Local Drug Delivery Systems in the Treatment of Periodontitis: A Literature Review

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Abstract

In order to complement non-surgical therapy in periodontitis, there are multiple options of antimicrobials, such as metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline, which can be locally delivered into the mucosa. These drugs are used in periodontal pockets and can inhibit or eliminate periodontopathogenic microorganisms as well as modulate the inflammatory response of tissues. However, limited data are available concerning the relationship between effect, efficacy and clinical status of the periodontium. This review aims to evaluate the effect and the efficacy of five types of local drug delivery systems in clinical parameters of periodontology. Researched papers using MEDLINE via PubMed, and LILACS databases related to five types of local drug delivery systems as chlorhexidine gluconate, doxycycline hyclate, metronidazole gel, minocycline ointment and tetracycline fibers, were reviewed aiming to address the mechanism of action and the evidence of clinical effectiveness of adjunctive use of these antimicrobials following surgical and/or non-surgical therapies. Inclusion criteria defined that articles must be randomized controlled trials performed in humans and published between 1996 and 2014. The adjunctive use of local drug delivery systems with controlled release properties may provide a defined, but limited, beneficial response on periodontal pockets. Furthermore, local drug delivery as an active treatment or maintenance therapy depends on clinical findings, responses to treatment described in the literature, desired clinical outcomes, and patients' dental and medical histories, including their past usage of antimicrobials.

Key words: Periodontitis, doxycycline, tetracycline, metronidazole, minocycline, chlorhexidine, local delivery

Introduction

The accumulation of bacterial biofilm is the main etiological factor of periodontal diseases. This can be defined as an infectious pathology that affects the surrounding tissues of the teeth, which can lead to progressive loss of conjunctive tissue attachment and alveolar bone if not properly treated (Liñares and Martín-Herrero, 2003).

The initial treatment of periodontitis involves scaling and root planing (SRP), mechanical debridement of surfaces and oral hygiene orientations (Meira *et al.*, 2007). To complement the non-surgical therapy, there are multiple options of antimicrobials that can be locally delivered into the mucosa, such as metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline. These drugs are used in periodontal pockets and can inhibit or eliminate the periodontopathogenic microorganisms as well as modulate the inflammatory response of the tissues (Greenstein and Tonetti, 2000).

Locally delivered antimicrobials are designed with the concerned drugs impregnated in a vehicle and available in the form of gels, fibers, chips, polymers or ointments. To be clinically effective they must fulfill some criteria: the drug must reach the targeted site of action, remain at an effective concentration and last for an adequate period of time (Goodson, 1989; Greenstein and Tonetti, 2000).

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Chlorhexidine gluconate

Chlorhexidine (CHX) gluconate is a chemical antiseptic, antifungal and bactericidal agent, capable of eliminating both Gram-positive and Gram-negative bacteria. It also has a bacteriostatic effect, inhibiting bacterial proliferation. (Heasman *et al.*, 2001). This bisbiguanide antiseptic is used as a locally applied slow release drug delivery system available in the form of gel, varnish, chip, etc. To enhance the efficacy of non-surgical therapy a chemomechanical treatment concept was introduced based on sequential SRP and the adjunctive subgingival administration of 35% CHX varnish (Cosyn *et al.*, 2007) and subgingival placement of a biodegradable CHX chip (Jeffcoat *et al.*, 2000).

The biodegradable CHX chip (PerioChip, Dexcel Pharma GmbH, Alzenau, Germany) for the controlled delivery of CHX to the periodontal pocket enables slow subgingival release of 2.5 mg CHX within the periodontal pocket, maintaining an average drug concentration in the gingival crevicular fluid greater than 125 μg/mL) for 7 - 10 days (Soskolne *et al.*, 1998). The concentration of the drug remains above the minimum inhibitory concentration for more than 99% of the subgingival microorganisms from periodontal pockets (Stanley *et al.*, 1989). The results of several clinical trials have shown that the use of the CHX chip in conjunction with scaling and root planing is effective in reducing probing depth (PD), clinical attachment loss (CAL), and bleeding on probing (BOP) over a 6- to 9-month period (Soskolne *et al.*, 1997; Jeffcoat *et al.*, 1998). In addition, the use of a controlled release CHX delivery system during maintenance therapy allows greater improvement in clinical signs of periodontitis (Heasman *et al.*, 2001).

Doxycycline hyclate

Doxycycline is a bacteriostatic antibiotic that demonstrates a wide spectrum of activity against common periodontal pathogens such as *Aggregatibacter actinomycetemcomitans* (*Actinobacillus actinomycetemcomitans*; Walker *et al.*, 1985), *Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum, Eikenella corrodens* and spirochetes (Kulkarni *et al.*, 1991). This antibiotic is a synthetic tetracycline compound whose main advantages over tetracycline when delivered systemically are increased oral absorption, prolonged serum half-life and decreased gastrointestinal side-effects (Pascale *et al.*, 1986).

Local application of doxycycline has resulted in several studies that reported the efficacy of 10% doxycycline hyclate as a local delivery antimicrobial agent for attaining probing depth reduction and gaining clinical attachment (Polson *et al.*, 1997a; Polson *et al.*, 1997b). Furthermore, doxycycline may be useful in diseases characterized by excessive collagen loss: it has the highest rate of reduction in the action of collagenase (70%), followed by minocycline (45%) and tetracycline (23%; Gabler and Creamer, 1991).

Metronidazole gel

Metronidazole (MTZ) is a synthetic compound derivative of nitroimidazole that interferes with bacterial DNA synthesis, causing cell death (Miani, 2010). It is an efficient antimicrobial agent used against anaerobic bacteria and protozoa, and is prescribed in support of conventional periodontal therapy in systemic or local administration (Noyan *et al.*, 1997; Haffajee *et al.*, 2003).

A type of local presentation includes metronidazole in gel form, which is a bioabsorbable delivery device consisting of metronidazole benzoate in a matrix containing glyceryl mono-oleate and sesame oil (Norling *et al.*, 1992). In contact with gingival crevicular fluid, MTZ gel forms reversed hexagonal liquid crystals (Norling *et al.*, 1992). This prevents the gel from easily coming out of the periodontal pocket, maintaining a therapeutic drug level in the subgingival area for a long period of time (Leiknes *et al.*, 2007).

Rizzo *et al.* (2010) investigated the effects of metronidazole on the capacity to modulate cytokine secretion using a human periodontal ligament cell model stimulated with a lipopolysaccharide from *P. gingivalis*. The results showed that MTZ inhibited the production of IL-1β, IL-6, IL-8, IL-12, and TNF-α cytokines, indicating that this antibiotic may help reduce the influx of inflammatory cells to diseased sites and prevent periodontal tissue destruction, including alveolar bone resorption, with no cytotoxic effect on human periodontal ligament cells.

Minocycline ointment

The minocycline ointment utilized for subgingival application consists of a bioresorbable delivery system loaded with 2% minocycline hydrochloride. The matrix is a mixture of hydroxyethyl-cellulose, aminoalkyl methacrylate triacetine, and glycerinum. Magnesium chloride is used to modify the release properties. The elimination half-life based on the assumption of a single compartment open model is estimated to be 3.9 h, and the total time of effective antimicrobial activity is expected to be approximately 1 day (Satomi *et al.*, 1987).

Local administration of minocycline has been shown to be effective for the treatment of bacteria associated with periodontal disease (Jeong *et al.*, 1994). The study of Meinberg *et al.* (2002) utilized scaling and root planing with four subgingival doses of minocycline, which resulted in greater probing depth reduction and less frequent bone height loss compared to conventional periodontal maintenance.

Tetracycline fibers

Tetracycline is a bacteriostatic antibiotic that interferes with bacterial protein synthesis and inhibits tissue collagenase activity (Jain *et al.*, 2008). It has a broad spectrum of activity, inhibiting both Gram-negative and Gram-positive organisms, including the beta-lactamase-producing strains that occur in approximately 50% of 6 - 7 mm deep periodontal pockets and against which penicillin is ineffective (Jain *et al.*, 2008).

These semi-synthetic chemotherapeutic agents are effective against rapidly multiplying bacteria (Sachdeva and Agarwal, 2011). In the treatment of periodontal disease, tetracycline and its derivatives have been used systemically as well as locally. Local drug delivery avoids adverse effects associated with systemic therapy by limiting the drug to its target site with little or no systemic uptake (Sachdeva and Agarwal, 2011).

Discussion

This review researched papers using MEDLINE via PubMed, and LILACS databases related to five types of local drug delivery systems: chlorhexidine gluconate, doxycycline hyclate, metronidazole gel, minocycline ointment and tetracycline fibers, which were reviewed aiming to address the mechanism of action and the evidence of clinical effectiveness in the adjunctive use of these agents following surgical and/or non-surgical therapies. Inclusion criteria defined that articles must be randomized controlled trials performed in humans and published between 1996 and 2014 (*Table 1*).

Considering chlorhexidine studies, Jagadish Pai *et al.* (2013) analyzed three groups: SRP, SRP + CHX varnish, and SRP + CHX chip. All three groups showed reduction in PPD, and the application of CHX varnish and placement of CHX chips as adjuncts to SRP produced a clinically significant reduction in the PPD and BOP and a gain in CAL at 30 and 90 days from baseline when compared to SRP alone, though the results were not statistically significant. The mean reduction in PPD was 2.4 mm in SRP sites, 2.5 mm in SRP + CHX varnish sites and 2.8 mm in SRP + CHX chip sites. The mean gain in CAL was 2.4 mm in SRP sites, 2.3 mm in SRP + CHX varnish sites and 2.8 mm SRP + CHX chip sites. A smaller sample size (15 patients) over a shorter period (three months) and single application/insertion of the varnish/chip could be the limitations of this study (Jagadish Pai *et al.*, 2013).

The results of a study done by Grover *et al.* (2011) showed that a chlorhexidine chip containing 2.5 mg chlorhexidine gluconate is an effective adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis. It provides a safe, easily applied single-dose means of achieving significantly better clinical results than scaling and root planing alone. The adjunctive use of the chlorhexidine chip with scaling and root planing resulted in a clinically meaningful improvement in pocket depth reduction and clinical attachment level gain (1.15 ± 1.30 mm) compared with scaling and root planing alone (0.47 ± 1.26 mm; Grover *et al.*, 2011).

Medaiah *et al.* (2014) analyzed the effect of a controlled release chlorhexidine chip on clinical parameters of moderate to severe periodontitis. After the 3-month follow-up, no statistically significant difference was found between SRP and SRP + CHIP group in all clinical parameters. The mean reductions in PPD were 2.8 mm (SRP group), 2.6 mm (SRP + CHIP group) and 0.8 mm (chip alone group). The mean gain in CAL were 2.8 mm (SRP group), 2.5 mm (SRP + CHIP group) and 0.7 mm (chip alone group). Reduction in BOP was significant for the SRP and SRP + CHIP groups but not for the chip alone group.

Polson *et al.* (1997a, b) described clinical effectivity of a subgingivally biodegradable drug delivery system containing doxycycline hyclate (DH) in a polylactic acid polymer vehicle. In a 9-month multi-center, randomized and with parallel design study, Polson analyzed 173 patients, comparing results of a subgingivally administered biodegradable drug delivery system containing either 10% doxycycline hyclate, 5% sanguinarium chloride or no agent in reducing the clinical signs associated with periodontitis. They reported that doxycycline was superior to sanguinarine and vehicle without medication in probing depth reduction (2 mm at 5 months), BOP reduction and in attachment level gain (1.2 mm at 6 months). Furthermore, doxycycline was more efficient in deep pockets (attachment level gain: 1.7 mm) than moderate pockets (attachment level gain: 0.8 mm; Polson *et al.*, 1997a, 1997b).

Garrett *et al.* (1999) reported two multi-center clinical trials. Each trial completed a modified double-blind and randomized study with 684 adults with moderate to severe periodontitis. The groups were divided into doxycycline, placebo control, oral hygiene only, and SRP groups. All treatment groups in both studies showed clinical improvements from the baseline over the 9-month period. Thereby, all efficacy parameters were clinically and statistically superior for subjects treated with doxycycline compared to oral hygiene only and vehicle alone.

Deo *et al.* (2011) performed a randomized clinical trial in 60 chronic periodontitis patients with follow-up over 6 months. The control group was treated by SRP along with placebo while the test group was treated by SRP followed by local delivery of doxycycline hyclate 10%. The results concluded that the use of doxycycline hyclate 10% as an adjunct to scaling and root planing provides more favorable and statistically significant ($p < 0.001$) reductions in probing pocket depth (test group: 3.03 ± 0.92 mm; control group: 2.3 ± 0.65 mm), and gains in clinical attachment level (test group: 2.0 ± 0.64 mm; control group: 1.13 ± 1.07 mm), compared to SRP alone.

There are studies that did not find effective results utilizing doxycycline hyclate 10% (Ainamo *et al.*, 1992; Drisko, 1996; Jorgensen *et al.*, 2004). However, the main difference is in the use of the parallel design and the large numbers of subjects enrolled. The small sample size used and short study durations in many other trials with ineffective results do not compare favorably to the randomized clinical trials studies with long follow-up presented in this review article (Polson *et al.*, 1997a; Polson *et al.*, 1997b; Garrett *et al.*, 1999; Deo *et al.*, 2011). On the other hand, Bogren *et al.* (2008) analyzed 128 patients assigned to local application of doxycycline as an adjunct to mechanical debridement with follow-up of 36 months. In this study, they concluded the doxycycline had statistically significant differences in clinical parameters only at the 3-month examination; after that period, doxycycline and mechanical debridement were able to reduce just a minority of the microbiological pathogens

Evaluating metronidazole, the studies of Riep *et al.* (1999) and Leiknes *et al.* (2007) indicated that a locally applied 25% metronidazole gel does not improve the treatment outcome over SRP alone in sites with recurring chronic inflammation in maintenance-care patients after a 3-month period, and also for a 6-month period in the study of Leiknes *et al.* (2007). Another study showed that local application of this antimicrobial did not exert an adjunctive effect on healing following periodontal surgery either (Needleman *et al.*, 2000).

Other studies did report significant improvement when comparing adjunctive therapy to individual treatment (Griffiths *et al.,* 2000; Al-Mubarak *et al*, 2000). Griffiths *et al.* (2000) concluded that the combined therapy of SRP + 25% metronidazole gel was superior to the conventional treatment of SRP alone, and these differences were maintained for 9 months. In this study, the mean reductions for PPD and clinical attachment level were 1.0 mm and 0.4 mm for the SRP group and 1.5 mm and 0.8 mm for SRP + 25% metronidazole gel group, respectively. Furthermore, Al-Mubarak *et al.* (2000) reported a randomized clinical trial with metronidazole 25% dental gel in 14 patients with follow-up of 3 months, and results showed that SRP adjunctive to metronidazole had statistically significantly greater improvement ($p < 0.03$) in PPD than all experimental groups. SRP alone and metronidazole 25% alone had statistically significantly greater improvement ($p < 0.05$) in PPD than did the control group. However, the groups were not statistically significantly different from each other.

The differences between the studies might be due to the variability in the number of the patients. Needleman *et al.* (2000) and Leiknes *et al.* (2007) evaluated 38 and 21 patients respectively, while Griffiths *et al.* (2000) performed the study in 92 patients in two different centers and followed the patients for a longer time (9 months).

The long-term efficacy and safety of locally applied minocycline in adult periodontitis patients was investigated in a randomized study with 18 months of follow-up that compared local application of 2% minocycline hydrochloride gel and placebo gel in patients with moderate to severe chronic adult periodontitis. Results showed a statistically significant improvement in all clinical parameters, including probing depth, attachment loss, and papillary bleeding index, irrespective of the treatment modality (Timmerman *et al.*, 1996).

A study with 18 weeks of follow-up performed a split-mouth clinical trial evaluating the efficacy of adjunctive use of subgingival 2% minocycline hydrochloride application plus SRP compared with the results of one episode of SRP in the treatment of chronic periodontitis. At weeks 10, 14, and 18, the experimental group showed significantly greater improvement in pocket reduction than the control group ($p < 0.05$). Gingival index reductions at weeks 10, 14, and 18 were statistically significant in favor of the experimental group ($p < 0.05$). Furthermore, the experimental group had more attachment gain than the control group at weeks 14 and 18 ($p < 0.05$), but the incidence of BOP showed no differences ($p > 0.05$) between groups for all time intervals (Lu and Chei, 2005).

Jung *et al.* (2012) aimed to determine the effectiveness of adjunctive minocycline ointment (MO) with flap surgery for the treatment of patients with chronic severe periodontitis and the effect of repeated application of MO during the post-operative maintenance period. Twenty patients with chronic severe periodontitis received the application of locally delivered minocycline ointment in association with flap surgery or flap surgery only. At 6 months after surgery, although both sites exhibited clinical improvement, the reductions in PPD and BOP were significantly greater at the flap surgery associated with the minocycline ointment site than at the flap surgery site. The plaque index was similar at the two sites at each follow-up time point. The results revealed a greater attachment gain at the flap surgery associated with the minocycline ointment site than at the flap surgery site, which was dependent on the reduction in PPD during the follow-up period. Adjunctive application of locally delivered minocycline during flap surgery or in the maintenance phase for treatment of chronic severe periodontitis appears to enhance the beneficial effect of surgical therapy by reducing PPD and BOP and improving clinical attachment levels. Sachdeva and Agarwal (2011) found that tetracycline fiber therapy enhances the benefits of SRP in the treatment of chronic periodontitis. The adjunctive benefit of the fiber was maintained for 3 months following therapy without additional fiber treatment.

The authors showed the mean pocket depth reduction, plaque index, gingival index, and the mean clinical attachment gain on test and control groups at different time intervals. Within one month, the test group presented a pocket depth reduction of 1.6 mm and clinical attachment gain of 1.11 mm, while the control group showed a reduction of 1.03 mm and a gain of 0.8 mm. The reduction and the gain in the test group within two months were respectively 2.54 mm and 1.63 mm, and in the control group 1.43 mm and 1 mm, respectively. The results of the 3-month follow-up were: 2.69 mm of pocket depth reduction and 1.89 mm of clinical attachment gain for the SRP + tetracycline fibers group, and 1.57 mm of pocket depth reduction and 1.03 mm of clinical attachment gain for SRP alone. In this study, the majority of improvement in the groups treated could be ascribed to SRP. Tetracycline does not remove any calculus deposits; scaling removes some of the bacteria but provides no bactericidal activity. Thus, neither is an ideal control of the other. Locally delivered tetracycline therapy has a specific purpose, to control localized infection, whereas scaling is utilized to remove calculus and other deposits. In conclusion, the authors related that the application of tetracycline in a modified collagen matrix following SRP might be beneficial in the treatment of chronic adult periodontitis and improving periodontal parameters for a 3-month duration, but although it presents a safe and effective treatment modality, further clinical and microbiological studies are required (Sachdeva and Agarwal, 2011).

Singh *et al.* (2009) evaluated both clinical and microbiological parameters at baseline as well as after the placement of tetracycline hydrochloride and metronidazole in periodontal pockets, and, thus, permitted correlation of the results. They reported no difference in the results achieved with local tetracycline hydrochloride or local metronidazole as adjuncts to mechanotherapy. However, both antibiotic therapies resulted in greater improvement in microbiological parameters when compared to mechanotherapy alone.

Sadaf *et al.* (2012) demonstrated that overall tetracycline fiber therapy significantly enhanced the clinical benefits obtained by SRP in chronic periodontitis patients. The authors found a higher reduction in plaque index, gingival index and in clinical probing depths in the test group compared to the control group at all time intervals (15, 30, 60 and 90 days). A combination of scaling and local drug delivery results in benefits in control of periodontal disease. Together with frequent monitoring, which includes a comprehensive periodontal examination, tetracycline fiber therapy can provide dental professionals an additional means to maintain significantly improved clinical health in periodontal diseases. Thus, the use of the medication may improve periodontal maintenance results and help to extend the intervals between patient visits.

A six-month comparison of periodontal therapies using 2% minocycline gel, 25% metronidazole gel and 25% tetracycline fibers associated with SRP in persistent periodontal pockets showed that the three periodontal local antimicrobial therapies offered an extra benefit over SRP alone; however, the group treated with 25% tetracycline fibers had a greater reduction in probing depth after the period of the treatment. The mean probing depth reductions at 6 months were: scaling + tetracycline = 1.38 mm; scaling + metronidazole = 0.93 mm; scaling + minocycline = 1.10 mm; and scaling alone = 0.71 mm (Kinane and Radvar, 1999). However, a limitation of this study was the use of tetracycline fibers with non-resorbable carrier material, as those materials are out-dated and no longer used.

According to the present study, drugs in association with root planing may assist in improving the clinical parameters of the periodontium. However, one of the major causes for treatment failure of periodontal disease is the emergence of antimicrobial-resistant human pathogens, due to the widespread use of antibiotics in medicine and dentistry (Walker, 1996; van Winkelhoff *et al.*, 1997). Furthermore, several investigators have discussed the acquisition of antibiotic resistance in periodontal pockets (Olsvik *et al.*, 1995 (a, b); Walker, 1996; van Winkelhoff *et al.,* 2000; Walker *et al.*, 2000). For minimal adverse effects, local drug delivery could be used in specific conditions, as for non-responding sites after scaling and root planing or for recurrent deep pockets during maintenance. However, few studies (Collins *et al.,* 1993; Olsvik *et al.*, 1995(a); Vandekerckhove *et al.,* 1997) discussed the use of local drug delivery in refractory periodontitis.

Conclusion

Studies suggest the viability of using local drug delivery systems in periodontal pockets as an adjunct to the treatment of deep periodontal pockets, or to sites that do not favorably respond to scaling and root planing, to provide a significant improvement in periodontal clinical aspects. Additional randomized, controlled and long-term studies are needed to help delineate the types of lesions, periodontal diseases, or specific situations where local drug delivery systems would be more beneficial.

Table 1. Comparison of five types of local delivery devices used in periodontology. All studies are randomized clinical trials.

Author	Drug	Number of subjects	Duration of study	Improvement of clinical parameters
Medaiah *et al.* (2014)	Biodegradable chlorhexidine chip	15	3 months	No statistically significant differences between SRP and SRP + CHIP group in all clinical parameters.
Grover *et al.* (2011)	Biodegradable chlorhexidine chip	40	3 months	Chlorhexidine chip and SRP resulted in a clinically significant improvement in PPD and CAL compared with SRP alone.
Jagadish Pai *et al.* (2013)	Chlorhexidine varnish and chlorhexidine chip	15	3 months	Clinically significant reduction in PPD, BOP and CAL, but the results were not statistically significant when compared with SRP alone.
Polson *et al.* (1997a, b)	Doxycycline hyclate in a polylactic acid polymer vehicle	173	9 months	Doxycycline was superior to sanguinarine and vehicle without medication in PPD reduction, BOP and CAL.
Garrett *et al.* (1999)	Doxycycline polymer	684	9 months	All efficacy parameters were clinically and statistically superior for subjects treated with doxycycline compared to oral hygiene only and placebo alone.
Bogren *et al.* (2008)	Doxycycline polymer	128	3 years	Doxycycline had statistically significant differences in clinical parameters only at 3-month examination; after that period, doxycycline and mechanical debridement were effective in reducing just a minority of microbiological pathogens.
Deo *et al.* (2011)	Doxycycline hyclate 10%	60	6 months	Doxycycline hyclate 10% as an adjunct to SRP provided statistically significant ($p < 0.001$) reductions in PPD and gains in CAL compared to SRP alone.
Riep *et al.* (1999)	Metronidazole 25% dental gel	30	3 months	PPD reduction and CAL gain were statistically significant ($p < 0.001$) after both treatments (SRP + subgingival application of metronidazole 25% dental gel and SRP alone). However, there were no statistically significant differences between the groups.
Griffiths *et al.* (2000)	Metronidazole 25% dental gel	45	9 months	Combined therapy of SRP + metronidazole 25% dental gel was superior to the conventional treatment of SRP alone.
Al-Mubarak *et al.* (2000)	Metronidazole 25% dental gel	14	3 months	Scaling adjunctive to metronidazole 25% had statistically significant improvement ($p < 0.03$) in PPD compared to all experimental groups. SRP alone and metronidazole 25% alone had statistically significantly greater improvement ($p < 0.05$) in PPD than control group. However, the treatment groups were not statistically significantly different from each other.

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Author	Drug	Number of subjects	Duration of study	Improvement of clinical parameters
Leiknes *et al.* (2007)	Metronidazole 25% dental gel	21	6 months	SRP + 25% metronidazole gel (test sites) and SRP alone (control sites) yielded a statistically significant ($p = 0.001$) reduction in PPD, CAL, and reduction of BOP for test and control sites, respectively. However, there were no statistically significant differences between the groups.
Timmerman *et al.* (1996)	Minocycline hydrochloride 2%	20	18 months	Results showed a statistically significant improvement in all clinical parameters, including probing depth, attachment loss, and papillary bleeding index, irrespective of the treatment modality.
Lu and Chei *et al.* (2005)	Minocycline hydrochloride 2%	15	18 weeks	The experimental group showed significantly better and prolonged effect in PPD, gingival index and CAL than the control group at weeks 14 and 18 ($p < 0.05$), but the incidence of BOP was not different between the two groups for all time intervals.
Jung *et al.* (2012)	Minocycline hydrochloride 2%	20	6 months	Reductions in PPD, BOP and gain in CAL were significantly greater at the minocycline ointment in association with flap surgery site than at the flap surgery site alone ($p < 0.05$).
Singh *et al.* (2009)	Tetracycline hydrochloride and metronidazole	120	3 months	There was no difference in the results achieved with local tetracycline hydrochloride or local metronidazole as adjuncts to mechanotherapy. However, both antibiotic therapies resulted in greater improvement in microbiological parameters when compared to mechanotherapy alone.
Sachdeva and Agarwal (2011)	Tetracycline fibers	35	3 months	The results of the 3-month follow-up were 2.69 mm of pocket depth reduction and 1.89 mm of clinical attachment gain for the SRP + tetracycline fibers group, and 1.57 mm of pocket depth reduction and 1.03 mm of clinical attachment gain for SRP alone.
Sadaf *et al.* (2012)	Tetracycline fibers	30	3 months	The authors found a higher reduction in plaque index, gingival index and in the clinical probing depths of the tested group than of the control group at all time intervals - 15, 30, 60 and 90 days.
Kinane and Radvar (1999)	2% Minocycline gel, 25% metronidazole gel and 25% tetracycline fibers	79	6 months	2% minocycline gel, 25% metronidazole gel and 25% tetracycline fibers offered an extra benefit over SRP alone, but the group treated with 25% tetracycline fibers had a greater reduction in PPD after treatment.

BOP, bleeding on probing; CAL, clinical attachment level; PPD, probing pocket depth; SRP, scaling and root planing

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