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A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis

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Abstract

Aims: To update the existing scientific evidence on the efficacy of local antimicrobials as adjuncts to subgingival debridement in the treatment of chronic periodontitis.

Material and Methods: Fifty-six papers were selected, reporting data from 52 different investigations. All the studies reported changes in probing pocket depth (PPD) and clinical attachment level (CAL) and most in plaque index (PlI) and/or bleeding on probing (BOP). Meta-analyses were performed with the data retrieved from the studies fulfilling the inclusion criteria.

Results: The overall effect of the subgingival application of antimicrobials was statistically significant ($p = 0.000$) for both changes in PPD and CAL with a weighted mean difference (WMD) of −0.407 and −0.310 mm respectively. No significant differences occurred for changes in BOP and PlI. Subgingival application of tetracycline fibres, sustained released doxycycline and minocycline demonstrated a significant benefit in PPD reduction (WMD between 0.5 and 0.7 mm). The rest of the tested outcomes demonstrated a high heterogeneity. The local application of chlorhexidine and metronidazole showed a minimal effect when compared with placebo (WMD between 0.1 and 0.4 mm).

Conclusions: The scientific evidence supports the adjunctive use of local antimicrobials to debridement in deep or recurrent periodontal sites, mostly when using vehicles with proven sustained release of the antimicrobial.

Key words: chronic periodontitis; local antimicrobials; meta-analysis; scaling and root planing; systematic review

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Conflict of interest and source of funding statement

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The gold standard in the treatment of periodontitis is mechanical debridement of the pockets by scaling and root planing (SRP) (Hung & Douglass 2002). This approach is a demanding therapeutic procedure and it has limitations, mainly related with the inability to access to deep pockets and furcations and to eliminate certain pathogens (Caffesse et al. 1986, Greenstein 2000). Moreover, there are well-documented secondary effects (gingival recession, loss of tooth substance, dentin hypersensitivity, etc.) (Haffajee

et al. 1997). To overcome these limitations, different adjunctive therapies have been proposed, mainly the use of systemic or local antimicrobial agents (Quirynen et al. 2002, Bonito et al. 2005, Cosyn & Wyn 2006). Adjunctive systemic antimicrobials may improve clinical outcomes (Herrera et al. 2002, 2008, Haffajee et al. 2003), especially in particular disease conditions (Sanz & Teughels 2008); however, their use is not free of risks, and hence, they should be indicated for certain situations under optimal conditions (Herrera et al. 2002, 2008). Local application of antimicrobials has been indicated in localized forms of periodontitis and in non-responding and recurrent sites (Walker et al. 1993, Killoy 2002, Bonito et al. 2005), as in generalized periodontitis their application may be cumbersome and time consuming. The scientific rationale, therefore, is to support the mechanical treatment in these localized sites by further reducing the number of bacteria, while diminishing the adverse effects and dependence on patient's compliance associated with the use of systemic antimicrobials (Hanes & Purvis 2003).

Previous systematic reviews have demonstrated a significant beneficial effect on the adjunctive use of local antimicrobials when compared with SRP alone. The clinical magnitude of the effect, however, was limited, which raises the question of efficacy (Hanes & Purvis 2003, Bonito et al. 2005). In addition, the reported results were heterogeneous, both when comparing different products, as well as among studies assessing the same antimicrobial, and this prompted the authors to foster new randomized clinical trials (RCTs) evaluating further agents and/or formulations in targeted population (Hanes & Purvis 2003). After these publications, relevant studies have been published and it is, therefore, the aim of this investigation to update the existing information on the efficacy of local antimicrobials as adjuncts to subgingival debridement in the treatment of chronic periodontitis.

Material and Methods

Focused question

The following PICO question was constructed: "what are the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone or plus placebo, in chronic periodontitis patients, in terms of clinical outcomes?"

Inclusion criteria for studies

Studies were included if they:

- tested one or more antimicrobial agents as adjuncts to SRP (test intervention);
- had a control group that received the same SRP as the treatment group, alone or with a placebo (control intervention);
- reported clinical outcomes for specified, fixed time periods, and when multiple antimicrobials were tested, outcomes were reported for each agent separately; and
- both parallel and split-mouth designs were accepted, if they included healthy patients with chronic or "adult" periodontitis.

Studies were excluded if they:

- included systemic antimicrobials as an intervention;
- used local anti-infective therapy alone (monotherapy);
- used non-sustained release vehicles; and
- extended the time between SRP and the local antimicrobial administration.

Outcome variables

The primary outcome variable was changes in probing pocket depths (PPDs), and secondary outcome variables included changes of clinical attachment levels (CAL) and bleeding on probing (BOP). As control variables, also plaque index (PlI) and gingival inflammation were considered.

Studies were examined for reporting of adverse effects, whether by the clinician (clinical examination) or by the patient (interviews/questionnaire), and there was registration on whether the studies included other outcome variables.

Search protocol

An online search for RCT in humans and in English language was performed using MEDLINE (via PubMed), the Cochrane Oral Health Group Trials Register and EMBASE (via Ovid). All articles published until July 2011 were searched based on the following search terms (key words):

Disease: "periodontitis" OR "periodontal disease(s)."

Intervention: "local" OR "slow release" OR "antimicrobial(s)."

Disease AND Intervention.

Limits: Humans, English, RCTs.

A hand search of the following journals was implemented: *Journal of Periodontology*, *Journal of Clinical Periodontology* and *Journal of Periodontal Research*. Cross-references from relevant papers were also considered. The authors were consulted if information not available in the publication was deemed necessary. Two reviewers (P. M.-P. and M. G.-G.) evaluated the abstracts and titles for selection, and when differences occurred, they were solved by discussion with a third party (D.H.). The inter-observer agreement was assessed by means of the calculating kappa scores. Full-papers of selected papers were retrieved and evaluated for inclusion and exclusion criteria.

Assessment of bias

The risk of bias and quality assessment was conducted following the recommendations by Cochrane (Higgins et al. 2009). When the papers adequately described the inclusion/exclusion criteria, the representativeness of the population, the random patient assignment, the blindness to patient and examiner, the treatment allocation and reported follow-up, the studies were defined as low risk of bias (Table 1). When one of these criteria was missing, the study was classified as moderate potential risk of bias and missing two or more criteria, as a high potential risk of bias (Ten Heggeler et al. 2011).

Data extraction

Data were extracted by two reviewers (P. M.-P. and M. G.-G.). In cases where a study did not report raw data in any of variables of interest, but included precise graphic representations, data were extracted and if needed to solve some doubts or missing information the authors were contacted to supply it.

When the differences between (Δ) baseline-end were not reported, they

were calculated using the formula: $\Delta Vary = Var2 - Var1$, where, Var1 and Var2 were the mean values before and after treatment. In addition, the variance was estimated with the formula: $SVar^2 = SVar1^2 + SVar2^2 - (2*r*SVar1*SVar2)$, where $SVar1^2$ and $SVar^2$ were the variances of the mean baseline and end values. A correlation r of 0.5 was assumed (Paraskevas et al. 2008).

Assessment of Heterogeneity

The statistical heterogeneity among studies was assessed using the χ^2 test, and the percentage of variation in the global estimate that could be attributed to heterogeneity (5%: low; 50%: moderate; 75%: high heterogeneity) was calculated with the I^2 index (Higgins et al. 2009).

Data analysis and synthesis

Due to the nature of the obtained data, its presentation is largely descriptive, although where appropriate, a meta-analysis was performed. Data were pooled and analysed using means and 95% confidence intervals using the patient as the statistical unit. Negative values of the weighted mean difference (WMD) represent a better result for the test group.

All studies were analysed together subgrouping them by the antimicrobial utilized. In addition, each antimicrobial was assessed independently. The study-specific estimates were pooled using both the fixed (Mantel–Haenzel–Peto test) and random (Dersimonian–Laird test) models. If a significant heterogeneity was found, the random effect model results were presented, and whenever possible, a subgroup analyses was performed based on study design (split-mouth or parallel) and duration of follow-up (short: less than 6 months, medium: 6–12 months or long-term: more than 12 months). Forest plots were created to illustrate the effects of the different studies and the global estimation on the meta-analyses. A sensitivity analysis, to detect the influence of a particular study in the overall heterogeneity, was also performed (Tobías 2008). The publication bias was evaluated using a Funnel plot and the Egger's linear regression method. All these analyses were carried out using STATA® (StataCorp LP, College Station, TX, USA) intercooled software defining a statistical significance as a p-value < 0.05.

Results

The search (Fig. 1) provided 9550 titles, which rendered 1431 references once duplicates were eliminated. After evaluation of titles and abstracts, 1218 studies were discarded ($\kappa = 0.69$). The remaining 213 were evaluated and provided 56 final papers reporting data from 52 different investigations, as two pairs of papers reported the results of the same material at two different time points (Machion et al. 2004 at 6 months and Machion et al. 2006 at 24 months, Radvar et al. 1996 at 6 weeks and Kinane & Radvar 1999 at 6 months) or the same results in two different papers (Palmer et al. 1998, 1999 and Goodson et al. 2007, Bland et al. 2010). Therefore, 56 papers were included, presenting results of 52 studies with 41 of these studies included in the meta-analyses.

Study Design

The characteristics of the selected studies are shown in Tables 2–4. From the 52 investigations, three showed results for more than one test group (Radvar et al. 1996, Lie et al. 1998, Kinane & Radvar 1999, Gupta et al. 2008), and four had two control groups (Jeffcoat et al. 1998, 2000, Williams et al. 2001, Eickholz et al. 2002). In 27 investigations, a split-mouth design was selected. The minimum study length was 1 month and the maximum 36 months (Table 2).

Study Population

Data on age, although scarcely reported, was depicted normally by group (Table 2). The gender distribution was usually described, although few compared their distribution among the treatment groups. The periodontal status of the sample, as well as the treatments received before being included in the studies, is described in Table 3. In regards to smoking, two studies included only smokers (Machion et al. 2004, 2006), one studied separately smokers and non-smokers (Palmer et al. 1999) and in 12 smokers were excluded and 24 did not report it.

Clinical Outcomes

Table 4 depicts the clinical outcome variables evaluated in the selected studies. All reported changes in PPD and CAL and most of them also changes in PlI, Gingival index (GI) and/or BOP. Other outcome variables, reported in the selected studies, included microbiological (26 studies), immunological (five) or radiographical data (one). Few studies reported adverse effects.

Interventions

Table 3 shows the tested product evaluated in each study. Full-mouth SRP was rendered in most of the studies before the application of the antimicrobial, while less than one-third of the included studies only performed the mechanical treatment in the selected sites. Normally, a dental hygienist performed the SRP while the antimicrobial was placed by the investigators, thus keeping the hygienist blinded. The time spent in SRP was reported in some studies, ranging between 60 and 90 min when a full-mouth treatment was done, and 5 min per tooth when just the selected sites where instrumented subgingivally. The SRP method was seldomly mentioned as well as the report on whether anaesthesia was used or not. Most studies pointed out that patients were instructed in oral hygiene measures and reinforced in every recall visit. In 18 studies, it was not mentioned, and in two of them they reported that no oral hygiene instructions were given at the beginning of the study (van Steenberghe et al. 1993, Akalin et al. 2004). Each study specified their own post-operative instructions although the vast majority remarked the importance of avoiding inter-proximal hygiene devices such as dental floss, and almost all prohibited the use of adjunctive oral antiseptics, although it was not clearly stated in some of them. The medication intake and the adverse events occurring after the antimicrobial placement and during the trial were considered in most cases.

Efficacy of the tested adjunctive local antimicrobials

The first analysis evaluated the overall effect of the subgingival application of antimicrobials. In spite of the high heterogeneity among the

Table 1. Quality assessment of the included studies

Reference	Sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Risk of bias
Minabe et al. (1991)	nr	nr	nr	Yes	Yes	Yes	High
Nakagawa et al. (1991)	nr	nr	nr	Yes	Yes	Yes	High
van Steenberghe et al. (1993)	nr	nr	Double	Yes	Yes	Yes	High
Jones et al. (1994)	nr	nr	Simple	Yes	Yes	Yes	High
Jeong et al. (1994)	nr	nr	nr	nr	Yes	Yes	High
Newman et al. (1994)	nr	nr	Simple	Yes	Yes	Yes	High
Drisko et al. (1995)	nr	nr	Simple	Yes	Yes	Yes	High
Timmerman et al. (1996)	nr	nr	Double	Yes	Yes	Yes	High
Radvar et al. (1996)	nr	nr	Simple	Yes	Yes	Yes	High
Soskolne et al. (1997)	nr	nr	Simple	nr	No	Yes	High
Noyan et al. (1997)	nr	nr	No	Yes	Yes	Yes	High
Graca et al. (1997)	nr	nr	nr	Yes	Yes	Yes	High
Jarrold et al. (1997)	nr	nr	nr	nr	Yes	Yes	High
Tonetti et al. (1998)	nr	nr	Simple	Yes	Yes	Yes	High
Jeffcoat et al. (1998)	nr	nr	Double	Yes	Yes	Yes	High
Lie et al. (1998)	nr	nr	No	Yes	Yes	Yes	High
Wong et al. (1998)	nr	nr	No	Yes	Yes	Yes	High
Palmer et al. (1999)	nr	Yes	Simple	Yes	Yes	Yes	Moderate
Kinane & Radvar (1999)	nr	nr	Simple	Yes	Yes	Yes	High
Riep et al. (1999)	nr	nr	No	Yes	Yes	Yes	High
Yalcin et al. (1999)	nr	nr	No	Yes	Yes	Yes	High
Jeffcoat et al. (2000)	nr	nr	Double	Yes	Yes	Yes	High
Griffiths et al. (2000)	nr	nr	Simple	nr	Yes	Yes	High
Stelzel & Flores-de-Jacoby (2000)	nr	nr	nr	Yes	Yes	Yes	High
Wennstrom et al. (2001)	Yes	nr	Simple	Yes	Yes	Yes	Moderate
Heasman et al. (2001)	nr	nr	Simple	Yes	Yes	Yes	High
Williams et al. (2001)	nr	nr	Double	nr	nr	Yes	High
Azmak et al. (2002)	Yes	nr	No	Yes	Yes	Yes	High
Friesen et al. (2002)	nr	nr	Simple	Yes	Yes	Yes	High
Grisi et al. (2002)	nr	nr	Simple	Yes	Yes	Yes	High
Henderson et al. (2002)	nr	nr	No	Yes	Yes	Yes	High
Van Dyke et al. (2002)	nr	nr	Simple	Yes	Yes	Yes	High
Eickholz et al. (2002)	Yes	Yes	Double	Yes	Yes	Yes	Low
Meinberg et al. (2002)	nr	nr	nr	nr	Yes	Yes	High
Akalin et al. (2004)	nr	nr	No	Yes	Yes	Yes	High
Rodrigues et al. (2004)	nr	nr	Simple	Yes	Yes	Yes	High
Aimetti et al. (2004)	nr	nr	Simple	Yes	Yes	Yes	High
Machion et al. (2004)	nr	nr	Simple	Yes	Yes	Yes	High
Cosyn et al. (2005)	nr	nr	Simple	nr	Yes	Yes	High
Agan et al. (2006)	Yes	nr	No	Yes	Yes	Yes	High
Mizrak et al. (2006)	No	nr	No	Yes	Yes	Yes	High
Machion et al. (2006)	nr	nr	Simple	Yes	Yes	Yes	High
Cosyn & Wyn (2006)	nr	nr	Simple	nr	Yes	Yes	High
Cosyn et al. (2006)	nr	nr	Simple	Yes	Yes	Yes	High
Goodson et al. (2007)	nr	nr	Simple	nr	Yes	Yes	High
Carvalho et al. (2007)	Yes	nr	Simple	Yes	Yes	Yes	Moderate
Cosyn et al. (2007)	Yes	nr	Simple	Yes	Yes	Yes	Moderate
Kasaj et al. (2007)	nr	nr	Simple	Yes	Yes	Yes	High
Gupta et al. (2008)	nr	nr	No	Yes	Yes	Yes	High
Paolantonio et al. (2008)	Yes	nr	Simple	Yes	Yes	Yes	Moderate
Pradeep et al. (2008)	nr	nr	Simple	Yes	Yes	Yes	High
Bogren et al. (2008)	nr	nr	Simple	Yes	Yes	Yes	High
Gopinath et al. (2009)	nr	nr	No	Yes	Yes	Yes	High
Paolantonio et al. (2009)	nr	nr	Simple	Yes	Yes	Yes	High
Bland et al. (2010)	nr	nr	Simple	Yes	Yes	Yes	High
Sakellari et al. (2010)	Yes	Yes	Simple	Yes	Yes	Yes	Low

nr, not reported.

studies, there were statistically significant differences ($p = 0.000$) for both changes in PPD (Fig. 2a) and CAL (Fig. 2b), in favour of the test groups, with a WMD of −0.407 and −0.310 respectively. No significant differences between groups were achieved in the overall meta-analysis for changes in BOP and PlI.

Data were also analysed grouping results in terms of clinical changes by

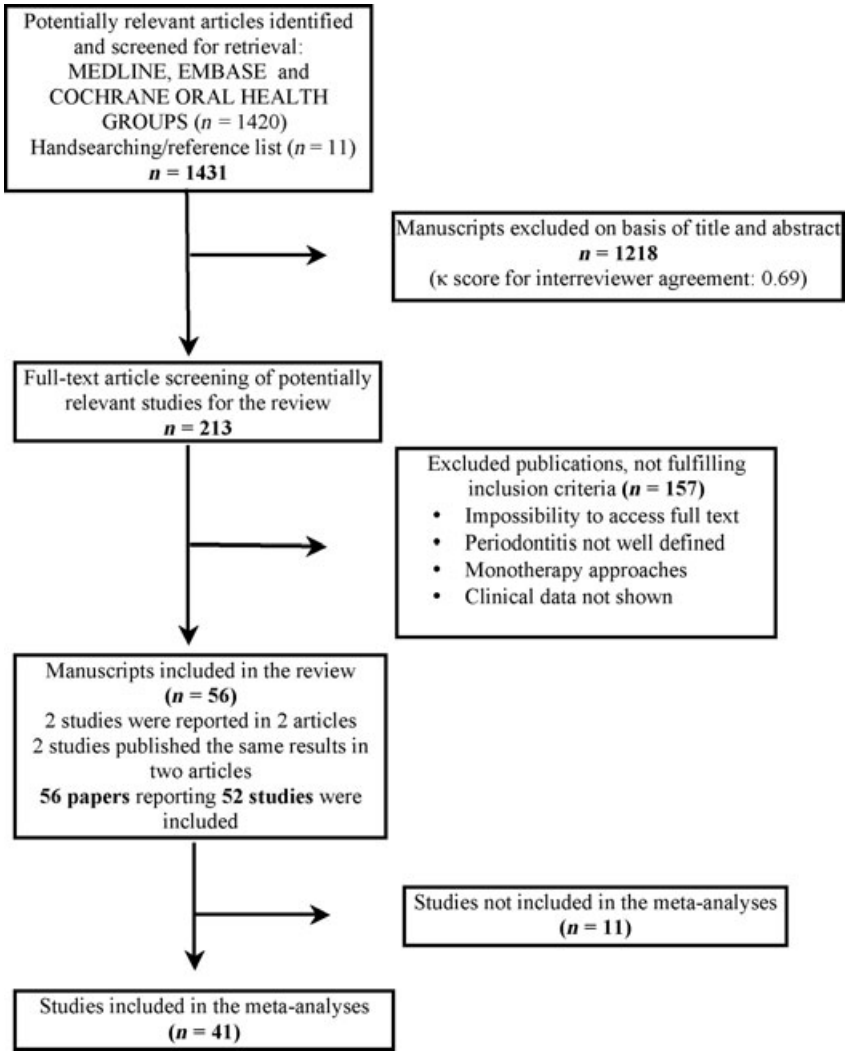

Fig. 1. Flow chart of inclusion of studies in the review process. Some of the studies has more than one test or control group, and the data have been used twice in the meta-analysis.

tested product and, in some studies, by follow-up period and study design (Tables 5–7).

Azithromycin

Only one study was included demonstrating significant PPD reductions in the test group ($p < 0.05$). CAL gains were also statistically significant in the test group at 3 months. Changes in BOP and PlI were not evaluated.

Chlorhexidine

Different chlorhexidine (CHX) concentrations using different administration vehicles were evaluated: CHX chip, CHX varnish and CHX plus xanthan gel.

Eleven studies tested CHX chips. For changes in PPD, nine studies were included in the meta-analysis, demonstrating a significant heterogeneity ($p = 0.000$). In the subgroup analysis, statistically significant differences were found both in split-mouth (WMD:−0.486, $p = 0.000$, Table 5) and parallel RCTs (WMD: −0.157, $p = 0.036$, Table 5), but only split-mouth studies did not demonstrate a significant heterogeneity ($p = 0.210$). Medium-term studies demonstrated significant differences between groups (WMD: −0.180, $p = 0.000$, Table 5), but not short-term studies (WMD: −0.447, $p = 0.321$, Table 5). For CAL changes, ten studies included in the meta-analysis demonstrated a high degree of heterogeneity ($p < 0.001$), which did not disappear in the subgroup analysis. The random model analysis showed significant differences between test and control for all subgroups, except for short-term studies (split-mouth: $p = 0.005$; parallel: $p = 0.000$; medium-term: $p = 0.000$; short-term: $p = 0.097$, Table 6). For BOP changes, lack of appropriate data prevented a meta-analysis. For the changes in PlI, the meta-analysis of three studies demonstrated significant differences in favour of the control group (WMD: 0.147, $p = 0.000$, Table 7).

Four investigations from the same research group tested the efficacy of adjunctive CHX varnish. These studies did not demonstrate a significant heterogeneity for the tested clinical variables, except for the BOP changes ($p = 0.000$). Significant differences were demonstrated for both PPD (WMD: −0.413, $p = 0.007$, Table 5) and BOP changes (WMD: −4.840, $p = 0.001$, Table 7) in favour of the test group. Neither changes in CAL nor PlI demonstrated significant benefits in the test groups in the meta-analyses.

CHX plus xanthan gel was evaluated in two studies and only the variable CAL changes could be subjected to meta-analysis, demonstrating significant differences favouring the test group (WMD: −0.891, $p = 0.000$, Table 6).

Doxycycline

Of the seven available studies, five provided adequate data for PPD, which did not show a significant heterogeneity ($p = 0.225$), and the fixed effect model demonstrated a significant greater reduction with adjunctive doxycycline (WMD = −0.573, $p = 0.000$, Fig. 2, Table 5). For CAL changes, seven studies were included in the meta-analysis, and a significant heterogeneity was observed ($p = 0.000$), therefore a subgroup analyses based on the length of follow-up and in the study design was performed: in split-mouth and both short- and medium-term studies, significant differences were demonstrated in favour of the test group (WMD: −0.483, $p = 0.002$; WMD: −0.546, $p = 0.023$; WMD: −0.400, $p = 0.027$ respectively; Table 6), but not for parallel nor long-term studies ($p = 0.139$ in both groups). The lack of comparable data prevented any meta-analysis for BOP. For the changes in PlI, two studies were included in the meta-analysis, but no statistically significant differences were found between the study groups (WMD = 0.107, $p = 0.509$, Table 7).

Table 2. Material and methods of the selected studies: country, economic support, sample size, age and follow-up

Reference	Country	Support	*n* (baseline)	*n* (final)	Mean (range) age	Follow-up (months)
Minabe et al. (1991)	Japan	Not stated	16*	na	46	2
Nakagawa et al. (1991)	Japan	Sunstar	11*	11	na	3
van Steenberghe et al. (1993)	Belgium	Not stated	103	81	na	1.5
Jeong et al. (1994)	Korea and USA	Not stated	16*	na	28-58	3
Jones et al. (1994)	USA	Lederle	51	39	28–68	6
Newman et al. (1994)	USA	P&G	113*	105	51	6
Drisko et al. (1995)	USA	Palo Alto	122*	116	45.1 (25–54)	12
Radvar et al. (1996)	Scotland	Not stated	67	54	na	1.5
Timmerman et al. (1996)	The Netherlands	American Cynanamid	20	20	44.9 (39–59)	18
Graca et al. (1997)	UK	Not stated	30	26	29–50	3
Jarrold et al. (1997)	UK	Not stated	22*	na	60 (53–73)	4
Noyan et al. (1997)	Denmark	Dumex	10**	10	35–51	1.5
Soskolne et al. (1997)	UK and Israel	Perio Products	118*	94	47.5 (30–65)	6
Jeffcoat et al. (1998)	USA	Perio Products	447	418	46.4 (27–79)	9
Lie et al. (1998)	Norway	Colgate	18*	na	36–77	6
Tonetti et al. (1998)	Italy	Alza	127	123	49.7 ± 9.2	6
Wong et al. (1998)	China	Public funds	30*	30	42.7	6
Kinane & Radvar (1999)	UK	Not stated	60	41	45 ± 6.4	6
Palmer et al. (1999)	UK	Public funds	84	84	35–65	6
Riep et al. (1999)	Germany	Not stated	30*	29	47	3
Yalcin et al. (1999)	Turkey	Not stated	17*	na	na	1.75
Griffiths et al. (2000)	UK	Not stated	88*	na	34–71	9
Jeffcoat et al. (2000)	USA	Perio Products	45	42	30–80	9
Stelzel & Flores-de-Jacoby (2000)	Germany	Dumex	64*	59	47 (23–70)	8.5
Heasman et al. (2001)	UK	Not stated	26*	24	42.6 (34–59)	6
Wennstrom et al. (2001)	Sweden, UK, USA	Kalpesh Patel	105	101	47.2 (30–69)	3
Williams et al. (2001)	USA	OraPharma	748	696	29-79	9
Azmak et al. (2002)	Turkey	Not stated	20*	20	36–68	6
Eickholz et al. (2002)	Germany	Ivoclar Vivadent	111*	108	49.9 (23–71)	6
Friesen et al. (2002)	USA	P&G	24	24	43.6 (26–69)	6
Grisi et al. (2002)	Brazil	Not stated	20	19	41.8 (35–56)	9
Henderson et al. (2002)	New Zealand	OraPharma	15*	15	46.3 (35–69)	6
Meinberg et al. (2002)	USA	OraPharma	48	48	na	12
Van Dyke et al. (2002)	USA	Not stated	24	24	na	6
Aimetti et al. (2004)	Italy	Dental Triy	19*	19	47 ± 10.78	12
Akalin et al. (2004)	Turkey	Not stated	45*	na	30–61	1.75
Machion et al. (2004)	Brazil	Public funds	43	43	na	6
Rodrigues et al. (2004)	Brazil	Various	30	na	46 ± 11	12
Cosyn et al. (2005)	Belgium	Not stated	16	na	32–78	3
Agan et al. (2006)	Turkey	OraPharma	10*	na	55 (41–69)	6
Cosyn & Wyn (2006)	Belgium	Not stated	12	na	33–75	3
Cosyn et al. (2006)	Belgium	Not stated	26	na	33–78	9
Machion et al. (2006)	Brazil	Public funds	48	30	na	24
Mizrak et al. (2006)	Turkey	Not stated	34	34	35 (20–55)	6
Carvalho et al. (2007)	USA	Not stated	26*	26	54.5 (35–81)	9
Cosyn et al. (2007)	Belgium	Public funds	33	na	30–75	6
Goodson et al. (2007)	USA	Not stated	127	127	na	1
Kasaj et al. (2007)	Germany	Dexcle Pharma	20	20	42 ± 5.6	6
Bogren et al. (2008)	Sweden and USA	Public funds	128	124	34–82	36
Gupta et al. (2008)	India	Not stated	30*	na	25–75	3
Paolantonio et al. (2008)	Italy	Not stated	116*	116	33–65	6
Pradeep et al. (2008)	India	Not stated	80	80	25–50	3
Gopinath et al. (2009)	India	Not stated	15*	na	35–50	6
Paolantonio et al. (2009)	Italy	Not stated	98*	98	24–58	6
Bland et al. (2010)	USA	OraPharma	127	124	30–65	1
Sakellari et al. (2010)	Greece	Arrini	56	50	na	6

na, not available.
*Study with split-mouth design.
**Study with split-mouth and parallel design.

Metronidazole

Seven studies evaluated the effects of metronidazole. For PPD changes, five studies, without a significant heterogeneity ($p = 0.035$), were pooled in a meta-analysis, and the fixed effect model showed a significant difference in favour of the test group (WMD = −0.157, $p = 0.035$, Table 5). For

Table 3. Material and methods of the selected studies: periodontal status, previous periodontal treatments and evaluated local antimicrobials

Reference	Periodontal status	Previous treatments	Product
Minabe et al. (1991)	Gen. P.	Untreated 1–2 m	Tet film
Nakagawa et al. (1991)	PD.	SPT > 3 m	Min gel
van Steenberghe et al. (1993)	Mod., Sev., Ch. P.	na	Min gel
Jeong et al. (1994)	Mod. P.	Untreated > 3 m	Tet gel
Jones et al. (1994)	Mod., Sev. P.	Untreated or PP within a year	Min spheres
Newman et al. (1994)	na	SPT	Tet fibre
Drisko et al. (1995)	Sev. P.	2–3 w after PP	Tet fibre
Radvar et al. (1996)	Ch. P.	SRP > 6 m	Min gel, Tet fibre, Met gel
Timmerman et al. (1996)	Mod., Sev. Ch. P.	Untreated or PP within a year	Min gel
Graca et al. (1997)	Mod., Sev. P.	Untreated > 3 m	Min gel
Jarrold et al. (1997)	CPITN = 4	na	Min gel
Noyan et al. (1997)	Sev. P.	Untreated > 6 m	Met gel
Soskolne et al. (1997)	Mod. P.	na	Chx chip
Jeffcoat et al. (1998)	P.	na	Chx chip
Lie et al. (1998)	Mod., Sev. Ch. P.	Untreated	Tet ointment, Met gel
Tonetti et al. (1998)	na	Untreated > 3 m	Tet fibre
Wong et al. (1998)	Loc. recurrent P.	SPT	Tet fibre
Kinane & Radvar (1999)	Ch. P.	Untreated > 6 m	Min gel, Tet fibre, Met gel
Palmer et al. (1999)	Mod., Sev. P.	Untreated > 6 m	Met gel
Riep et al. (1999)	Mod., Sev. P.	SPT	Met gel
Yalcin et al. (1999)	Mod., Sev. P.	na	Tet fibre
Griffiths et al. (2000)	Ch. Ad. P.	na	Met gel
Jeffcoat et al. (2000)	Sev. Ch. P.	Untreated	Chx chip
Stelzel & Flores-de-Jacoby (2000)	P.	Untreated, pre-treated or recall	Met gel
Heasman et al. (2001)	Ch. P.	Untreated > 3 m	Chx chip
Wennstrom et al. (2001)	Mod., Sev. Ch. P.	Untreated > 2 m	Dox gel
Williams et al. (2001)	Mod., Sev. Ch. P.	Untreated > 6 m	Min spheres
Azmak et al. (2002)	Mod., Sev. Ch. P.	Untreated > 6 m	Chx chip
Eickholz et al. (2002)	Mod., Sev. P.	Untreated or recurrent	Dox gel
Friesen et al. (2002)	P.	na	Tet strips
Grisi et al. (2002)	Ch. P.	Untreated > 6 m	Chx chip
Henderson et al. (2002)	Ch. P.	Untreated > 3 m	Min gel
Meinberg et al. (2002)	Mod., Sev. Ch. P.	Untreated > 6 m	Min gel
Van Dyke et al. (2002)	Mod., Sev. P.	na	Min gel
Aimetti et al. (2004)	Ch. P.	Untreated > 3 m	Tet fibre
Akalin et al. (2004)	Ch. P.	Untreated > 6 m	Dox gel
Machion et al. (2004)	Ch. P.	Untreated > 6 m	Dox gel
Rodrigues et al. (2004)	Ch. P.	Untreated > 6 m	Tet fibre
Cosyn et al. (2005)	Ch. P.	na	Chx varnish
Agan et al. (2006)	Ch. P.	Untreated > 6 m	Dox gel
Cosyn & Wyn (2006)	Ch. P.	na	Chx varnish
Cosyn et al. (2006)	Ch. P.	na	Chx varnish
Machion et al. (2006)	Ch. P.	Untreated > 6 m	Dox gel
Mizrak et al. (2006)	P.	Untreated > 6 m	Chx chip
Carvalho et al. (2007)	Mod., Sev. Ch. P.	na	Chx chip
Cosyn et al. (2007)	Ch. P.	na	Chx varnish
Goodson et al. (2007)	Mod., Sev. P.	Untreated > 3 m	Min spheres
Kasaj et al. (2007)	Mod., Sev. Ch. P.	SPT	Chx chip
Bogren et al. (2008)	Mod., Sev. Ch. P.	SPT > 1 year	Dox gel
Gupta et al. (2008)	Mod., Sev. Ch. P.	Untreated > 2 m;post-surgery > 24 m	Dox gel, Chx xan-gel
Paolantonio et al. (2008)	Mod., Sev. P.	Untreated > 6 m	Chx chip
Pradeep et al. (2008)	Ch. P.	Untreated > 6 m	Azi gel
Gopinath et al. (2009)	Ch. P.	Untreated > 6 m	Min spheres
Paolantonio et al. (2009)	Mod., Sev. P.	Untreated > 6 m	Chx gel
Bland et al. (2010)	Mod., Sev. Ch. P.	Untreated > 3 m et al. (exception SPT)	Min spheres
Sakellari et al. (2010)	Gen. Ch. P.	Untreated > 12 m	Chx chip

Gen., generalized; Loc., localized; P., periodontitis; PD., periodontal disease; Ch. Chronic; Sev., severe; Mod., moderate.
SRP, scaling and root planing; SPT, supportive periodontal therapy; PP, professional prophylaxis; na, not available.
Min, minocycline; Dox, doxycycline; Tet, tetracycline; Chx, chlorhexidine; Azi, azithromycin; Met, metronidazole.

CAL changes, five studies, without a significant heterogeneity ($p = 0.900$) were included in the meta-analysis, but fixed effects model did not reveal any additional effect of the test product (WMD: 0.008, $p = 0.877$, Table 6). For BOP changes, three papers were included in the meta-analysis, and the random effect model showed statistically significant less BOP in the test group (WMD: −4.475, $p = 0.000$, Table 7). No meta-analysis could be performed on PII changes.

Table 4. Material and methods of the selected studies: outcome variables and statistically significant inter-group differences as reported in the results

Reference	PPD/CAL probe and stent	Plaque index (PII)	Gingival index (GI)	Number of examiners	Calibrated examiners	Outcomes with significant differences
Minabe et al. (1991)	na	Silness & Löe	Löe & Silness	na	na	PD, BOP
Nakagawa et al. (1991)	Williams	–	–	na	na	PD, CAL, BOP
van Steenberghe et al. (1993)	15 mm et al. (0.5 mm intervals)	Silness & Löe	Löe & Silness	na	na	PD
Jeong et al. (1994)	na	Silness & Löe	Sulcus bleeding index	na	na	No differences
Jones et al. (1994)	Florida	Silness & Löe	Löe & Silness	na	na	CAL
Newman et al. (1994)	Controlled-force et al. (20 g)	–	–	na	na	CAL
Drisko et al. (1995)	Conventional	Silness & Löe	–	3	Yes	PPD
Radvar et al. (1996)	Florida	Silness & Löe	Lobene's modified GI	1	–	PPD, MGI
Timmerman et al. (1996)	15 mm et al. (0.5 mm intervals)	Silness & Löe	Löe & Silness	na	na	GI, PI
Graca et al. (1997)	Borodontic	Dichotomous	Bleeding on marginal probing	1	na	PPD, BOP
Jarrold et al. (1997)	Hunter	Silness & Löe	Löe & Silness	1	Yes	No differences
Noyan et al. (1997)	Calibrated probe & oclusal stent	Silness & Löe	Löe & Silness	2	na	PPD, CAL
Soskolne et al. (1997)	UNC & stent	Silness & Löe	Modified gingival Index	3	intra-centre	PPD, CAL
Jeffcoat et al. (1998)	UNC	Silness & Löe	Löe & Silness	At least one/centre	Yes	PPD, CAL, BOP
Lie et al. (1998)	Florida	–	–	1	na	No differences
Tonetti et al. (1998)	Pressure sensitive probe	O'Leary PII	–	1	Yes	No differences
Wong et al. (1998)	Inter-probe	Silness & Löe	Gingival index	na	na	No differences
Kinane & Radvar (1999)	Florida & stent	Silness & Löe	Lobene's Modified GI	1	na	PPD
Palmer et al. (1999)	Florida	Dichotomous	–	1	na	No differences
Riep et al. (1999)	UNC & stent	Approximal PII	Papilla bleeding index	1	na	No differences
Yalcin et al. (1999)	Borodontic	Silness & Löe	Löe & Silness	1	na	PPD, PI
Griffiths et al. (2000)	EN15 probe & stent	–	–	2	Yes	PPD, BOP
Jeffcoat et al. (2000)	UNC	–	–	na	na	PPD, CAL
Stelzel & Flores-de-Jacoby (2000)	PCP-12	–	–	na	na	PPD, BOP
Heasman et al. (2001)	Florida & stent	Silness & Löe	Bleeding Index of Muhlemann	2	Yes	CAL, BI
Wennstrom et al. (2001)	15-mm probe	Silness & Löe	Bleeding on probing	3	Yes	BOP
Williams et al. (2001)	UNC	–	–	18	Yes	PPD, BOP
Azmak et al. (2002)	Williams	Silness & Löe	Papilla bleeding index	1	na	no differences
Eickholz et al. (2002)	UNC & stent	Silness & Löe	Löe & Silness	6	Yes	PPD, CAL
Friesen et al. (2002)	UNC	Silness & Löe	Löe & Silness	na	na	PPD
Grisi et al. (2002)	Florida & stent	Löe 1967	Papillary bleeding Index	1	na	BOP
Henderson et al. (2002)	Manual probe et al. (1-mm intervals)	Silness & Löe	Bleeding index of Muhlemann	1	na	no differences
Meinberg et al. (2002)	na	–	–	1	Yes	PPD
Van Dyke et al. (2002)	Florida & stent	Silness & Löe	Bleeding index/Löe & Silness	na	na	no differences
Aimetti et al. (2004)	Williams	Dichotomous	–	1	na	PPD, CAL, BOP
Akalin et al. (2004)	Williams	Silness & Löe	Sulcular bleeding index	na	na	PPD, CAL, SBI, PI
Machion et al. (2004)	Florida & stent	Dichotomous	Bleeding on probing	1	Yes	CAL
Rodrigues et al. (2004)	UNC	Dichotomous	–	2	Yes	No differences
Cosyn et al. (2005)	UNC	Quigley & Hein	Sulcus bleeding index	1	Yes	No differences
Agan et al. (2006)	na	Quigley & Hein	Probe bleeding index	na	na	No differences
Cosyn & Wyn (2006)	UNC	Quigley & Hein	Sulcus bleeding index	1	Yes	No differences
Cosyn et al. (2006)	UNC	Quigley & Hein	Sulcus bleeding index	1	Yes	PPD
Machion et al. (2006)	Florida stent probe	Dichotomous	Bleeding on probing	2	Yes	CAL
Mizrak et al. (2006)	na/stent	Silness & Löe	Löe & Silness	na	na	PPD, CAL, PI
Carvalho et al. (2007)	UNC	–	–	2	Yes	No differences
Cosyn et al. (2007)	UNC	Quigley & Hein	Sulcus bleeding index	1	Yes	No differences

Table 4. (continued)

Reference	PPD/CAL probe and stent	Plaque index (PII)	Gingival index (GI)	Number of examiners	Calibrated examiners	Outcomes with significant differences
Goodson et al. (2007)	na	–	–	na	na	No differences
Kasaj et al. (2007)	PCP-15	Silness & Löe	Löe & Silness	1	Yes	PPD, CAL, BOP
Bogren et al. (2008)	UNC	–	–	2	Yes	No differenes
Gupta et al. (2008)	UNC & stent	Silness & Löe	Löe & Silness	na	na	PPD, CAL
Paolantonio et al. (2008)	na & stent	Silness & Löe	Modified gingival index	4	Yes	PPD, CAL (PD > 7 mm)
Pradeep et al. (2008)	Williams	–	Modified GI/modified SBI	1	na	MGI, PPD, CAL
Gopinath et al. (2009)	na & stent	na	na	na	na	PPD, BOP, PI, GI
Paolantonio et al. (2009)	Manual 15-mm probe	–	–	4	Yes	PPD, CAL
Bland et al. (2010)	na	–	–	5	Yes	PPD, CAL, BOP
Sakellari et al. (2010)	Williams	–	–	1	Yes	No differences

UNC, University North Carolina; SBI, sulcus bleeding index; PPD, probing pocket depth; CAL, clinical attachment level; BOP, bleeding on probing; MGI, modified gingival index; na, not available.

Minocycline

Thirteen papers evaluated the clinical efficacy of minocycline. Eight studies were included in a meta-analysis evaluating the PPD changes, which did not show a significant heterogeneity ($p = 0.210$), and the fixed effect model demonstrated a significant greater PPD reduction when using adjunctive minocycline (WMD: −0.472, $p = 0.000$, Table 5). For CAL changes, seven studies were included in the meta-analysis, demonstrating a significant heterogeneity ($p = 0.000$) and a non-significant adjunctive effect (WMD: −0.189, $p = 0.008$, Table 6). For BOP changes, three papers were pooled in the meta-analysis, with a significant heterogeneity ($p = 0.000$), and without showing significant differences (WMD: −0.871, $p = 0.634$, Table 7). For PlI changes, three studies were included in the meta-analysis demonstrating statistically significant differences favouring the control groups (WMD: 0.239, $p = 0.000$, Table 7), without significant heterogeneity (χ^2 $p = 0.626$).

Tetracycline products

Eight studies evaluated the adjunctive efficacy of tetracycline fibres, and five were used for the meta-analysis of the PPD changes. The fixed effect model showed significant PPD reductions in the test group (WMD: −0.727, $p = 0.000$, Table 5). For CAL changes, five papers were included in the meta-analysis, but these data showed a significant heterogeneity ($p = 0.000$). In the sub-group analysis, the short-term studies showed significant heterogeneity ($p = 0.000$), but both the split-mouth and parallel trials demonstrated significant differences favouring the test groups (WMD: −0.304, $p = 0.020$ and WMD: −0.606, $p = 0.012$ respectively; Table 6). For changes in BOP, meta-analysis was done with the data from two studies. Despite a highly significant heterogeneity ($p = 0.00$), differences achieved with the random effects model in favour of the test were statistically significant ($p = 0.007$, Table 7). For PlI, the meta-analysis performed with data from two studies revealed significant differences between the groups in favour of the test (WMD: −0.150, $p = 0.000$, Table 7).

Two studies evaluated the clinical efficacy of tetracycline strips, demonstrating significant CAL gains ($p < 0.05$).

Quality assessment (Table 1)

In most studies, the quality parameters were considered unclear or not fulfilled, and all the selected studies, except two (Eickholz et al. 2002, Sakellari et al. 2010), were qualified with a high or moderate risk of bias.

Publication bias and sensitivity analyses

No publication bias was detected in the main outcome variable ($p = 0.324$; Egger′s test for changes in PPD). The sensitivity analyses detected the influence of particular studies in the overall heterogeneity, being two studies (Jeffcoat et al. 1998, 3.2%; Newman et al. 1994, −5.2%) the two extremes. As the elimination of these two articles from the the meta-analyses did not imply any significant change in the overall WMD, we decided to keep all selected studies.

Occurrence of adverse effects

Only few studies reported adverse effects with the use of local antimicrobials. They included gingival redness, pain on the first day, dislodgement of the chip, gingival tingling, fever, headache, diarrhoea, smarting, periodontal abscesses, root sensitivity, caries, taste disturbances and stomatitis.

Discussion

This systematic review was based on data extracted from 52 RCTs, reported in 56 publications. In most of these studies, the subgingival application of an antimicrobial adjunctively to SRP demonstrated additional clinical benefits (especially in PPD reductions). The overall meta-analysis combining all the antimicrobial products showed significant PPD reductions and CAL gains (0.407 and 0.310 mm, respectively) when compared with the control groups. These results are in agreement with previously published systematic reviews reporting similar changes, ranging between 0.3 and 0.6 mm (Hanes & Purvis 2003, Bonito et al. 2005). When the studies were analysed depending on the antimicrobial used, there was a high degree of heterogeneity that necessitated subgrouping by study design and time of follow-up to reduce the

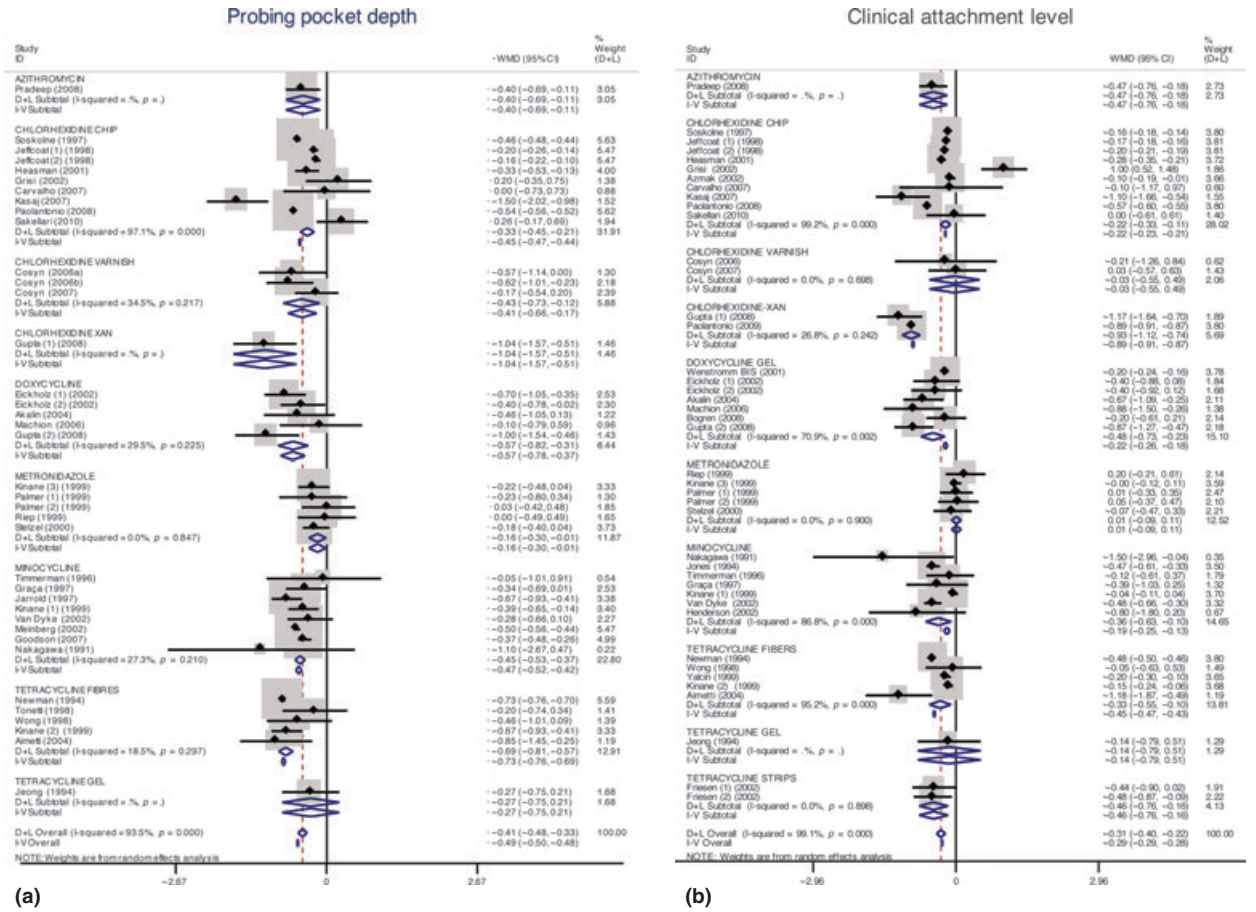

Fig. 2. (a) Meta-analysis: changes in probing pocket depth. I+V stands for inverse-variance weighted (fixed effect) model. D+L stands for DerSimonian and Laird (random effect) model. In the fixed effect model, studies are weighted according to the amount of information that they contain. The random effect model incorporates an estimate of between-study variation (heterogeneity) in the weighting. (b) Meta-analysis: changes in clinical attachment level. I + V stands for inverse-variance weighted (fixed effect) model. D+L stands for DerSimonian and Laird (random effect) model. In the fixed effect model, studies are weighted according to the amount of information that they contain. The random effect model incorporates an estimate of between-study variation (heterogeneity) in the weighting. [For papers used more than once: Jeffcoat (1), SRP versus SRP & chx chip; Jeffcoat (2), SRP & placebo versus SRP & chx chip; Gupta (1), SRP versus SRP & chx xanthan gel; Gupta (2), SRP versus SRP &doxy gel; Eickholz (1), SRP versus SRP & doxy gel; Eickholz (2), SRP & placebo versus SRP & doxy gel; Kinane (1), SRP versus SRP & min; Kinane (2), SRP versus SRP & tet fibres; Kinane (3), SRP versus SRP & met; Palmer (1), SRP versus SRP & met (smokers); Palmer (2), SRP versus SRP & met (non-smokers); Friesen (1), SRP versus SRP & tet strips (single application); Friesen (2), SRP versus SRP & tet strips (multiple applications).]

heterogeneity for some of the variables. This subgrouping, however, did not vary the main trend in the results, demonstrating significant differences in most of the tested clinical variables favouring the test group. In the sensitivity analysis, the exclusion of studies reporting more heterogeneous data did not significantly alter the results. Similarly, the analysis of the publication bias did not demonstrate significant bias.

In spite of these significant differences, the magnitude of the effect was different among the tested antimicrobials. The largest effect in the primary outcome (PPD) was demonstrated with the application of tetracycline fibres (meta-analysis of five RCTs with 350 patients, PPD reduction of 0.727 mm), followed by doxycycline (0.573 mm) and minocycline (0.472 mm). The effect of CHX chips and metronidazole, however, rendered minimal additional PPD reductions, below 0.4 mm. For CAL gains the highest effect was demonstrated by the application of CHX-xanthan gel, although these data are based in only one study (0.9 mm). Conversely, the application of metronidazole and other CHX products did not add any effect to SRP alone. These results are in agreement with previous systematic reviews. Hanes & Purvis (2003) reported the best results in PPD reductions for minocycline, whereas Bonito et al. (2005) reported significant efficacy for minocycline, metronidazole, CHX and local tetracycline.

These different effects demonstrated by the different antimicrobial compounds applied topically depends not only on its pharmacology but also on its pharmacodynamics or the vehicle employed that are responsible of its sustained release. This effect is very clear when analysing the results of the three different CHX formulations. The biggest effect was shown by CHX plus xanthan gel, followed by CHX chips and then by CHX varnish, reflecting

Table 5. Meta-analyses of different local antimicrobials for probing pocket depth changes expressed as weighted mean difference (WMD), with 95% confidence interval (CI) and evaluation of heterogeneity

Product	Analyses	Subgroup	*n*	WMD	95% CI	*p*-value	I^2	*p*-value
Chlorhexidine chip	Overall		9	−0.328	−0.447; -0.209	0.000	97.1%	0.000
	Follow-up*	*Short*	7	−0.447	−0.542; −0.352	0.321	91%	0.000
		Medium	2	−0.18	−0.220; −0.140	0.000	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	5	−0.486	−0.499; −0.473	0.000	91.9%	0.000
		Parallel	4	−0.157	−0.239; −0.075	0.000	55.3%	0.081
Chlorhexidine varnish	Overall		3	−0.413	−0.655; −0.170	0.007	34.5%	0.217
	Follow-up*	*Short*	2	−0.286	−0.549; 0.021	0.068	25.3%	0.247
		Medium	1	−0.620	−1.014; −0.226	0.002	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	0	np	np	np	np	np
		Parallel	3	−0.413	−0.655; −0.170	0.007	34.5%	0.217
Doxycycline	Overall		5	−0.573	−0.778; −0.367	0.000	29.5%	0.225
	Follow-up*	*Short*	3	−0.757	−1.156; −0.358	0.006	42.6%	0.187
		Medium	1	−0.562	−0.818; −0.306	0.000	23.9%	0.252
		Long	1	−0.100	−0.791; 0.591	0.777	np	np
	Study design	*Split-mouth*	3	−0.619	−0.834; −0.404	0.000	19.0%	0.295
		Parallel	2	−0.100	−0.791; 0.591	0.777	np	np
Metronidazole	Overall		5	−0.157	−0.303; −0.011	0.035	0.0%	0.847
	Follow-up*	*Short*	4	−0.139	−0.332; 0.053	0.155	0.0%	0.726
		Medium	1	−0.180	−0.404; 0.044	0.116	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	2	−0.148	−0.352; −0.005	0.153	0.0%	0.510
		Parallel	3	−0.165	−0.375; 0.044	0.122	0.0%	0.626
Minocycline	Overall		8	−0.472	−0.520; −0.424	0.000	27.3%	0.210
	Follow-up*	*Short*	6	−0.405	−0.494; −0.315	0.000	13.7%	0.327
		Medium	1	−0.500	−0.557; −0.443	0.000	np	np
		Long	1	−0.050	−1.012; 0.912	0.919	np	np
	Study design	*Split-mouth*	2	−0.681	−0.934; −0.428	0.000	0.0%	0.597
		Parallel	6	−0.464	−0.513; −0.415	0.000	24.5%	0.250
Tetracycline fibre	Overall		5	−0.727	−0.759; -0.695	0.000	18.5%	0.297
	Follow-up*	*Short*	4	−0.726	−0.758; −0.694	0.000	36.8%	0.191
		Medium	1	−0.850	−1.455; −0.245	0.006	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	3	−0.729	−0.762; −0.697	0.000	0.0%	0.583
		Parallel	2	−0.581	−0.816; −0.346	0.028	57.0%	0.127

np, not performed; *n*, number of studies.
*Short- (<6 months), medium- (6–12 months) or long-term (>12 months) studies.

the capacity of the vehicle to sustain the release of the antimicrobial product (Soskolne et al. 1998, Paolantonio et al. 2009). It is, therefore important, not only to select the therapeutic agent, but the resulting pharmacokinetic profile, mainly due to the vehicle utilized for its topical application.

In most of the studies, the site selection for the local application of the antimicrobial was based in the presence of deep PPD (≥ 5 mm). Studies with initially deeper PPDs demonstrated a higher magnitude of the effect, with PPD reductions of up to 2.3 mm, although this enhanced effect also occurred at the control sites (Timmerman et al. 1996, Eickholz et al. 2002). In the study of Aimetti et al. (2004), however, despite shallower initial mean PPD than the previously mentioned studies, the reductions were highly significant in the group applying tetracycline fibres ($\geq$ 2 mm).

The occurrence of adverse effect/complications with the use of local antimicrobials was minimal, without reporting significant adverse effects. These results are also similar to previously published systematic reviews (Hanes & Purvis 2003, Bonito et al. 2005). Only minor gingival complications were reported affecting both the control and the test groups.

All studies, except two (Eickholz et al. 2002, Sakellari et al. 2010), were catalogued with a high risk of bias, due to lack of reporting some key methodological aspects such as: randomization, allocation concealment or patient drop-outs. In spite of the meticulous methods used in the literature search and data extraction/management, retrieving more potentially relevant articles than previous systematic reviews (Hanes & Purvis 2003, Bonito et al. 2005) the resulting data for most of the outcome variables showed a high degree of heterogeneity. This might be due to differences in the populations studied, or to differences in the disease severity, the quality of treatment rendered, or to lack of relevant data (e.g. proportion of smokers). This heterogeneity may therefore overestimate or underestimate the real effect of the tested products, hence limiting the results of this systematic review. The length of the follow-up was also heterogeneous, ranging from 1 to 36 months, necessitating stratification of studies into short- (<6 months), medium- (6–12 months) or long-term (>12 months) follow-up, although these categories were made arbitrarily and some studies with really short

Table 6. Meta-analyses of different local antimicrobials for clinical attachment level changes expressed as weighted mean difference (WMD), with 95% confidence interval (CI) and evaluation of heterogeneity

Product	Analyses	Subgroup	*n*	WMD	95% CI	*p*-value	I^2	*p*-value
Chlorhexidine chip	Overall		10	−0.218	−0.329; −0.107	0.000	99.2%	0.000
	Follow-up*	*Short*	8	−0.194	−0.422; 0.035	0.097	99.2%	0.000
		Medium	2	−0.185	−0.214; −0.156	0.000	92.4%	0.000
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	6	−0.357	−0.606; −0.108	0.005	99.4%	0.000
		Parallel	4	−0.172	−0.220; −0.124	0.000	91.9%	0.000
Chlorhexidine varnish	Overall		2	−0.029	−0.550; 0.492	0.914	0.0%	0.698
Chlorhexidine xanthan gel	Overall		2	−0.891	−0.914; −0.867	0.000	26.8%	0.242
Doxycycline	Overall		7	−0.218	−0.260; −0.176	0.023	86.7%	0.001
	Follow-up*	*Short*	4	−0.546	−1.017; −0.075	0.002	75.2%	0.003
		Medium	1	−0.400	−0.754; −0.046	0.027	0.0%	1.000
		Long	2	−0.408	−0.750; −0.066	0.139	69.0%	0.072
	Study design	*Split-mouth*	4	−0.483	−0.787; −0.180	0.002	75.2%	0.003
		Parallel	3	−0.408	−0.750; −0.066	0.139	69.0%	0.072
Metronidazole	Overall		5	0.008	−0.091; 0.107	0.877	0.0%	0.900
	Follow-up*	*Short*	4	0.013	−0.089; 0.115	0.803	0.0%	0.824
		Medium	1	−0.070	−0.465; 0.325	0.729	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	2	0.060	−0.226; 0.345	0.683	0.0%	0.354
		Parallel	3	0.001	−0.105; 0.106	0.989	0.0%	0.969
Minocycline	Overall		7	−0.189	−0.251; −0,126	0.008	86.8%	0.000
	Follow-up*	*Short*	6	−0.404	−0.698; −0.110	0.007	89.0%	0.000
		Medium	0	np	np	np	np	np
		Long	1	−0.120	−0.614; 0.374	0.634	np	np
	Study design	*Split-mouth*	2	−1.025	−1.852; −0.198	0.015	0.0%	0.439
		Parallel	5	−0.301	−0.573; −0.028	0.031	90.2%	0.000
Tetracycline fibre	Overall		5	−0.327	−0.552; −0.101	0.005	95.2%	0.000
	Follow-up*	*Short*	4	−0.256	−0.487; −0.024	0.030	96.2%	0.000
		Medium	1	−1.180	−1.871; −0.489	0.001	np	np
		Long	0	np	np	np	np	np
	Study design	*Split-mouth*	3	−0.304	−0.560; −0.049	0.020	93.7%	0.000
		Parallel	2	−0.606	−1.608; 0.397	0.0236	88.1%	0.004
Tetracycline strip	Overall		2	−0.463	−0.401; −0.163	np	np	np

np, not performed; *n*, number of studies.
*Short- (<6 months), medium- (6–12 months) or long-term (>12 months) studies.

Table 7. Meta-analyses of different local antimicrobials for plaque index (PlI) and bleeding on probing (BOP) changes expressed as weighted mean difference (WMD), with 95% confidence interval (CI) and evaluation of heterogeneity

Variable	Product	*n*	WMD	95% CI	*p*-value	I^2 (%)	*p*-value
BOP	Chlorhexidine varnish	3	−4.840	−7.692; −1.988	0.001	97.4	0.000
	Metronidazole	3	−4.475	−6.734; −2.216	0.000	98.9	0.000
	Minocycline	3	−0.871	−4.449; 2.708	0.634	99.9	0.000
	Tetracycline fibre	2	−24.948	−43.077; −6.818	0.007	100.0	0.000
PlI	Chlorhexidine chip	3	0.147	0.099; 0.194	0.000	0.0	0.000
	Chlorhexidine varnish	4	−0.112	−0.331; 0.106	0.313	0.0	0.313
	Doxycycline	2	0.107	−0.211; 0.426	0.509	75.5	0.509
	Minocycline	3	0.239	0.060; 0.419	0.009	0.0	0.009
	Tetracycline fibre	2	−0.150	−0.188; −0.112	0.000	0.0	0.227

n, number of studies.

follow-ups were included (Daneshmand et al. 2002, Goodson et al. 2007, Bland et al. 2010).

The analysed publication bias did not demonstrate significant results, although relevant factors in the selected studies should be highlighted. Most of the included studies were supported by private funds that might have influenced the results due in light of the commercial interests. Some studies made multiple comparisons using one single control group, while in others each test group was compared with a control group. We thus considered the data of each group as an independent study: this fact might have given the studies with multiple comparisons more weight in the meta-analysis.

When analysing the significant added beneficial effect demonstrated by most of the antimicrobials in this systematic review, it is important to focus on the magnitude of the effect and its clinical relevance. Although some agents, especially tetracycline fibres, doxycycline and minocycline achieved a significant added benefit, with others, the small magnitude of

the differences precludes any clear recommendation for its adjunctive use in the management of localized deep or recurrent pockets in chronic periodontitis patients. When considering the adjunctive use of these products clinicians should also consider other factors, such as the easy of handling, the time employed in its application and its cost; all potentially influencing the overall efficiency of these therapies.

In conclusion, the scientific evidence supports the adjunctive use of local antimicrobials to SRP in deep or recurrent periodontal sites, mostly when the vehicle has shown pharmacodynamic properties assuring the sustained release of the antimicrobial. This evidence must be interpreted with caution, as the reported data were highly heterogeneous and most of the selected studies were categorized with a high degree of bias. There is a need for further clinical trials with strict methodological criteria for allowing a more precise assessment of the efficacy of local antimicrobials in the treatment of chronic periodontitis.

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Clinical Relevance

Scientific rational for the study: Previous systematic reviews have demonstrated significant benefits on adjunctive local antimicrobials when compared with debridement alone. Nevertheless, the need for evaluating the new evidence published in the last years fostered the development of a new systematic review.
Principal findings: Statistically significant differences for both changes in probing pocket depth and clinical attachment level in favour of the adjunctive local antimicrobials groups were found.
Practical implications: Although the scientific evidence supports this strategy of treatment, no definitive practical advice could be given in view of the high risk of bias of the evidence published up to our days.