, or a third reviewer (MTO) determined inclusion or exclusion. All reports excluded at this stage were formally recorded, as well as the reason/s for their exclusion.

Data extraction and risk-of bias were assessed by two investigators

(MTO and MVR) in duplicate and thereafter discussed to find an agreement. In case of disagreement, the judgment of a third reviewer (MT) was decisive. Following data were extracted: 1) authors and year of publication; 2) study design; 3) number of patients and implants; 4) peri-implantitis treatment; 5) antibiotic and dosage; 6) delivery vehicle; 7) follow-up time, 8) BoP reduction and 9) PPD reduction.

Additionally, data concerning sample size, age of participants, PI clinical criterion, number of sites measured per implant, microbiological evaluation, biomarkers measurement in gingival fluid, systemic or radiological outcomes and adverse effects were also registered.

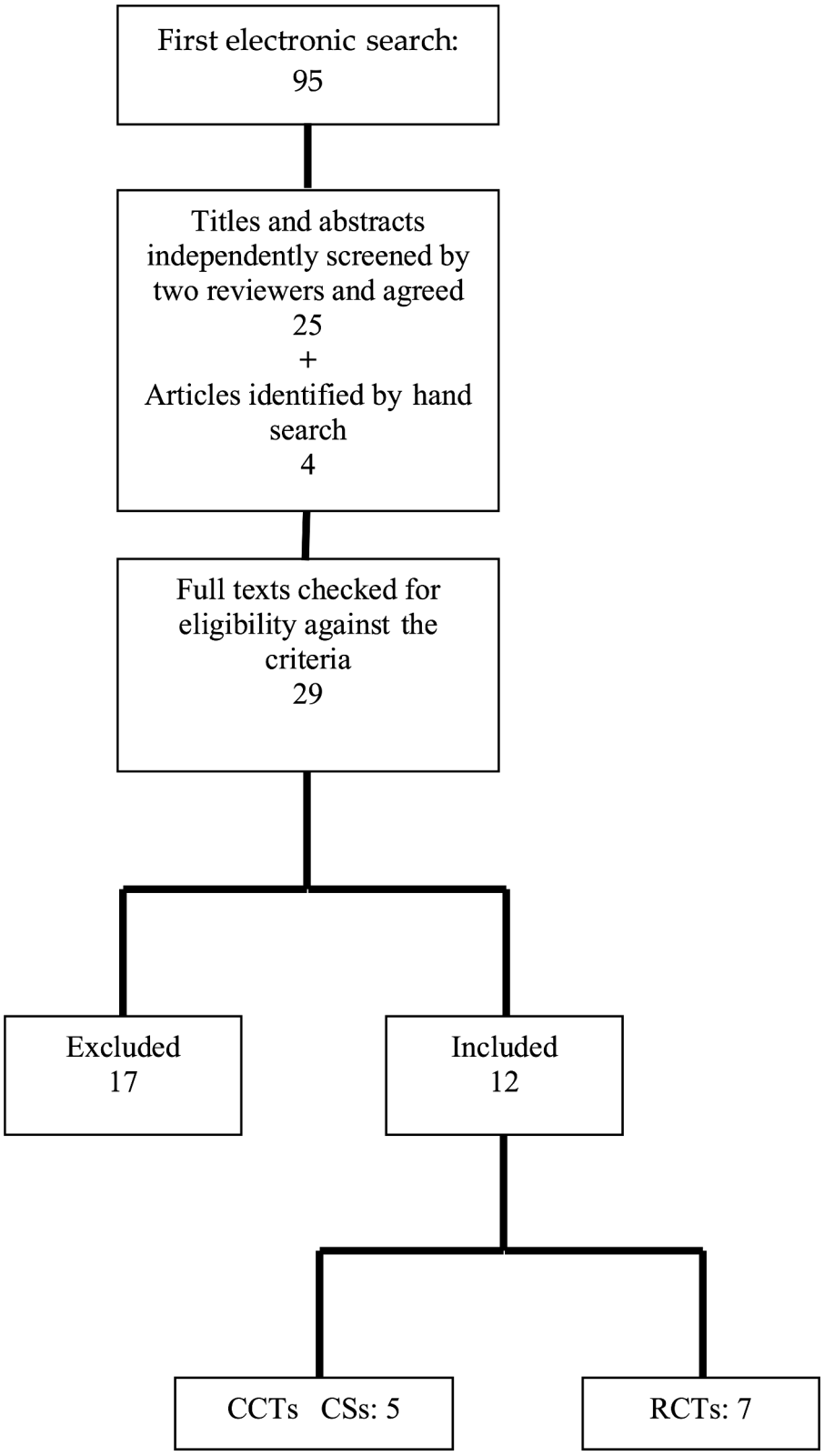

Fig. 1. Flowchart of the manuscripts selection and inclusion undertaken in the systematic review. CCTs: Controlled Clinical Trials; CSs: Case Series; RCTs: Randomized Clinical Trials.

The study quality and designs were evaluated according to: i) The Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins Scale) [27]. Studies were considered as having a high, unclear or low risk of bias; ii) The Joanna Briggs Institute Critical Appraisal tool for the included non-randomized studies. Studies were considered as having a high, medium or low risk of bias [28].

2.6. Data analyses

Descriptive statistics were used to present the primary outcome: PPD [in terms of probing pocket depth (mm) reduction] and BoP (in terms of percentage of implants with bleeding on probing reduction). For PPD reduction, weighted means (CI 95%) were calculated, including total sample size, inverse variance and standard error of the treatment effect. For BoP reduction, odds ratio (OR) (CI 95%) was calculated using chi-square test [Mantel-Haenszel (M-H)]. Heterogeneity was determined using Higgins (I^2). Due to the encountered heterogeneity between the studies being combined, random-effects models were applied in order to analyze effect sizes. Statistical significance was set at 0.05. Data were analyzed with RevMan 5.4 (The Cochrane Collaboration, Oxford, UK). Funnel plot was produced by MedCalc 18.2.1 (MedCalc Software Ltd. Ostend, Belgium) to represent systematic heterogeneity.

3. Results

3.1. Search results

The electronic search was performed in March 2021, resulting in 95 articles. After duplicate removal and the reading of titles and/or abstracts, 25 articles were selected. Manual search permits to identify 4 more manuscripts. Then the full-text of all the selected articles was reviewed for the inclusion criteria. 17 articles were excluded after full reading. 12 articles were then included in the final selection. A flowchart of the selection and inclusion method undertaken in the meta-analysis

Table 1
General overview of the included studies, investigating as primary outcomes BoP and PPD reduction in the treatment of peri-implantitis, when using local antibiotics.

Author	Study design	Patients and implants	Test group	Control group	Delivery vehicle	Follow-up	BoP reduction (percentage)	PPD reduction Mean±SD (mm)
Bassetti *et al.* 2014 [9]	RCT	38 patients 38 implants	Minocycline (*Arestin*) (n=19)	PDT *(HELBO)* (n=19)	Test: Microspheres	12 months	Control: 57.0% Test: 65.0%	Control: 0.11±0.63 Test: 0.56±0.70
Schär *et al.* 2013 [19]	RCT	40 patients 40 implants	Minocycline (*Arestin*) (n=20)	PDT (*HELBO)* (n=20)	Test: Microspheres	6 months	Control: 63.0% Test: 52.0%	Control: 0.36±0.48 Test: 0.49±0.66
Cha *et al.* 2019 [8]	RCT	46 patients 46 implants	Minocycline *(Periocline)* (n=24)	Placebo (n=22)	Control: Ointment Test: Ointment	6 months	Control: 31.0% Test: 49.0%	Control: 1.55±1.86 Test: 2.68±1.73
Emanuel *et al.* 2020 [4]	RCT	27 patients 32 implants	Doxycycline *(D-Plex $_{500}$)* (n=18)	SRP alone (n=14)	Test: Bone graft	12 months	Control: 15.2% Test: 36.3%	Control: 0.96±1.70 Test: 2.40±1.16
Renvert *et al.* 2008 [34]	RCT	32 patients 95 implants	Minocycline *(Arestin)* (n=58)	Chlorhexidine (n=37)	Control: Gel Test: Microspheres	12 months	Control: 25.7% Test: 38.4%	Control: 0.15±0.94 Test: 0.30±0.87
Büchter *et al.* 2004 [21]	RCT	28 patients 48 implants	Doxycycline *(Atridox)* (n=24)	SRP alone (n=24)	Test: Gel	4 months	Control: 13.0% Test: 27.0%	Control: 0.56±0.30 Test: 1.15±0.23
Renvert *et al.* 2006 [33]	RCT	30 patients 30 implants	Minocycline *(Arestin)* (n=16)	Chlorhexidine *(Corsodyl)* (n=14)	Control: Gel Test: Microspheres	12 months	Control: 8.0% Test: 17.0%	Control: 0.00±0.31 Test: 0.30±0.56
Mercado *et al.* 2018 [29]	PS	30 patients 30 implants	Doxycycline (n=30)		Test: Powder	12 months	Test: 50.0%	Test: 5.35±1.63
Diachkova *et al.* 2020 [30]	CS	3 patients 5 implants	Doxycycline *(Ligosan)* (n=2) Lincomycin (n=1) Erythromycin (n=2)		Test: Gel	6 months	Test: 100%	Test: 1.03±1.05
Mombelli *et al.* 2001 [49]	CCS	23 patients 27 implants	Tetracycline *(Actisite)* (n=27)		Test: Fibers	12 months	Test: 37.0%	Test: 1.19±1.03
Salvi *et al.* 2007 [32]	CCS	21 patients 25 implants	Minocycline (Arestin) (n=25)		Test: Microspheres	12 months	Test: 50%	Test: 1.00±1.01
Al-Khureif *et al.* 2020 [31]	CCS	47 patients 47 implants	Metronidazole (Elyzol) (n=24)	PCT (n=23)	Test: Gel	12 months	Control: 2.7% Test: 3.6%	Control: 0.65±0.74 Test: 0.68±0.50

PPD: Pocket Probing Depth; BoP: Bleeding on Probing; SD: Standard Deviation; RCT: Randomized Clinical Trial; PS: Prospective Study; CS: Case Series; CCS: Cohort/Case-Control Study; PDT: Photodynamic Therapy; SRP: Scaling and Root Planing; PCT: Photochemotherapy.

process, based on PRISMA recommendations, is presented in Fig. 1. The extracted data for each reviewed article are shown in Table 1.

3.2. Studies quality assessment and bias risk

The quality assessment and bias risk of the selected papers are summarized in Fig. 2. Most of the selected studies are classified as low or moderate risk of bias.

3.3. Outcomes: PPD reduction and BoP reduction

Twelve studies (365 patients and 463 implants) analyzed both the PPD reduction and BoP reduction. Main study characteristics are displayed in Table 1. Due to incomplete outcome data, the study from Büchter et al. [21] was excluded from the meta-analysis. Therefore, eleven studies (337 patients and 415 implants) were finally included in the meta-analysis.

The mean of additional PPD reduction in experimental groups, if compared to control groups, was 0.30 mm, ranging from 0.07 to 0.53 mm (CI 95%). Heterogeneity was slightly high I^2=45% (CI 95%), but the random-effects model was highly significant P=0.01. When only the experimental group (with local antibiotics application) was considered, the PDD reduction attained a mean of 1.40 mm ranging from 0.82 to 1.98 (CI 95%). Heterogeneity was high I^2=97% (CI 95%) and significance of the random-effects model was also highly significant P<0.001. PPD forest plot graphs are displayed in Fig. 3a and b. Systematic heterogeneity is displayed at the funnel plot graph (Fig. 4).

The mean of BoP reduction, when comparisons were established between both experimental and control groups, attained an odds ratio of 1.82, ranging from 1.09 to 3.04 (CI 95%), indicating that the likehood of bleeding on probing, after treatment, is almost twofold when antibiotics are not locally administrated. Heterogeneity was not found (I^2=0%) and significance of the fixed-effect model was P=0.02. BoP forest plot graph is displayed in Fig. 5. Systematic heterogeneity is displayed at the funnel plot graph (Fig. 6).

4. Discussion

To the best of our knowledge, it is the first systematic review conducted to identify the effectiveness of local antibiotic application in the treatment of peri-implantitis. The aim of this systematic review and meta-analysis was to obtain the most reliable scientific information regarding the efficacy of local antibiotic administration, in terms of probing pocket depth and bleeding reduction on probing.

A great variety of results interpreted as treated peri-implantitis does exist. Trying to gain in homogeneity, only studies that counted with PPD and BoP reduction were included in this review. The present systematic review and meta-analysis supports that the local antibiotic administration did reduce both PPD and BoP in patients affected by peri-implantitis.

Twelve studies were included, from which 7 were randomized clinical trials. Case series, prospective and case cohorts were also comprised

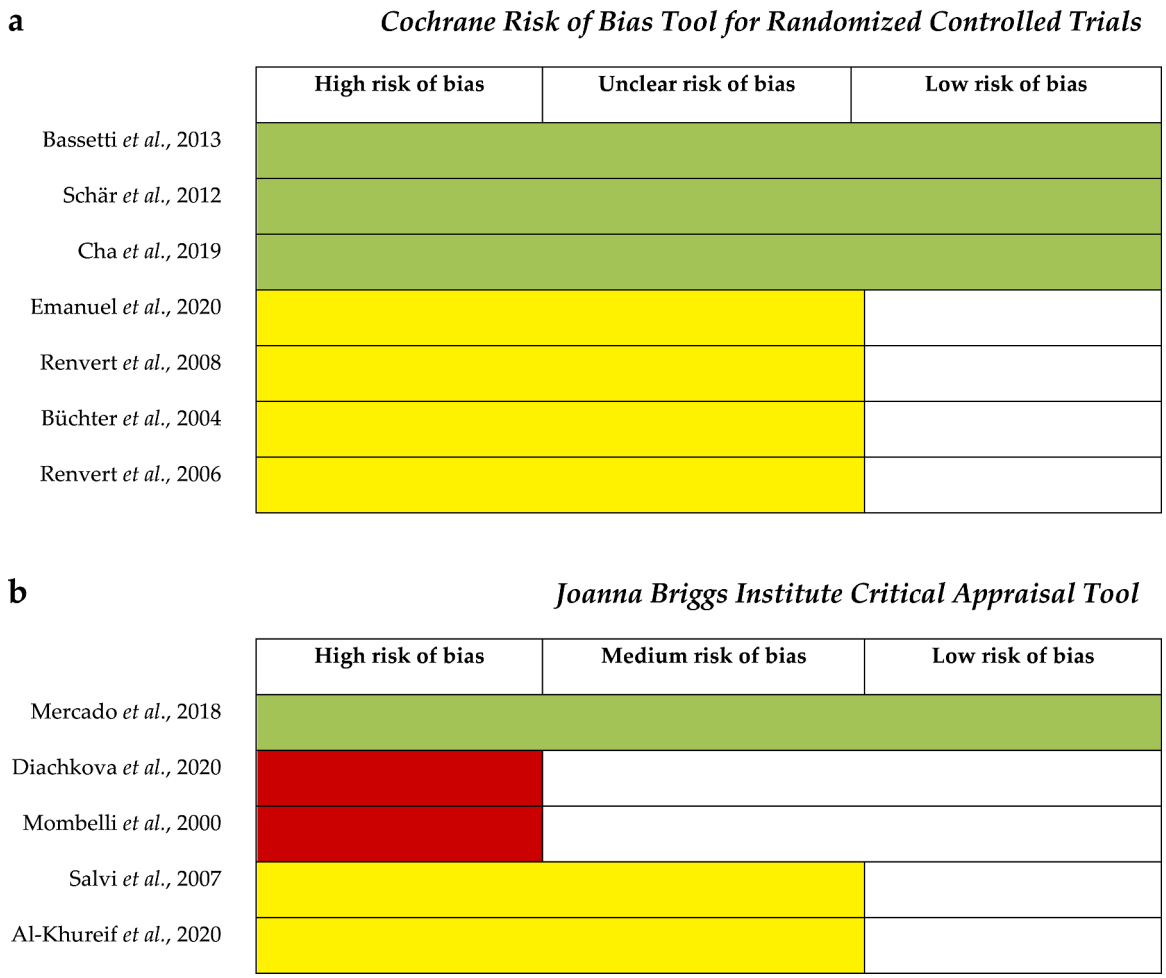

Fig. 2. Studies quality assessment and bias risk following Cochrane Risk of Bias Tool for randomized controlled trials. Studies were considered as having a low (green), unclear (yellow) or high (red) risk of bias. The Joanna Briggs Institute Critical Appraisal tool was used for included non-randomized studies. Studies were considered as having high (red), medium (yellow) or low (green) risk of bias.

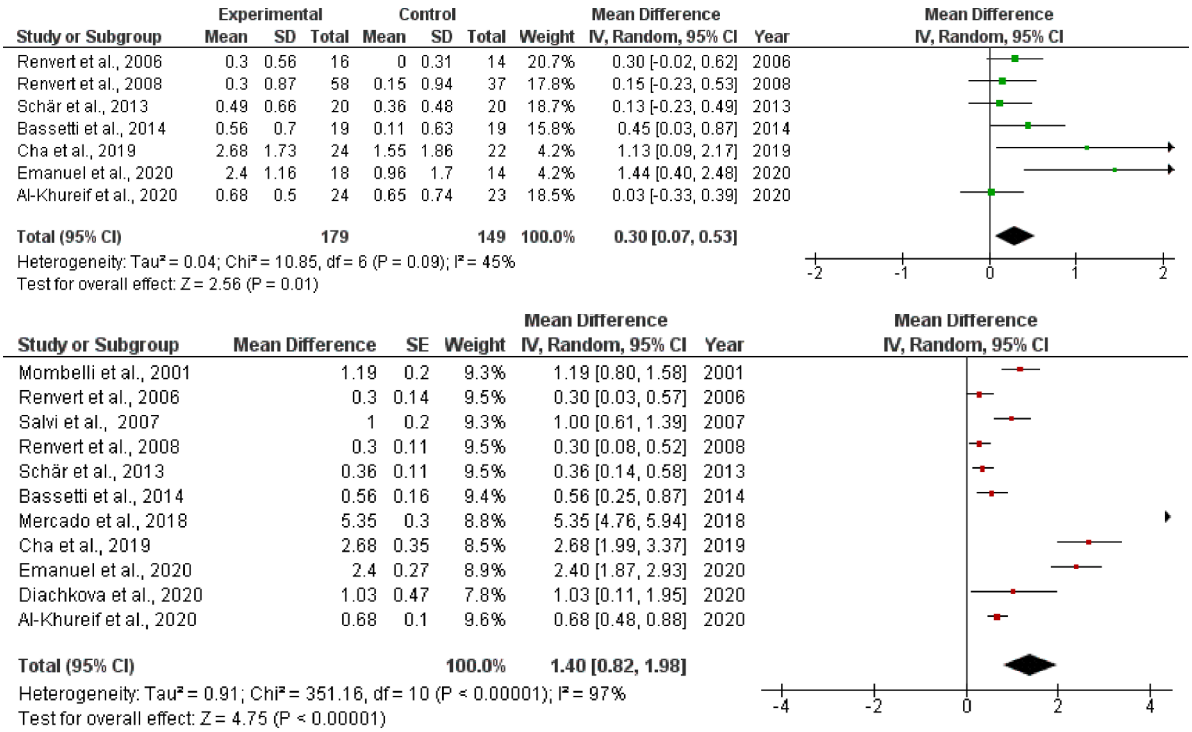

Fig. 3. (a). Probing pocket depth forest plot (experimental *vs* control groups). Weighted mean is presented at CI 95%. Heterogeneity was determined using Higgins (I^2). A random-effects model was applied. Statistical significance was set at 0.05.(b). Probing pocket depth forest plot (only antibiotic group). Weighted mean is presented at CI 95%. Heterogeneity was determined using Higgins (I^2). A random-effects model was applied. Statistical significance was set at 0.05.

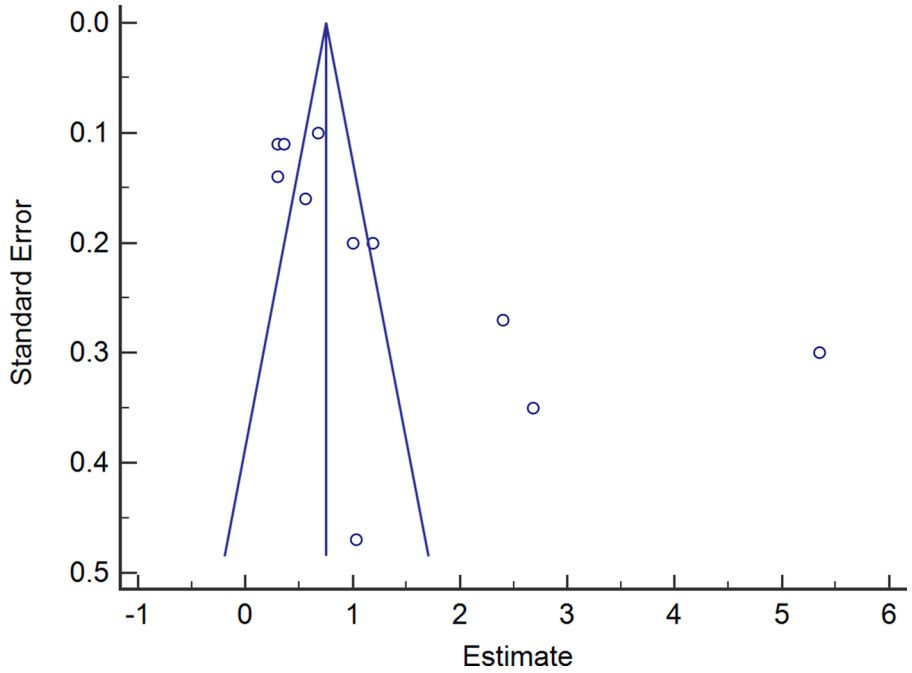

Fig. 4. Probing pocket funnel plot graph. Estimate probing pocket depth reduction measurement is on the horizontal axis, and study precision (standard error) appears on the vertical axis.

to achieve the maximum data. 463 implants have been analyzed, involving the mandible and the maxilla. Six studies evaluated minocycline application, 4 assessed doxycycline, 1 polymeric tetracycline, 1 metronidazole, whereas 1 more analyzed doxycycline, lincomycin and erythromycin local use in three different patients in a case series publication (Table 1).

An additional PPD reduction of 0.30 mm was obtained when the experimental group (with local antibiotics) was compared with the group where antibiotics were not applied (Fig. 3a). The total PPD reduction when peri-implantitis treatment included local antibiotics application was 1.40 mm (Fig. 3b). Attending to obtained 95% CI, it may be that sometimes the reduction in PPD can achieve up to 3.38 mm of probing pocket depth, which is 100% of PPD regain, in those cases where the average of PPD at baseline was approximately 2.2 mm [4].

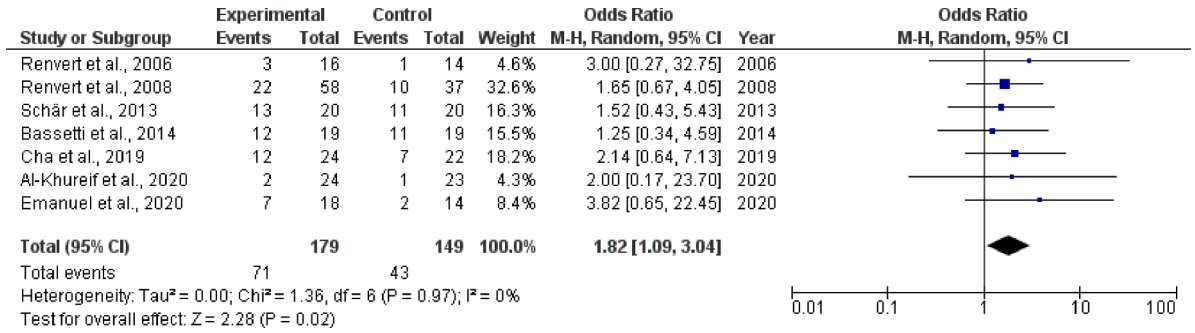

Fig. 5. Bleeding on probing forest plot. Weighted mean is presented at CI 95%. Heterogeneity was determined using Higgins (I^2). A random-effect model was applied. Statistical significance was set at 0.05.

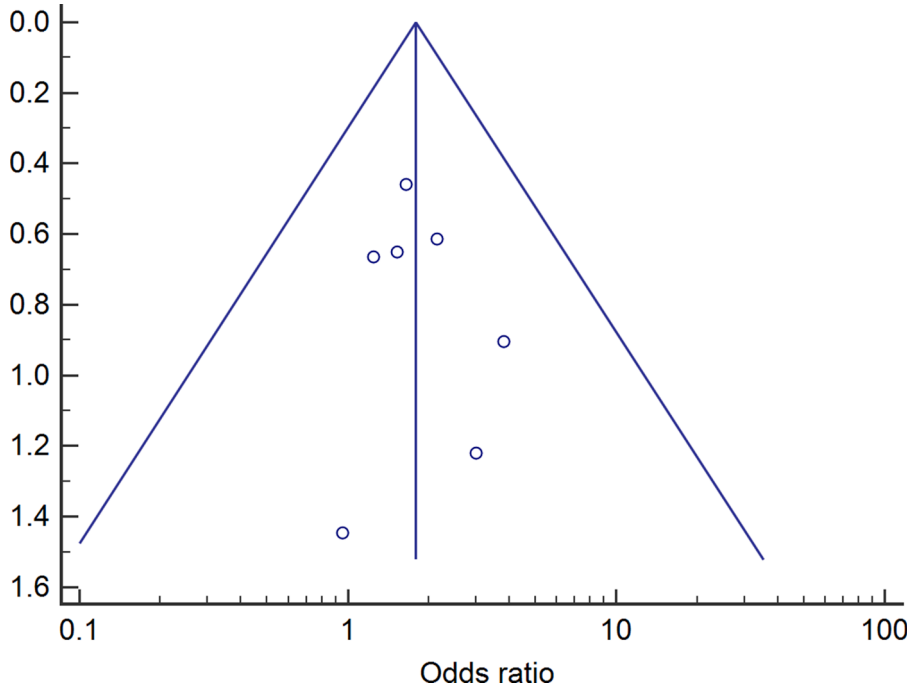

Fig. 6. Bleeding on probing funnel plot graph. Estimate bleeding on probing reduction measurement is on the horizontal axis, and study precision (standard error) appears on the vertical axisTable 1. General overview of the included studies, investigating as primary outcomes BoP and PPD reduction in the treatment of peri-implantitis, when using local antibiotics.

Nevertheless, other times, this regain was roughly 60% of the average baseline (4.29 mm), as it occurs in Bassetti et al. (2014) [9]. Among the RCTs, Emanuel et al. (2020) [4] reported the highest PPD reduction respect to the control group, with a PPD reduction of 2.88 ± 1.52 mm when antibiotics were applied over the PPD values of the control group. Mercado et al. (2018) [29] attained the highest overall values of PPD reduction after 12 m follow-up; 5.35 mm of PPD were reduced (Table 1). It is a prospective study where the probing depth reduction showed the effectiveness of combining deproteinized bovine bone mineral with 10% collagen, plus enamel matrix derivative and doxycycline in the regenerative therapy of peri-implantitis. Nevertheless, the contribution of the various components of the "cocktail" should be explored in controlled long-term randomized clinical trials. Therefore, in light of our results about that the achieved PPD, after local applications of antibiotics should be indicated to treat PI. Schär et al. (2013) [19] stated that the greatest reduction in PPD occurred predominantly during the first three months after therapy.

The local application of antibiotics did significantly reduce the BoP in patients affected by peri-implantitis. Between the RCTs, the one that reported the highest BoP reduction over the control group was Bassetti et al. (2014) [9] with a BoP reduction of 65%. These authors stated that the reduction in the number of BoP sites occurred predominantly during the first three months after therapy [9]. Diachkova et al. (2020) [30] attained the highest values of BoP reduction after 6 m of study; bleeding on probing was reduced 100% after applying doxycycline, lincomycin and erythromycin in three consecutive patients through a case series study (Table 1). After the present meta-analysis, it was found an 85% increase in the odds of BoP reduction after local antibiotic application, meaning that the likelihood of bleeding is almost two-fold when local antibiotics are not applied.

In the treatment of PI disease, local application of antibiotics was compared with photodynamic therapy in three studies [9,19,31]. Two manuscripts presented control patients treated with oral hygiene and scaling [21,32] and two other papers used chlorhexidine [33,34]. The rest of them used placebo [8], Bios-Oss®, collagen and enamel matrix derivative [29] or just no treatment [4]. It is crucial to stress that no study presented adverse effects after local antibiotic administration. This poses an important finding, as it has been reported that systemic delivered antibiotics in periodontitis have produced diverse adverse effects including gastrointestinal reactions, allergic reaction, toothache,

headache or fever [22]. The biofilm development favors PI development [19]. In ten of the included studies, tetracyclines (doxycycline or minocycline) were locally applied in the site of the PI. Because of the inhibition of bacterial protein synthesis by the bacteriostatic antimicrobial properties, tetracyclines exhibit high substantivity to periodontal pocket hard tissues and root surfaces. Minocycline and doxycycline are second-generation semisynthetic derivatives of tetracycline that show higher antimicrobial activities in comparison to predecessors, which, because of their enhanced binding properties and good absorption with prolonged duration of action, include strains of tetracycline-resistant bacteria [35]. This finding is in line with the systematic review and meta-analysis performed by Herrera et al. [36] about adjunctive effect of locally delivered antimicrobials in periodontitis therapy.

Doxycycline and minocycline-based products demonstrated similar weighted mean difference (21% [4] and 29% [34] respectively) (Table 1). Nevertheless, some other studies [37,38] did not report any benefit when using minocycline microspheres in conjunction with the scaling root planning in case of periodontitis. Considering that PI is the object of the present systematic review, comparisons are not possible. The use of minocycline as local antibiotic though reduces inflammatory cytokines at 6-12 m evaluation [8], has raised some controversial, as bacterial resistance when repeated applications may occur [9]. Lincosamides have been demonstrated to stimulate the metabolism of osteoblasts [39] and to reduce the probing pocket depth and bleeding on probing [40]. Erythromycin has both antimicrobial and anti-inflammatory effects [41], and has induced osteoblastic cells proliferation enhancing bone regeneration while treating periodontal defects [41,42]. Metronidazole is considered an efficient antimicrobial agent against a wide range of microorganisms, including anaerobic bacteria and protozoa by inhibiting DNA synthesis [35], and is prescribed in support of conventional periodontal therapy in patients with refractive periodontitis or systemic associated manifestations [43]. Concerns indicate that the high concentration used in local delivery may suppress or eliminate normal microbiota and initiate the development of antibiotic-resistant species within the pocket itself [35].

The relatively high heterogeneity that was detected in studies reporting PPD values as it is observable at the funnel plot graph (Fig. 4), may be explained by differences in implemented surgical techniques, employed biomaterials and operators [44]. Some other sources of heterogeneity have been stated, as study design, types of assessment and control groups of PI treatments [36]. It may be considered a study limitation that may reduce the quality of the encountered evidence. However, the use of placebo-controlled studies [8] might also minimize subject and investigator bias, increasing the ability to detect adverse effects [36,45]. Heterogeneity could also be explained by different products and formulations, as the pharmacokinetic and pharmacodynamics features of the different drugs, as for instance the number of applications [36]. The high heterogeneity between studies may also be due to the small sample sizes of the included studies (namely: “small--studies effect”) [46]. It should be considered that the experiment’s sample size ranges from 3 to 47 patients and from 5 to 95 implants. The study with the greatest sample size (n=47) was Al-Khureif et al. [31] in which a cohorts study is presented reporting, after 12 m of analysis, a PPD reduction of 0.68 mm, and BoP reduction of about 3.6% after applying metronidazole gel. It is, nevertheless, remarkable that a high statistical significance was obtained at both random-effects models ($p<0.001$ in PPD, and $p=0.02$ in BoP assessments) respectively.

The main limitations of this systematic review and meta-analysis are the biased quality of two of the included papers and the lack of appropriately conducted RCTs. Only 7 RCTs were eligible for the present study. Therefore, 5 cases series reports were also analyzed. A meta-analysis should mainly be conducted on RCTs, which have a high level of evidence, but cases series are frequently included when RCTs are in a limited number. It’s not a replacement for the gold standard RCTs, but an alternative for research in those circumstances when RCTs are lacking. Four of the studies [8,9,19] were considered to have a low risk of bias, six of them showed moderate risk of bias and other two were assessed as high risk of bias. Lack of description in methods of randomization, allocation and blinding in their methodology, and incomplete outcome data have been encountered. Implant surface characteristics and location may be of paramount importance to clinical outcomes [47], but there was a lack of this information. With regard to the multiplicity of antibiotics used, it is difficult to determine the true clinical effect. It is not scientifically accurate to compare efficiency of multiple antibiotics as it may lead to different host response. Confounding factors in antibiotics group warrant interpretation of the meta-analysis results with caution. Even more, various definitions of PI impact the calculation of pooled estimates. The follow-up of the patients included in the present review was set as between 4 and 12 months.

The results of the present study are not only highly significant at the statistical analysis, but also report a result with important clinical significance as it is the improvement of treatment efficacy with the local use of antibiotics in PI lesions, without any adverse effect. Based on the results of this review, future clinical trials are suggested to validate clinical parameters, microbiological factors and immunological parameters to assess the efficacy of antibiotics locally administered. The consensus report from the European Federation of Periodontology recommended evaluating treatments of PI disease for at least 6 to 12 m [48]. Therefore, further studies with longer follow-up periods and larger sample size are needed to determine the sustained effect of the present study protocol [8].

5. Conclusions

Through this systematic review and meta-analysis, we have been able to conclude that the existing scientific evidence suggests that the local antibiotic administration did reduce, without adverse effects, both PPD and BoP in patients affected by peri-implantitis. Clinicians can expect to obtain an additional PPD reduction of 0.30 mm, when using locally administered antibiotics, and a likelihood of bleeding on probing almost two-fold when antibiotics are not locally applied.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by: 1) the Ministry of Economy and Competitiveness and European Regional Development Fund [Project PID2020-114694RB-I00]. Funding for open access charge: University of Granada / CBUA.

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