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SYSTEMATIC REVIEW

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Adjunctive effect of locally delivered antimicrobials in periodontitis therapy: A systematic review and meta-analysis

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Abstract

Aim: To answer the following PICOS question: in adult patients with periodontitis, which is the efficacy of adjunctive locally delivered antimicrobials, in comparison with subgingival debridement alone or plus a placebo, in terms of probing pocket depth (PPD) reduction, in randomized clinical trials with at least 6 months of follow-up.

Material and methods: A systematic search was conducted: 59 papers, reporting 50 different studies, were included. Data on clinical outcome variables changes were pooled and analysed using weighted mean differences (WMDs) and 95% confidence intervals (CI), and prediction intervals (PI), in case of significant heterogeneity.

Results: Statistically significant differences were observed, in 6- to 9-month studies, for PPD (WMD = 0.365, 95% CI [0.262; 0.468], PI [−0.29; 1.01]) and clinical attachment level (CAL) (WMD = 0.263, 95% CI [0.123; 0.403], PI [−0.43; 0.96]). For long-term studies, significant differences were observed for PPD (WMD = 0.190, 95% CI [0.059; 0.321]), but not for CAL. For adverse events, no differences were observed. Results were affected by study design (split-mouth versus parallel studies) and assessment (full- or partial-mouth), as well as by the formulation tested.

Conclusions: The use adjunctive locally delivered antimicrobials in periodontitis therapy results in statistically significant benefits in clinical outcomes, without relevant side effects.

KEYWORDS

local antimicrobials, meta-analysis, scaling and root planing, systematic review

1 | INTRODUCTION

Periodontitis are infectious diseases associated with the dysbiosis of the subgingival microbiota. They are very relevant conditions due to their prevalence (Carasol et al., 2016) and global burden (Kassebaum et al., 2014), their impact on the quality of life (Ferreira, Dias-Pereira, Branco-de-Almeida, Martins, & Paiva, 2017) or on systemic health (Sanz et al., 2018). In the mouth, the main consequence of periodontitis is the destruction of the tooth-supporting tissues, eventually leading to tooth loss.

Basic or initial periodontal therapy, including subgingival debridement or scaling and root planing (SRP), has demonstrated an important clinical impact (Badersten, Nilvéus, & Egelberg, 1981). However, SRP is not free of limitations, and its impact in some patients (e.g. grade C periodontitis; Tonetti, Greenwell, & Kornman, 2018) or in specific sites may be not enough to achieve the desired results. Therefore, other forms of therapies, including different debridement approaches or adjunctive therapies (antimicrobials, probiotics, anti-inflammatory drugs, antioxidant micronutrients), have been proposed and tested (Graziani, Karapetsa, Alonso, & Herrera, 2017).

Antimicrobials can be used locally or systemically in the treatment of periodontitis. The main advantages of the local treatment are fewer side effects and improved compliance, in

comparison with drugs used systemically, and reduced chances of developing bacterial tolerance to medications (Rams & Slots, 1996). Several studies and a few systematic reviews have assessed the effects of local antimicrobials delivered in fibres, gels, chips or microspheres, mainly in untreated patients but also in treated sites, with poor response or with recurrent disease (Bonito, Lux, & Lohr, 2005; Hanes & Purvis, 2003; Herrera, Matesanz, Bascones-Martínez, & Sanz, 2012; Matesanz-Pérez et al., 2013; Smiley et al., 2015). Although some of these studies have shown significant additional benefits with the use of certain agents/devices, the clinical value of these effects and the cost–benefit of these treatments have been controversial. Thus, the precise indications of locally delivered antimicrobials have not been clearly established.

Thus, the objective of the present systematic review was to answer the following PICOS question: in adult patients with periodontitis, which is the efficacy of adjunctive locally delivered antimicrobials, in comparison with subgingival debridement alone or plus a placebo, in terms of probing pocket depth (PPD) reduction, in randomized clinical trials (RCTs) with at least 6 months of follow-up?

Clinical Relevance

Scientific rationale for the study: The efficacy of the adjunctive use of local antimicrobials to scaling and root planing (SRP), on different clinical outcome measures, is insufficiently clear to provide solid recommendations in clinical practice.

Principal findings: Local antimicrobials show significant benefits in probing pocket depth (PPD) and clinical attachment level (CAL) changes, in short-term studies, with no associated adverse effects. In long-term studies, significant benefits were observed for PPD, but not for CAL.

Practical implications: There is consistent evidence showing that the adjunctive use of local antimicrobials improves the outcomes of SRP, with no associated adverse effects.

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

A protocol was prepared by the authors and presented to the Workshop Committee for the XVI European Workshop. Before starting the study, the protocol was approved and registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42019142370).

2.2 | Eligibility: inclusion and exclusion criteria for studies

2.2.1 | Population

Patients with periodontitis, older than 18 years, with any type of untreated periodontitis (aggressive or grade C periodontitis patients were analysed separately), including patients with already treated or "refractory"/recurrent periodontitis, also considered as a subgroup. Studies exclusively on patients with diabetes or smokers were excluded.

2.2.2 | Interventions

For the test groups, SRP plus an adjunctive locally delivered antimicrobial, including antibiotics and antiseptics (e.g. chlorhexidine), at concentrations/dosages, recommended by the manufacturer, with sustained delivery (at least 24 hr, according to the product information), adjunctive to subgingival debridement, either full-mouth or localized or in single or repeated sessions.

2.2.3 | Comparisons

Control groups received subgingival debridement plus a placebo or a negative control, including subgingival debridement alone.

2.2.4 | Outcome

Primary outcome is change in PPD, either full-mouth and at selected treated areas. Secondary clinical outcomes were also registered: changes in clinical attachment level (CAL), "pocket closure" (from PPD ≥ 4 to PPD ≤ 3 mm), frequency distribution of pockets in different categories and bleeding on probing (BOP). Patient-based outcomes were also extracted: patient-reported outcome measures (PROMs), possible adverse effects and oral health-related quality of life (OHRQoL).

2.2.5 | Study design and duration

Only RCTs were included, since they provide the best level of evidence in the evaluation of medications, of a minimum duration of 6 months, with parallel or split-mouth designs.

2.3 | Information sources and search

The search strategy is presented in Appendix S1, with a combination of MeSH terms and free text words. Due to limitations in timing, no hand-search was done and only publications written in English

were included. Three databases were searched: MEDLINE/PubMed, EMBASE and Cochrane.

2.4 | Study selection

Study selection was based on a two-step approach: (a) screening of titles and abstracts analysis; and (b) full-text analysis, with reasons for exclusion in this section reported. Both steps were performed in duplicate and results of the agreement are reported.

Two reviewers (PM, DH) 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 (CM) determined inclusion or exclusion. All reports excluded at this stage were formally recorded, as well as the reason/s for their exclusion. Inter-observer agreement value for the screening of complete articles was assessed via κ score.

2.5 | Data collection process and items

Data collection was done in specifically designed Excel sheet and included aspects related to methods and results from the selected studies (Appendix S2). Based on the Cochrane recommendations, a standardized, pre-piloted data extraction form was designed and used. Data were extracted from eligible studies and recorded by an initial reviewer. Second and third examiners cross-checked the accuracy and validity of all the data obtained from the studies.

In case of missing data, an attempt to contact primary authors was done in the systemic antimicrobials section. Studies without enough data for meta-analyses were kept in the systematic review, but excluded from the meta-analyses.

2.6 | Risk of bias in individual studies

Quality assessment was conducted by two reviewers, following the recommendations by Cochrane for randomized clinical trials (Higgins et al., 2011), using the original Risk of Bias (RoB) tool. When the papers adequately showed a random sequence allocation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), no bias of outcome assessment (detection bias), complete outcome data (attrition bias), no selective reporting (reporting bias) and no other bias (conflict of interest bias), the studies were defined as low risk of bias. When one of these criteria was not fulfilled, the study was classified as moderate potential risk of bias and, when missing two or more criteria, as a high potential risk of bias (Ten Heggeler, Slot, & Weijden, 2011).

2.7 | Summary measures

The main outcome variables have already been described.

2.8 | Data analyses and synthesis of the results

Meta-analyses on the mean treatment effects were performed (changes from v1 to vn) with v1 being baseline, and vn being 6-month, 12-month and final visits.

To compare the selected studies, data on the primary and secondary outcomes were pooled and analysed using weighted mean differences (WMDs) and 95% confidence intervals (CI). When the differences between (Δ) baseline-end were not reported, they were calculated using baseline and final values. The variance of ΔVar was estimated with the formula: SVar2 = SVar12 + SVar22 − (2*r*SVar1*SVar2), where SVar2 is the variance of the difference, SVar12 is the variance of the mean baseline value, and Svar22 is the variance of the mean end value. A correlation *r* of .5 was assumed.

The statistical heterogeneity among studies was assessed using the *Q* test according to Dersimonian and Laird (DerSimonian & Laird, 1986). As a complement to the *Q* test, the I2 index was calculated in order to know the percentage of variation in the global estimate that was attributable to heterogeneity (I2 = 25%: low; I2 = 50%: moderate; I2 = 75%: high heterogeneity).

The study-specific estimates were pooled using both the fixed effect model (Mantel-Haenszel-Peto test) and the random effect model (Dersimonian-Laird test). If a significant heterogeneity was found, the random effect model results were presented. For subgroup analysis, meta-regression was applied, in case of enough available data.

Forest plots were created to illustrate the effects in the meta-analysis of the global estimation and the different sub-analysis. STATA® 14 (StataCorp LP) intercooled software was used to perform all analyses. Statistical significance was set at $p \leq .05$.

In case of heterogeneity in the primary outcome, in addition to the summary estimate (WMD) and CI, prediction intervals (PI) were reported to allow more informative inferences and illustrate which range of true effects can be expected in future settings, presenting the heterogeneity in the same metric as the original effect size measure (IntHout, Ioannidis, Rovers, & Goeman, 2016).

2.9 | Risk of bias across studies: publication bias

Egger's test and funnel plots, in case of a sufficient number of included studies (at least 10 studies), were used to assess publication bias. Sensitivity analysis was performed assessing the contribution made to the totality of the evidence by each study after omitting each of them.

3 | RESULTS

3.1 | Study selection

A total 2,184 references were identified by the electronic search. After the screening of titles and abstracts (κ = 0.658, 95% CI [0.587; 0.728]), 97 papers were selected, plus two additional references, which were associated with one of selected references. After full-paper assessment (κ = 0.873, 95% CI [0.775; 0.972]), 59 articles were included in the review, while the remaining 40 were finally excluded (see Appendix S3).

In total, data from 50 independent investigations were extracted since, in six cases, data came from two papers [(Eickholz et al., 2002; Ratka-Krüger et al., 2005); (Goodson et al., 2012; Socransky et al., 2013); (Wong, Lu, Liu, & Hou, 1999; Wong, Lu, Liu, Hou, & Chang, 1998); (Jeffcoat et al., 1998, 2000); (Palmer, Matthews, & Wilson, 1998, 1999); (Tomasi, Koutouzis, & Wennström, 2008; Tomasi & Wennstrom, 2011)], and for one study, data came from three papers (Colombo et al., 2003; Gonzales et al., 2011; Rodrigues et al., 2004). When reporting these studies, only the primary clinical papers were quoted (Eickholz et al., 2002; Gonçalves, Rodrigues, Feres-Filho, & Colombo, 2004; Goodson et al., 2012; Jeffcoat et al., 1998; Palmer, Matthews, & Wilson, 1998; Tomasi et al., 2008; Wong et al., 1998). In addition, one paper reported a longer-term follow-up (5 years) in a subset of patients (Wilson, McGuire, Greenstein, & Nunn, 1997), from a study sample already described in another manuscript (Newman, Kornman, & Doherty, 1994).

3.2 | Study characteristics

3.2.1 | Study design

Among the 50 selected studies, there were differences in study design (split-mouth, parallel or both), the number of centres involved, the type of clinical setting (private, university or both) and study duration (Table 1). Although most of the studies were carried out in USA and Europe, selected studies were performed in 16 different countries from four continents.

3.2.2 | Disease definition

In 22 studies, periodontitis was defined as chronic or adult; in eleven studies, the terminology used was recurrent/"refractory"/relapsing in already treated patients or patients in supportive periodontal therapy (SPT), while in five studies the only definition of disease was "periodontitis" and it was not reported in 9 studies (Appendix S4, Table A4.1). In two studies, two groups were included: both aggressive and chronic periodontitis (Agan, Sönmez, & Serdar, 2006), and untreated and recurrent (Eickholz et al., 2002). In just one study, additional microbiological criteria were used (Jones, Kornman, Newbold, & Manwell, 1994).

With regard to the extension of the disease, in two studies it was considered as localized and in four as generalized. For severity, in 20 studies it was "moderate-severe" or "advanced," while in two were "severe" or "advanced" and in other two "mild" or "initial to moderate."

3.2.3 | Selected samples

The characteristics of the population samples recruited in the different studies are shown in Table A4.2. Among the selected papers, sample sizes strongly differed, ranging from large samples, with more than 100 patients (Bogren et al., 2008; Eickholz et al., 2002; Goodson et al., 2012; Jeffcoat et al., 1998; Newman et al., 1994; Paolantonio, D'Angelo, et al., 2008a; Tonetti et al., 1998, 2012; Williams et al., 2001) to just 10 patients (Agan et al., 2006; Goodson, Hogan, & Dunham, 1985).

The age of participants ranged from 20 (Kasaj, Chiriachide, & Willershausen, 2007) to 85 (Killeen, Harn, Erickson, Yu, & Reinhardt, 2016) while percentage of females ranged from 31.4% to 77.8%. With regard to smoking profiles, twelve studies included only non-smoker patients, while in studies including smoker patients, the proportion of smokers ranged 4%–47%. Minor differences were detected in the distribution of patients, age, gender and smoking profiles among the study groups (Table A4.3).

3.2.4 | Outcome assessment

Seventeen studies used a full-mouth approach to assess clinical outcome variables, either by evaluating all sites, or a group of sites according to a part of the mouth (e.g. a quadrant) or according to a clinical criterion (e.g. PPD > 4 mm); in contrast, 36 studies selected some specific sites/teeth for evaluation, based on clinical, radiological or biomarkers criteria, including furcation lesion sites (Dannewitz, Lippert, Lang, Tonetti, & Eickholz, 2009; Tomasi et al., 2008; Tomasi & Wennstrom, 2011; Tonetti et al., 1998) (Tables A4.1 and A4.4). In three studies, both full-mouth and partial-mouth evaluations were reported (Gonçalves et al., 2004; Timmerman et al., 1996).

The number of sites measured per tooth was 4–6 in 25 studies, and just one in 14 (in two of them, two sites were measured but just the maximum (Leiknes, Leknes, Böe, Skavland, & Lie, 2007), or the mean (Lie, Bruun, & Boe, 1998) were reported). In 21 studies, only one examiner was used, with 13 studies not reporting on this. A higher quality of probing was considered when describing calibration exercises (22 studies), using force-controlled (7 studies) or force-controlled and computer-assisted probes (9 studies), using stents (6 studies), duplicate measurements (5 studies) or both (3 studies).

TABLE 1 Study design of the selected studies:

Study reference	Blinding	Design	Centres	Setting	Country	Follow-up
Agan et al. (2006)	Single	Split-mouth	Single	University	Turkey	6
Ahamed et al. (2013)	NR	Parallel	Single	University	India	6
Aimetti et al. (2004)	Single	Split-mouth	Single	University	Italy	12
Akncbay, Senel, and Ay (2007)	NR	Parallel	Single	University	Turkey	6
Azmak, Atilla, Luoto, and Sorsa (2002)	Single	Split-mouth	Single	University	Turkey	6
Bogren et al. (2008)	Single	Parallel	Multi (3)	Private practice and university	USA and Sweden	36
Buduneli, Tünger, Evrenosoglu, and Bilgiç (2001)	Single	Split-mouth	NR	NR	Turkey	12
Carvalho, Novak, and Mota (2007)	Single	Split-mouth	Single	University	USA	9
Cortelli, Querido, Aquino, Ricardo, and Pallos (2006)	Double	Parallel	Single	University	Brazil	12
D'Aiuto et al. (2006)	Single	Parallel	Single	University	UK	6
Dannewitz et al. (2009)	Single	Parallel	Single	University	Germany	12
Eickholz et al. (2002) and Ratka-Krüger et al. (2005)	Double	Split-mouth	Multi (3)	University	Germany and the Netherlands	6
Flemmig et al. (1996)	Single	Split-mouth	Single	University	Germany	6
Friesen, Williams, Krause, and Killoy (2002)	Single	Split-mouth	Single	University	USA	6
Gonçalves et al. (2004), Colombo et al. (2003) and Rodrigues et al. (2004)	Single	Parallel	Single	University	Brazil	12
Gonzales et al. (2011)	Double	Parallel	Single	University	Germany	6
Goodson et al. (2012) and Socransky et al. (2013)	Single	Parallel	Multi (NR)	NR	USA and Sweden	24
Goodson et al. (1985)	NR	Split-mouth	Single	University	USA	12
Griffiths et al. (2000)	Single	Split-mouth	Dual	University	UK	9
Grisi et al. (2002)	Single	Parallel	Single	University	Brazil	9
Heasman et al. (2001)	Single	Split-mouth	Single	University	UK	6
Henderson et al. (2002)	Single	Split-mouth	Single	University	New Zealand	6
Jeffcoat et al. (1998) and Jeffcoat et al. (2000)	Double	Parallel & split-mouth	Multi (10)	University	USA	9
Jones et al. (1994)	Single	Parallel	Single	University	USA	6
Kasaj et al. (2007)	Single	Split-mouth	NR	NR	Germany	6
Killeen et al. (2016)	Single	Parallel	Single	University	USA	12
Kinane and Radvar (1999)	Single	Parallel	Single	University	UK	6
Lauenstein, Kaufmann, and Persson (2013)	Single	Parallel	NR	NR	Switzerland	6
Leiknes et al. (2007)	Single	Split-mouth	Single	University	Norway	6
Lie et al. (1998)	Single	Split-mouth	Single	University	Norway	6
Matesanz et al. (2013)	Triple	Parallel	Single	University	Spain	6
Mizrak et al. (2006)	Single	Parallel	Single	University	Turkey	6
Newman et al. (1994) and Wilson et al. (1997)	Single	Split-mouth	Multi (7)	Private practice	USA	6
Palmer et al. (1998) and Palmer, Matthews, and Wilson (1999)	Single	Parallel	Single	University	UK	6
Paolantonio, Dolci, et al. (2008b)	Single	Split-mouth	NR	University	Italy	6
Paolantonio, D'Angelo, et al. (2008a)	Single	Split-mouth	Multi (4)	University	Italy	6

(Continues)

TABLE 1 (Continued)

Study reference	Blinding	Design	Centres	Setting	Country	Follow-up
Paolantonio et al. (2009)	Single	Split-mouth	Multi (4)	University	Italy	6
Romano, Torta, Debernardi, and Aimetti (2005)	NR	Split-mouth	Single	University	Italy	12
Sakellari et al. (2010)	Single	Parallel	Single	University	Greece	6
Soeroso et al. (2017)	Single	Parallel	Single	University	Indonesia	6
Stelzel and Florès-de-Jacoby (2000)	Single	Split-mouth	NR	University	Germany	9
Tabenski et al. (2017)	Single	Parallel	Single	University	Germany	12
Timmerman et al. (1996)	Double	Parallel	NR	NR	Netherlands	18
Tomasi et al. (2008), Tomasi and Wennstrom (2011)	Single	Parallel	Single	University	Sweden	9
Tonetti et al. (2012)	Single	Parallel	Multi (5)	Private practice	Italy, Germany, Greece, the Netherlands, Switzerland	12
Tonetti et al. (1998)	Single	Parallel	Multi (6)	Private practice	Italy	6
Van Dyke, Offenbacher, Braswell, and Lessem (2002)	Double	Parallel	Single	University	USA	6
Williams et al. (2001)	Single	Parallel	Multi (18)	University	USA	9
Wong et al. (1998) and Wong et al. (1999)	NR	Split-mouth	Single	University	China	6
Zingale, Harpenau, Bruce, Chambers, and Lundergan (2012)	Single	Split-mouth	Single	University	USA	6

Note: Multi (*n*), multicentre study (number of centres).
Abbreviation: NR, not reported.

Most studies used a patient-based approach for data analysis (34). Additional non-clinical outcomes were evaluated in 36 studies, including microbiological evaluation in 23 studies, biomarkers in gingival crevicular fluid (GCF) in 11, and also systemic or radiological outcomes.

In 26 studies, adverse events and/or PROMs were evaluated, most frequently with no clear specification of the findings ("unspecified by authors"). Some studies clearly identified these effects, including gingival/periodontal abscess/infection, gingival tenderness/gingivitis, pain and root/tooth sensitivity.

3.3 | Type of interventions

3.3.1 | Interventions before the study

For studies dealing with untreated patients, a minimum period with no periodontal therapy was normally suggested as inclusion criterion, ranging from 3 to 12 months; for refractory/recurrent cases, patients were either enrolled in a SPT program or had been periodontally treated within the previous 3–6 months; no criteria were described in five studies (Table A4.5).

In most cases, the studies described periodontal therapies which were rendered before the main intervention, for all study groups, including oral hygiene instructions (OHI) alone (*n* = 15) or in combination with supragingival professional mechanical plaque removal (PMPR) (*n* = 12) or with SRP (*n* = 4); in some studies, the intervention was PMPR alone (*n* = 3), and in 16 studies, no intervention was mentioned.

3.3.2 | Subgingival debridement

The study intervention was local SRP in 19 studies, full-mouth SRP in 22 studies, while supragingival PMPR was the main mechanical therapy in two studies (Gonzales et al., 2011; Heasman, Heasman, Stacey, & McCracken, 2001) (Tables A4.5 and A4.6). Information on the performance of subgingival debridement is described in the tables. It should be highlighted that 48 out of the 50 studies clearly explained that the local antimicrobial was placed/delivered immediately after debridement, with two exceptions: in one study, it was placed before debridement (Tonetti et al., 1998), and SRP was rendered at fibre removal; and in other study, it was placed one week after debridement (Flemmig et al., 1996).

3.3.3 | Local antimicrobials and control groups

In 35 studies, there were just two study groups, while 8 had three groups and 6 had four groups (Table 2). One study had eight groups

TABLE 2 Different study groups in the selected studies: number and description of test and control groups

Study reference	*n* groups	Control group	Additional control group	Test group	Additional test group/s
Agan et al. (2006)	2	SRP alone		Atridox	
Ahamed et al. (2013)	2	SRP alone		Atridox	
Aimetti et al. (2004)	2	SRP alone		Actisite	
Akncbay et al. (2007)	3	SRP alone		Chitosan and Metronidazole	Chitosan
Azmak et al. (2002)	2	SRP alone		PerioChip	
Bogren et al. (2008)	2	SRP alone		Atridox	
Buduneli et al. (2001)	2	SRP alone		Elyzol	
Carvalho et al. (2007)	2	SRP alone and cyanoacrylate		PerioChip	
Cortelli et al. (2006)	2	SRP and vehicle		Arestin	
D'Aiuto et al. (2006)	2	SRP alone		Arestin	
Dannewitz et al. (2009)	2	SRP alone		Ligosan	
Eickholz et al. (2002) and Ratka-Krüger et al. (2005)	3	SRP alone	SRP and vehicle	Ligosan	Vehicle control
Flemmig et al. (1996)	2	SRP alone		Actisite	
Friesen et al. (2002)	4	SRP alone	untreated	tetracycline strips (one)	Tetracycline strips (multiple)
Gonçalves et al. (2004), Colombo et al. (2003) and Rodrigues et al. (2004)	3	SRP alone		Actisite	Systemic tetracycline
Gonzales et al. (2011)	2	SRP and vehicle		PerioChip	
Goodson et al. (2012; Socransky et al. (2013)	8	SRP alone		Actisite	Six additional groups
Goodson et al. (1985)	4	SRP alone	untreated	Actisite	Actisite alone
Griffiths et al. (2000)	2	SRP alone		Elyzol	
Grisi et al. (2002)	2	SRP alone		PerioChip	
Heasman et al. (2001)	2	SRP alone		PerioChip	
Henderson et al. (2002)	3	SRP alone (remote)	SRP alone (adjacent)	Arestin	
Jeffcoat et al. (1998; Jeffcoat et al. (2000)	3	SRP alone	SRP and vehicle	PerioChip	
Jones et al. (1994)	4	SRP and vehicle	untreated	minocycline powder	Minocycline powder alone
Kasaj et al. (2007)	2	SRP alone		PerioChip	
Killeen et al. (2016)	2	SRP alone		Arestin	
Kinane and Radvar (1999)	4	SRP alone		Dentomycin[a]	Actisite, Elyzol
Lauenstein et al. (2013)	2	SRP alone		Periofilm	
Leiknes et al. (2007)	2	SRP alone		Elyzol	
Lie et al. (1998)	3	SRP alone		Elyzol	Aureomycin
Matesanz et al. (2013)	2	SRP and vehicle		Chlosite	
Mizrak et al. (2006)	2	SRP alone		PerioChip	
Newman et al. (1994) and Wilson et al. (1997)	2	SRP alone		Actisite	
Palmer et al. (1998) and Palmer et al. (1999)	2	SRP alone		Elyzol	Systemic metronidazole
Paolantonio, Dolci, et al. (2008b)	2	SRP alone		PerioChip	
Paolantonio, D'Angelo, et al. (2008a)	2	SRP alone		PerioChip	

(Continues)

TABLE 2 (Continued)

Study reference	*n* groups	Control group	Additional control group	Test group	Additional test group/s
Paolantonio et al. (2009)	2	SRP alone		Chlosite	
Romano et al. (2005)	2	SRP alone		Actisite	
Sakellari et al. (2010)	2	SRP alone		PerioChip	
Soeroso et al. (2017)	2	SRP alone		Periocline[a]	
Stelzel and Florès-de-Jacoby (2000)	2	SRP alone		Elyzol	
Tabenski et al. (2017)	3	SRP alone		Arestin	SRP & PDT
Timmerman et al. (1996)	2	SRP and vehicle		Periocline[a]	
Tomasi et al. (2008), Tomasi and Wennstrom (2011)	2	SRP alone		Atridox	
Tonetti et al. (2012)	2	SRP alone		Ligosan	
Tonetti et al. (1998)	2	SRP alone		Actisite	
Van Dyke et al. (2002)	4	SRP alone	no SRP	Arestin	Arestin alone
Williams et al. (2001)	3	SRP alone	SRP and vehicle	Arestin	
Wong et al. (1998) and Wong et al. (1999)	2	SRP alone		Actisite	
Zingale et al. (2012)	4	SRP alone		Arestin	

Abbreviations: PTD, photodynamic therapy; SRP, scaling and root planing.

[a]Same formulation with different brand names.

(Goodson et al., 2012). Forty-three studies had SRP alone as main control group, while eight had a vehicle control (placebo), with three of the studies presenting both control groups. Four studies presented an additional untreated control, while one study presented two SRP alone control, one in adjacent sites and another in remote sites (Henderson, Boyens, Holborow, & Pack, 2002).

The test groups with commercialized local antimicrobials aimed to assess tetracyclines, including tetracycline [Actisite (10), Aureomycin (1)], minocycline [Arestin (8); Dentomycin (1) and Periocline (2), same formulations with different brand names] and doxycycline [Atridox (4), Ligosan (3)]; chlorhexidine [Chlosite (2), PerioChip (11)]; metronidazole [Elyzol (7)]; and piperacillin and sodium tazobactam [Periofilm (1)]. Among those not commercially available, chitosan (1), chitosan with metronidazole (1), minocycline powder (1) and tetracycline strips [just using one (1), or multiple (1)] were tested. In the text, brand names are used for consistency, but a detailed information on composition is presented in Table A4.7.

Additional test groups, not relevant for this review, included local antimicrobials alone, systemic antimicrobials or photodynamic therapy.

The number of applications (Table A4.8) varied among products and study protocols, being the most frequent just one application, in 34 study groups; two applications were performed in 10 study groups and more than two in five. In six study groups, one initial application was performed, while a second (three studies) or a third one (three studies) was decided based on the dislodging on the first application or on the presence of pockets. When more than one application was scheduled, the protocols were highly heterogeneous. In some cases (16 study groups), a dressing was used after the local antimicrobial application, with cyanoacrylate or a periodontal dressing, that was kept on place for 3–13 days; dislodging of the antimicrobial or dressing was recorded in 12 study groups.

3.4 | Risk of bias within studies

In most studies (Table A4.9), quality parameters were considered unclear or not fulfilled, and all the selected studies, except three (Eickholz et al., 2002; Killeen et al., 2016; Tabenski et al., 2017), were qualified with a high risk of bias.

3.5 | Results of individual studies

These results are shown in the different forest plots associated with the meta-analyses. It was not possible to report information on pocket closure or on the frequency distribution of PPD categories, since these outcomes were not reported in the individual studies.

3.6 | Synthesis of the results

3.6.1 | Probing pocket depth, short-term (6–9 months)

Data from 38 comparisons between test and control groups were combined in a meta-analysis, showing a statistically significant benefit ($p < .001$) for test groups (WMD = 0.364, 95% CI [0.236; 0.491]), with significant heterogeneity (I^2 = 96.8%; PI [−0.29; 1.01; Table 3a and Appendix S5, Figure A5.1).

TABLE 3 Meta-analyses and meta-regression for probing pocket depth (PPD) changes in (a) short-term studies (6–9 months) and (b) long-term studies (12 or more months)

(a)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	Control	Test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
All	38	2,137	2,111	0.364	0.236	0.491	<.001	96.8	<.001
Parallel	21	1,259	1,233	0.231	0.136	0.326	<.001	91.3	<.001
Split-mouth	17	878	878	0.521	0.322	0.72	<.001	95.1	<.001
Partial-Mouth	31	1,468	1,467	0.427	0.307	0.547	<.001	97.4	<.001
Full-Mouth	7	669	644	0.249	0.179	0.32	<.001	36.7	.148
Vehicle	5	621	595	0.308	0.29	0.327	<.001	0.0	.858
SRP	33	1,516	1,516	0.384	0.238	0.531	<.001	97.2	<.001
Untreated	25	1,565	1,545	0.291	0.208	0.375	<.001	91.0	<.001
Refractory	11	356	350	0.443	0.25	0.636	<.001	62.9	.003
Both	2	216	216	0.562	0.306	0.818	<.001	23.9	.252
Test product									
Atridox	2	19	19	0.8	0.084	1.516	.028	0.0	.502
Actisite	7	255	257	0.729	0.696	0.761	<.001	0.0	.834
Periochip	9	718	719	0.23	0.12	0.341	<.001	96.4	<.001
Elyzol	5	136	135	0.14	−0.041	0.322	.130	0.0	.783
Ligosan	3	236	232	0.525	0.283	0.767	<.001	3.9	.353
Arestin	6	567	564	0.279	0.203	0.356	<.001	0.0	.91
Dentomycin	2	65	41	0.377	−0.036	0.79	.073	0.0	.915
Periofilm	1	14	18	−0.1	−1.053	0.853	.837	–	–
Aureomycin	1	18	18	0.6	−0.339	1.539	.219	–	–
Chlosite	2	109	108	0.486	−0.238	1.211	.188	89.3	0.002

		95% CI		
Meta-regression	Coefficient	Lower	Upper	*p*-value
Parallel/split-mouth	0.282	0.098	0.466	.004
Partial/full-mouth	−0.248	−0.479	−0.016	.037
Vehicle/SRP	0.085	−0.194	0.363	.54
Untreated/refractory	0.138	−0.091	0.367	.229

(b)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	Control	Test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
All	10	291	230	0.19	0.059	0.321	.004	28.1	.185
Parallel	7	228	167	0.079	−0.098	0.257	.381	0.0	.912
Split-mouth	3	63	63	0.313	−0.164	0.789	.198	72.1	.028
Partial-Mouth	7	137	130	0.243	0.07	0.415	.006	48.1	.072
Full-Mouth	3	154	100	0.118	−0.082	0.319	.247	0.0	.948
Vehicle	2	90	40	0.144	−0.165	0.452	.361	0.0	.803
SRP	8	201	190	0.2	0.056	0.344	.007	43.3	.089
Untreated	5	136	86	0.061	−0.193	0.314	.640	0.0	.781

(Continues)

TABLE 3 (Continued)

(b)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	Control	Test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
Refractory	5	155	144	0.236	0.084	0.389	.002	57.5	.052
12 months	6	111	104	0.082	−0.191	0.354	.526	46.4	.097
18 months	2	90	40	0.144	−0.165	0.452	.458	0.0	.803
36 months	1	64	60	0.1	−0.164	0.364	.361	–	–
60 months	1	26	26	0.35	0.128	0.572	.002	–	–
Test product									
Atridox	2	77	73	0.112	−0.147	0.372	.396	0.0	.614
Actisite	2	45	45	0.41	0.201	0.618	.028	56.9	.128
Elyzol	1	18	18	−0.21	−0.72	0.3	.420	–	–
Ligosan	1	19	15	0.18	−0.633	0.993	.664	–	–
Arestin	2	42	39	−0.191	−0.643	0.261	.408	0.0	.747
Dentomycin	2	90	40	0.144	−0.165	0.452	.361	0.0	.803

		95% CI		
Meta-regression	Coefficient	Lower	Upper	*p*-value
Parallel/Split-mouth	0.240	−0.125	0.604	.168
Partial/Full-Mouth	−0.077	−0.567	0.413	.728
Vehicle/SRP	0.039	−0.556	0.633	.884
Untreated/Refractory	0.182	−0.291	0.656	.4
Follow-up months	0.005	−0.006	0.015	.315

Abbreviations: CI, confidence interval: SRP, scaling and root planing.

Significant differences ($p < .001$), favouring the test groups, were found independently of study design, type of assessment, use or not of placebo or periodontitis type (untreated versus "refractory/recurrent"). Meta-regression showed a significant influence of study design and type of assessment.

Ten different local antimicrobials were included in the analysis, with five of them demonstrating statistically significant benefits for test groups, four of them with no heterogeneity (Atridox: $n = 2$,WMD = 0.800; Actisite: $n = 7$, WMD = 0.729; Ligosan: $n = 3$, WMD = 0.525; Arestin: $n = 6$, WMD = 0.279) and another with significant heterogeneity (Periochip: $n = 9$, WMD = 0.23). Among the other products, four demonstrated not significant benefits in test groups (Elyzol: $n = 5$, WMD = 0.140; Dentomycin: $n = 2$, WMD = 0.377; Aureomycin: $n = 1$, WMD = 0.600; Chlosite: $n = 2$, WMD = 0.486), while Periofilm ($n = 1$) showed non-significant differences favouring the control group.

3.6.2 | Probing pocket depth, long-term (12–60 months)

Data from 10 comparisons between test and control groups were combined in a meta-analysis, showing a statistically significant benefit ($p < .05$) for test groups (WMD = 0.190, 95% CI [0.059; 0.321]), with no heterogeneity ($I^2 = 28.1\%$) (Table 3b and Figure A5.2).

Significant differences ($p < .05$) were also found in studies with partial-mouth assessment, studies with "refractory/recurrent" patients and those with a 60-month follow-up ($p = .002$), but not in other groups of studies. Meta-regression did not show a significant impact for any of the factors considered.

Six different local antimicrobials were included in the long-term analysis, with four of them demonstrating benefits for test groups (Atridox: $n = 2$, WMD = 0.112; Actisite: $n = 2$, =0.410; Ligosan: $n = 1$, WMD = 0.180; Dentomycin: $n = 2$, WMD = 0.144), and the other two, in favour of control groups (Elyzol: $n = 1$, WMD = −0.210; Arestin: $n = 2$, WMD = −0.191). However, the only comparison showing statistically significant differences was for Actisite ($p = .028$).

3.6.3 | Clinical attachment level, short-term (6–9 months)

Data from 37 comparisons between test and control groups were combined in a meta-analysis, showing a statistically significant benefit ($p < .001$) for test groups (WMD = 0.263, 95% CI [0.123; 0.403]),

TABLE 4 Meta-analyses and meta-regression for clinical attachment level (CAL) changes in (a) short-term studies (6–9 months) and (b) long-term studies (12 or more months)

(a)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	control	test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
All	37	1,717	1,667	0.263	0.123	0.403	<.001	85	<.001
Parallel	17	782	732	0.05	−0.134	0.234	.596	69.8	<.001
Split-mouth	20	935	935	0.44	0.404	0.475	<.001	82.6	<.001
Partial-Mouth	31	1,527	1,503	0.357	0.211	0.503	<.001	82.5	<.001
Full-Mouth	6	190	164	−0.155	−0.494	0.184	.370	78.3	<.001
Vehicle	4	409	361	0.116	−0.021	0.252	.666	55.8	.079
SRP	33	1,308	1,306	0.293	0.139	0.447	<.001	85.3	<.001
Untreated	25	1,156	1,111	0.264	0.076	0.451	.006	82.3	<.001
Refractory	10	345	340	0.266	0.056	0.476	.013	62.8	.004
Both	2	216	216	0.4	0.046	0.754	.027	0.0	1.000
Test product									
Atridox	1	6	6	0.64	−0.005	1.285	.052	-	–
Actisite	8	265	267	0.276	−0.172	0.723	.227	89	<.001
Periochip	10	745	749	0.183	−0.055	0.421	.132	86.1	<.001
Elyzol	4	124	122	0.035	−0.175	0.245	.746	0.0	.538
Ligosan	3	236	232	0.408	0.063	0.753	.020	0.0	.982
One_TetraStrip	1	24	24	0.44	−0.025	0.905	.064	–	–
Multiple_TetraStrip	1	24	24	0.48	0.087	0.873	.017	–	–
Arestin	4	67	66	0.517	0.151	0.883	.019	38.5	.181
Dentomycin	3	110	61	−0.116	−0.371	0.138	.426	14.6	.31
Aureomycin	1	18	18	1,000	−0.204	2.204	.103	–	–
Chlosite	1	98	98	0.84	0.452	1.228	<.001	–	–

		95% CI		
Meta-regression	Coefficient	Lower	Upper	*p*-value
Parallel/Split-mouth	0.374	0.040	0.708	.029
Partial/Full-Mouth	−0.535	−0.946	−0.124	.012
Vehicle/SRP	0.237	−0.322	0.795	.396
Untreated/Refractory	−0.009	−0.43	0.412	.965

(b)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	control	test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
All	10	288	224	0.09	−0.253	0.433	.607	75.3	<.001
Parallel	6	215	151	0.025	−0.208	0.259	.862	48.6	.083
Split-mouth	4	73	73	0.305	−0.339	0.95	.353	88.7	<.001
Partial-Mouth	7	169	134	−0.001	−0.518	0.518	.999	78.4	<.001
Full-Mouth	3	119	90	0.27	0.036	0.504	.024	0.0	.897
Vehicle	2	90	40	0.264	−0.127	0.655	.186	0.0	.759
SRP	8	198	184	0.062	−0.351	0.475	.768	79.6	<.001

(Continues)

TABLE 4 (Continued)

(b)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	control	test	WMD	Lower	Upper	*p*-value	I2 (%)	*p*-value
Untreated	5	133	83	0.126	−0.094	0.347	.430	29.4	.225
Refractory	5	155	141	0.192	−0.464	0.848	.567	86	<.001
12 months	5	98	88	0.119	−0.682	0.919	.772	83.4	<.001
18 months	2	90	40	0.264	−0.127	0.655	.186	0.0	.759
24 months	1	10	10	0.33	−0.079	0.739	.114	–	–
36 months	1	64	60	0.2	−0.185	0.585	.309	–	–
60 months	1	26	26	−0.43	−0.752	−0.108	.009	–	–
Test product									
Atridox	1	64	60	0.2	−0.185	0.585	.309	–	–
Actisite	3	55	55	0.493	−0.5	1.487	.330	92.5	<.001
Elyzol	1	18	18	−0.06	−0.426	0.306	.748	–	–
Ligosan	1	19	12	0.38	−1.25	2.01	.648	–	–
Arestin	2	42	39	−0.586	−1.048	−0.125	.013	0.0	.482
Dentomycin	2	90	40	0.264	−0.127	0.655	.186	0.0	.759

		95% CI		
Meta-regression	Coefficient	Lower	Upper	*p*-value
Parallel/Split-mouth	0.372	−0.666	1.411	.432
Partial/Full-Mouth	0.271	−0.824	1.365	.584
Vehicle/SRP	−0.151	−1.499	1.198	.803
Untreated/Refractory	0.163	−0.911	1.238	.735
Follow-up months	−0.010	−0.043	0.023	.514

Abbreviations: CI, confidence interval; SRP, scaling and root planing; TetraStrip, tetracycline strip.

with significant heterogeneity (I^2 = 85.0%; PI [−0.43; 0.96]) (Table 4a and Figure A5.3).

Significant differences (p < .001), favouring the test groups, were also observed in split-mouth studies, those with partial-mouth assessment, or with SRP alone as control, and in all types of periodontitis (p < .05). Meta-regression detected a statistically significant impact of study design and type of assessment.

Eleven different local antimicrobials were included in the analysis, with four of them demonstrating statistically significant benefits for test groups, with no heterogeneity (Ligosan: n = 3, WMD = 0.408; multiple tetracycline strips: n = 1, WMD = 0.480; Arestin: n = 4, WMD = 0.517; Chlosite: n = 1, WMD = 0.840). Among the other products, six demonstrated benefits for test groups, but not significant (Atridox: n = 1, WMD = 0.640; Actisite: n = 8, WMD = 0.276; Periochip: n = 10, WMD = 0.183; Elyzol: n = 4, WMD = 0.035; one tetracycline strip: n = 1, WMD = 0.440; Aureomycin: n = 1, WMD = 1.000), while Dentomycin (n = 3, WMD=−0.116) showed not significant differences favouring the control group.

3.6.4 | Clinical attachment level, long-term (12–60 months)

Data from 10 comparisons between test and control groups were combined in a meta-analysis, showing no significant benefits (p = .607) for test groups (WMD = 0.090, 95% CI [−0.253; 0.433]), with significant heterogeneity (I^2 = 75.3%; PI [−1.01; 1.19]) (Table 4b and Figure A5.4).

Significant differences were also observed, in favour of the test groups, in studies with full-mouth assessment (p = .024) and 60-month follow-up (p = .009). Meta-regression did not show a significant impact for any of the factors considered.

Six different local antimicrobials were included in the long-term analysis, with four of them demonstrating benefits for test groups (Atridox: n = 1, WMD = 0.200; Actisite: n = 3, WMD = 0.493; Ligosan: n = 1, WMD = 0.380; Dentomycin: n = 2, WMD = 0.264), and the other two, in favour of control groups (Elyzol: n = 1, WMD = −0.060; Arestin: n = 2, WMD = −0.586). The only comparison showing statistically significant differences was for Arestin (p = .013).

3.6.5 | Bleeding on probing

Data from nine comparisons (only short-term) between test and control groups were combined in a meta-analysis, showing a non-statistically significant overall benefit for test groups (WMD = 2.495, 95% CI [−1.996; 6.986], p = .276), with significant heterogeneity (I^2 = 86.9%; PI [−10.63; 15.62]) (Table 5 and Figure A5.5).

No significant differences were detected in studies with different types of assessment or of patients. Meta-regression did not show a significant impact for any of the factors considered.

When the meta-analysis was performed by local antimicrobial, three products achieved statistically significant differences, but with just one study each: Atridox (WMD = 12.500), Chlosite (WMD = 22.000) and PerioChip (WMD = −7.000, favouring the control group). Only two products showed results for two or more studies: Actisite (n = 2, WMD = −0.458) and Elyzol (n = 3, WMD = 4.315), and none of them showed statistically significant differences. Finally, Dentomycin, with one study, reported a WMD = 0.080, and no significant differences.

3.6.6 | Patient-reported outcome measures and adverse event

In 26 studies, PROMs were evaluated, focusing on adverse events, and normally with no clear description of the events (Tables A5.1 and A5.2). In the cases in which they were identified, their description included gingival/periodontal abscess/infection, gingival tenderness/gingivitis, pain and root/tooth sensitivity.

Twenty-seven comparisons were available for adverse events not specified by the authors, being the most frequent result "no adverse event" (for 19 test and 21 control groups), with 19 comparisons with the frequency of not specified adverse event being 0% for both groups. The remaining eight comparisons, coming from five different studies, were meta-analysed showing an odds ratio (OR) = 0.983 (95% CI [0.775; 1.246]), with no significant differences and with no heterogeneity (I^2 = 20.4%); p = .268). Similar results were observed when the analysis was repeated with the different subgroups. Five local antimicrobials were included in the analysis: Ligosan, Actisite, tetracycline strips (either one or multiple) and Arestin.

For gingival/periodontal abscess/infection, three comparisons were available, with no significant differences (OR = 1.277, 95% CI [0.845; 1.931]) and no heterogeneity (I^2 = 0%). Similar results were found for gingival tenderness/gingivitis (3 comparisons, OR = 1.194, 95% CI [0.774; 1.842]), pain (3 comparisons, OR = 1.154, 95% CI [0.754; 1.765]) and root/tooth sensitivity (3 comparisons, OR = 1.225, 95% CI [0.864; 1.735]).

3.7 | Risk of bias across studies (publication bias) and sensitivity analyses

No publication bias was detected in the main outcome variable (p = .118; Egger´s test for changes in PPD) (Figure A5.6). The

TABLE 5 Meta-analyses and meta-regression for bleeding on probing (BOP) changes in short-term studies (6–9 months)

	Number of			Weighted mean difference (WMD)				Heterogeneity	
		Patients			95% CI				
	Studies	control	test	WMD	Lower	Upper	p-value	I2 (%)	p-value
All	9	199	195	2.495	−1.996	6.986	.276	86.9	<.001
Partial-Mouth	6	88	85	4.71	−2.198	11.618	.181	64.8	.014
Full-Mouth	3	111	110	1.255	−9.38	11.889	.817	88.0	<.001
Untreated	5	127	126	1.496	−3.652	6.644	.569	92.2	<.001
Refractory	4	72	69	4.547	−2.433	11.526	.334	55.8	.079
Test product									
Atridox	1	6	6	12.5	1.746	23.254	.023	–	–
Actisite	2	30	29	−0.458	−1.543	0.628	.408	0.0	.351
Dentomycin	1	20	21	0.08	−13.343	13.503	.991	–	–
Elyzol	3	106	104	4.315	−1.239	9.87	.169	11.1	.325
Chlosite	1	12	10	22.0	5.957	38.043	.007	–	–
Periochip	1	25	25	−7	−8.793	−5.207	<.001	–	–

		95% CI		
Meta-regression	Coefficient	Lower	Upper	p-value
Partial/full-mouth	−3.917	−17.988	10.154	.531
Untreated/refractory	2.742	−12.171	17.655	.677

Abbreviation: CI, confidence interval.

sensitivity analyses detected the influence of particular studies in the overall heterogeneity, but as the global estimator did not change significantly after omitting each of the contributing studies, it was decided to keep all selected studies (Figure A5.7).

4 | DISCUSSION

The present systematic review was able to identify 50 RCTs (reported in 59 publications), assessing the use of locally delivered antimicrobials as adjuncts to subgingival debridement for, at least, 6 months. The overall meta-analysis, combining all test groups, demonstrated statistically significant PPD reductions and CAL gains (WMDs for 6- to 9-month studies, 0.365 mm and 0.263 mm, respectively), when compared with control groups. In addition, minor adverse effects were observed, with no differences between test and control groups. However, the significant heterogeneity observed in most of the analyses, together with the estimated prediction intervals calculated, highlighted the need for further analysis to deeply understand the results.

These results are similar to those reported in previous systematic reviews (Bonito et al., 2005; Hanes & Purvis, 2003; Matesanz-Pérez et al., 2013; Smiley et al., 2015), with additional PPD reductions ranging between 0.3 and 0.6 mm, and demonstrate that locally delivered antimicrobials, as adjuncts to SRP, can improve the clinical outcomes of mechanical treatment alone or with a placebo. As in the present work, benefits were statistically significant, although clinical relevance is more controversial, due to the small magnitude of some of the benefits. In addition, many factors have been identified as possibly influencing the outcomes and explaining the detected heterogeneity.

4.1 | Heterogeneity explained by study design

In order to identify sources of heterogeneity, subgrouping and meta-regressions were performed, including factors such as study design, and types of assessment, of control or of periodontitis. Meta-regression (for PPD and CAL changes in 6- to 9-month studies) identified a significant influence of study design (with larger benefits for split-mouth studies) and type of assessment (with larger benefits for partial-mouth assessments). Although not significant, studies on untreated patients tended to achieve larger PPD reductions, and studies with placebo tended to achieve smaller benefits in both PPD and CAL changes.

Split-mouth studies offer a clear advantage of isolating treatment comparisons from intersubject variability and consequently have the potential to require less number of subjects than in a parallel design with the same power (Shoukri, Colak, & Donner, 2011). However, there is a risk of potential leakage of the treatment effect from one site to another, which is called the carry-across effect (Lesaffre, Philstrom, Needleman, & Worthington, 2009). This limitation is seldomly acknowledged by the authors, with one specific exception (Jeffcoat et al., 1998), who recorded but did not analyse data from contra-lateral sites in the same patient. In addition, not having a placebo/vehicle control may have consequences, on top of the lack of blinding for patients, affecting different types of bias; placebo-controlled studies minimize subject and investigator bias and increase the ability to detect adverse effects (Food & Drug Administration, 2001). The influence of partial/limited sites evaluation has been shown to clearly affect misclassification bias in periodontitis (Heaton, Garcia, & Dietrich, 2018; Romano, Perotto, Castiglione, & Aimetti, 2019), and it has also been reported that partial- and full-mouth assessments should not be combined in clinical trials (Chilton, Fertig, & Talbott, 1978). Finally, a poorer response can be expected in non-responding/refractory patients, when compared with untreated periodontitis, due to a larger potential for healing in untreated sites (Harrel & Nunn, 2001), or to specific microbiological profiles or immunological conditions in non-responding/refractory cases (Haffajee et al., 2004); however, non-responding sites after therapy, or recurrent disease during SPT, may represent a reasonable indication for local antimicrobials (since only localized sites/teeth may be affected).

4.2 | Heterogeneity explained by different products/formulations

It may not be correct to discuss the overall use of sustained-released local antimicrobials, since each particular product poses unique properties that may prevent from assessing them globally. For example, the pharmacokinetic and pharmacodynamic characteristics of the different products show large variations. These have also consequences in the instructions of application/usage: strictly one application or repeated applications, or additional applications depending on the clinical outcomes; in addition, some products have to be removed after 7–10 days, and others may use some dressing or cyanoacrylate to protect the treated area.

The number of applications was not considered among those factors of study design discussed before, since in most cases the evaluated protocol was the one suggested by the manufacturer (see Table A5.3) and sometimes differed among the products evaluated.

The largest observed benefits were observed for doxycycline- or tetracycline-based products: Atridox (WMD = 0.8 mm for PPD), Actisite (WMD = 0.729 mm) and Ligosan, (WMD = 0.525 mm). Minocycline-based products (Dentomycin, Periocline) demonstrate similar benefits to the overall WMD for all products.

In the last years, an effort has been made to develop subgingival slow-released antiseptics, aiming at providing similar benefits to local antibiotics but with less adverse effects, especially the development of bacterial resistance. Two chlorhexidine-based products have been included in the present review, either delivered as chips (Periochip) or as gels (Chlosite). However, they seem to provide smaller benefits, when compared to the previously mentioned local antibiotics.

Other products have demonstrated limited improvements: Elyzol rendered no additional benefit over SRP alone, what is in agreement with previous systematic reviews (Bonito et al., 2005; Hanes & Purvis, 2003; Matesanz-Pérez et al., 2013; Smiley et al., 2015).

4.3 | Limitations

The main limitation of the analysed data is the limited quality of the papers reviewed and the lack of appropriately conducted research. Although some methodological aspects, such as blinding and randomization, were acceptable in most cases, the global risk of bias was considered as high in most of the included publications, and only three of them were classified as having a moderate risk of bias (Eickholz et al., 2002; Killeen et al., 2016; Tabenski et al., 2017). In addition, when combining data (meta-analysis), statistically significant heterogeneity was observed for most of the analyses, what limits the results of this systematic review as well. Furthermore, the risk of bias of the selected studies may have increased by the participation of the manufacturing companies in most of the studies, either by sponsoring them or even by including their personnel in the research teams. Finally, relevant outcomes are seldomly reported (pocket closure, frequency distribution of PPD categories) and could not be evaluated in the present review.

Due to high risk of bias and the heterogeneity of the studies and of the reported results, it is difficult to define an evidence-based protocol of usage of locally delivered antimicrobials in the clinical practice. The available information is scarce regarding the clinical scenarios to use them, which product/s to choose and the profile of the patients who would eventually benefit the most from this treatment option. Baseline characteristics of the patient, availability of products in the national markets or added economic costs and cost/benefit ratio (Henke et al., 2001) are also factors that need to be carefully assessed.

5 | CONCLUSIONS

Within the limitations of this systematic review, it can be concluded that:

- The adjunctive use of locally delivered subgingival antimicrobials results in statistically significant benefits in terms of PPD reduction and (only short-term) CAL gain.
- Significant heterogeneity was observed in most of the analyses, since they combined different products with different active agents, and also influenced by the study design (larger benefits for split-mouth studies and for partial-mouth assessments). Prediction intervals did not demonstrate significant benefits, and the magnitude of the benefits may not be clinically relevant.
- No increase in adverse effects or differences in PROMs were observed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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