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Review Article

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An Evidence-Based Update on the Impact of Local Antimicrobials as Adjunct to Periodontal Therapy

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Abstract: Local antimicrobials as adjunct to mechanical periodontal therapy have been used widely to enhance the outcome of treatment. However, consensus has yet to be achieved regarding what and how these antimicrobials can be used. Therefore, this narrative review highlights the most common antimicrobials examined and provides an updated analysis of the benefits, limitations, and clinical outcomes associated with use of antimicrobials as adjunct to mechanical periodontal therapy. Based on the evidences gathered, it is clear that combining local antimicrobial agents with scaling and root surface debridement offers significant therapeutic advantages in periodontal therapy and minimizing many side effects linked to systemic antibiotic therapy. Amongst the antimicrobials used, chlorhexidine (CHX) showed the most significant clinical improvement, followed by doxycycline (DOX), tetracycline, and metronidazole (MTZ), all of which helped reduce periodontal bacteria load and improve treatment outcome. CHX demonstrated the greatest clinical improvement due to its broad-spectrum antimicrobial activity, strong substantivity, and its application in sustained-release formulations. DOX followed closely in effectiveness, offering a unique advantage through its dual role as both an antimicrobial and a matrix metalloproteinase inhibitor. Tetracycline, though slightly less effective than DOX, still provided considerable clinical benefits, especially when used in sustained-release systems, despite increasing bacterial resistance in some cases. MTZ showed the lowest clinical improvement among the agents reviewed, but it remains valuable due to its targeted action against anaerobic bacteria, which are prominent in periodontal infections. The findings of this study will help the general practitioners select the most suitable local antimicrobial therapy as adjunct to mechanical periodontal therapy.

1. Introduction

The host's inflammation in response to the dysbiotic subgingival biofilm causes periodontal disease (PD), which can be defined as a chronic inflammatory disease that compromises the teeth's supporting structure [1]. In the established dental biofilm (DB), more periodontopathogens become apparent as the DB formation advances [2]. The host response to the DB is accountable as a major factor in

the breakdown of periodontal tissues [3, 4]. When periodontal bacteria infiltrate the periodontal tissues, they can destroy the alveolar bone and attachment apparatus of connective tissue such as periodontal ligament. This causes the gingival epithelium to migrate, which in turn causes periodontal pockets to form and thus alveolar bone loss [5].

The etiology of PD is strongly linked to the appearance of bacterial dysbiosis and proinflammatory markers [6], which occurs as a result of the overgrowth of certain microorganisms in DB, especially the gram-negative bacteria. As a result, the elimination of DB ought to be the primary objective of any treatment modalities of periodontal therapy. The non-surgical and mechanical removal of inflammation-associated DB from supra and sub gingival surfaces, as well as a regular home cleaning by the patient, are the gold standard treatment for periodontal disease [7].

The first line of periodontal therapy, especially for stage I, II and III periodontitis, is nonsurgical periodontal therapy of scaling and root surface debridement (RSD). Removing the causative microbiota that causes inflammation and infection in the periodontal tissues is the goal of this method of therapy [8]. In cases of severe periodontal disease, such as stage IV with grade C periodontitis, supplementary antibiotic therapy is recommended in addition to the mechanical removal of DB in order to eliminate the remaining microbial community within the periodontal tissues that cannot be removed by the RSD [9].

The combination of amoxicillin and metronidazole (MTZ) is the typical antibiotic treatment used as an adjuvant to RSD. The advanced form of the disease, known as "periodontitis", has been found to respond especially well to RSD+ antibiotics approach [10]. With a significant reduction in treatment duration and an improvement in the periodontal clinical measures of clinical attachment loss (CAL) and probing pocket depth (PPD), this adjunctive antibiotic combination showed promising clinical improvement [11].

On the other hand, due to the localized nature of periodontitis, localized adjunctive antimicrobials treatments are generally favored over systemic ones to minimize the risks associated with systemic antibiotic administration. The effectiveness of periodontal treatment relies heavily on choosing the appropriate antimicrobial agent and delivery method [12]. Considering many advantages over systemic antibiotic therapy, adjunctive local antimicrobial therapy can be applied locally via gels, fibers, chips, and strips [13]. Some of these advantages include, but are not limited to, the ability to target diseases specifically, avoiding the liver's first-pass metabolic breakdown, overcoming gastrointestinal problems, and a reduced chance of developing antibiotic resistance [14]. A variety of local antimicrobials, such as tetracycline, doxycycline (DOX), minocycline, MTZ, chlorhexidine (CHX), azithromycin, moxifloxacin, clindamycin, are currently incorporated into advanced drug delivery systems for periodontal therapy, each designed to enhance the precision and duration of antimicrobial action [12].

Providing the growing body of evidence supporting the effectiveness of these localized treatments, this review aims to summarize the findings concerning professionally applied local antimicrobial agents as adjunct to mechanical periodontal therapy. Further, it will also explore the various delivery systems currently employed in the management of PD, emphasizing their role in improving therapeutic outcomes and patient care.

2. Periodontal Therapy

PD can be treated with mechanical periodontal therapy (scaling and RSD) to establish conditions that allow the patient to maintain periodontal health without further breakdown of the periodontium. These conditions include: (1) Removing all plaque retentive factors such as calculus and overhang margin restorations to reduce DB accumulation, (2) preventing further episodes of periodontitis, (3) reducing and even eliminating gingival inflammation, (4) reducing and even eliminating deepened pockets, (5) regaining periodontal attachment of the tooth, and ultimately preventing tooth loss and loss of teeth function [15].

Scaling and RSD are typical treatments that consists of oral hygiene instructions, the removal of DB and calculus (known as initial or cause-related therapy), and may or may not include adjuvant antimicrobials. This kind of therapy is known as "active periodontal therapy". In fact, periodontal ther-

apy needs to be geared towards providing maximum advantages to the patient, such as the preservation or improvement of quality of life, increased chewing comfort, improved esthetics, and decreasing risk of tooth loss [16, 17].

2.1. Non-surgical Periodontal Therapy

Periodontal therapy consists of a wide variety of procedures that are performed in a sequential order with the intention of controlling the inflammation by motivation and instruction to obtain optimum oral hygiene measures by the patient and the professional treatment by scaling, polishing and RSD, as well as controlling the risk factors in the etiopathogenesis of PD [18]. When the DB is eliminated, this stage of treatment ought to be sufficient to stop the gingival inflammation in individuals who have been diagnosed with gingivitis. However, in periodontitis, it is necessary to complete the first stage before moving on to the second step, which involves the elimination of subgingival DB and calculus and other retentive factors [19]. This is the fundamental part of the treatment for PD. In certain cases, supplementary local or systemic antibiotic or anti-inflammatory drugs may be used in conjunction with RSD. For example, the combination of amoxicillin and MTZ are recommended only in stage III and IV periodontitis with grade B and C [20, 21].

In the literature, several different outcome measures have been investigated in order to measure the success of these two sequential steps of therapy. The most common endpoints are the average decreases in PPD and CAL [17, 22].

In recent years, there has been growing concern over the need to specify more acceptable objectives that should be accomplished following periodontal therapy. The European Federation of Periodontology published a clinical practice guideline to define the outcome measures following stage II-III periodontitis treatment [19, 23]. The reduced periodontium with BI ≤ 10% and non-bleeding shallow pocket of ≤ 4mm following receiving periodontal therapy would be considered "healthy periodontium patient" and "remission periodontitis patient" when the BI> 10% [19].

2.2. Surgical Periodontal Therapy

In the 1970s and 1980s, the results of multiple clinical studies demonstrated that RSD is an effective method to reduce the inflammation from deep pockets and for increasing clinical attachment levels. However, with the most careful and precise nonsurgical instrumentation, there is a possibility that calculus and DB will still be present after the RSD [24]. It was generally agreed that surgical periodontal treatment may be warranted in circumstances when symptoms of inflammation continue to be present.

In the past, it was advised to remove unhealthy tissues using periodontal surgery. The most frequent procedure was gingivectomy, which involved removing diseased gingival tissue and what was thought to be necrotic bone. Once it was demonstrated that PD did not cause bone necrosis and that gingival inflammation and bone loss were the result of a defensive response, this notion was abandoned. In order to decrease the periodontal pocket and enable access to the root surface for cleaning and other dental care procedures, apically positioned flap treatment was frequently performed. Eventually, the main goal of periodontal therapy shifted to eliminating the periodontal pocket [25].

3. Antibiotics as Adjunct to Periodontal Therapy

There are some restrictions and technical demands associated with non-surgical periodontal therapy. For instance, DB cannot be completely removed from furcation areas, deep pockets, and intrabony defects. It does highly rely upon the manual abilities of the operators as well as a number of patient-related factors, including smoking and diabetes which compromise response to periodontal therapy. According to reports, residual calculus may cover as much as 30% of the surface area of roots that have undergone RSD [26]. Therefore, in the areas where the use of mechanical instruments is challenging, the use of additional antimicrobial medications is advised in order to eradicate or inactivate pathogenic microorganisms.

According to recent researches, the use of extra systemic [27, 28] or local antibiotics [29, 30] and antimicrobials [31] may improve the results of periodontal therapy. However, the growing global pub-

lic health concern of bacterial resistance has led to a growing number of warnings against the unrestricted use of antibiotics as part of periodontal therapy [32, 33]. Therefore, only those with certain periodontal conditions, such as stages III–IV, grade C, "active" forms, "refractory" forms, and "recurrent" forms of the disease, should be treated with systemic antibiotics for periodontitis. Furthermore, systemic antibiotics must be used sparingly and sensibly [34].

3.1. Systemic Antimicrobials in Periodontal Therapy

The etiology of periodontitis is strongly linked to the appearance of proinflammatory bacterial dysbiosis [6], which occurs as a result of the overgrowth of certain microorganisms in DB, the majority of which are gram-negative. As a result, the elimination of DB ought to be the primary objective of any method of periodontal treatment. The non-surgical and mechanical removal of inflammation-associated DB from supra and sub gingival surfaces, as well as a regular oral hygiene measures by the patient, represent the basic treatment protocols for PD [7].

Although a majority of clinical intervention studies revealed the advantages of the use of adjunct administration of systemic antibiotics to boost the efficiency of mechanical treatment, the therapeutic significance of these findings is as yet a topic of discussion. Systemic antibiotic administration is associated with the risk of microbial resistance and adverse effect on the entire microbiome of the body. As a result, the empiric use of antibiotics needs to be critically questioned, particularly in light of the potential additional benefits and possible adverse drug reactions that may arise for the patient.

The number of circumstances in which systemically administered antibiotics can effectively address oral infections has significantly increased during the past 50 years. Despite this, the vast majority of systemic antimicrobials are linked to microbial resistance because of their nonprofessional use, inadequate tissue penetration and an inability to penetrate to the infection site and reach the ideal concentration [11].

Current guidelines concentrate on the indication and execution of the adjunctive systemic antibiotic therapy into evidence-based instructions that can be customized to clinical needs on the basis of the data that is available [35].

3.2. Local Antimicrobials in Periodontal Therapy

To address the above-mentioned risks associated with systemic antibiotics, local antimicrobials have been used [36]. Local antimicrobial therapy has gained popularity as a valuable approach in the treatment of PD. This method involves the direct application of antimicrobials to the affected periodontal tissues, allowing for targeted and controlled delivery of medication. The advantages of local antimicrobials in periodontal therapy are well-documented and have been supported by clinical studies [37]. Certainly, use of antimicrobials has several advantages and disadvantages as follow:

The main advantages of local application of the antimicrobials are [12]:

- Enhanced site-specific action: Local antimicrobial therapy allows for precise targeting of the infected areas, ensuring that the antimicrobial directly reaches the sites of bacterial activity. This approach maximizes the therapeutic effect while minimizing systemic exposure, reducing the risk of potential side effects.

- Reduced antibiotic resistance: Systemic antimicrobial use can contribute to the development of antibiotic resistance in various bacterial strains. Local application of antimicrobials can help mitigate this concern as the concentrations of antimicrobials used locally are lower compared to systemic administration, thus reducing the selective pressure on bacteria to develop resistance.

- Minimized systemic side effects: When antimicrobials are administered systemically, they can lead to various side effects ranging from gastrointestinal disturbances to allergic reactions. Local antimicrobial therapy minimizes the likelihood of systemic exposure, thereby reducing the incidence of systemic side effects.

- Improved patient compliance: Local antimicrobial therapy often involves the placement of antimicrobial-containing materials directly into periodontal pockets. This can enhance patient compliance by avoiding the need for regular administration of systemic antibiotics, which can be challenging for some patients to adhere to.

- Adjunct to mechanical therapy: Local antimicrobial therapy can complement traditional mechanical treatments, such as scaling and RSD. While mechanical therapy physically removes DB and calculus, local antimicrobials can help address any remaining bacteria and prevent their re-colonization.

- Immediate and prolonged release: Local antimicrobial delivery systems are designed to release antimicrobials over an extended period. This sustained release ensures that the therapeutic effect continues beyond the initial application, promoting better control of bacterial growth over time.

- Customizable treatment: Different antimicrobials can be used for specific cases, based on the bacterial profile of the individual patient. This level of customization enhances the effectiveness of treatment by targeting the specific bacteria causing the infection, therefore high concentration of the microbial is not required. For example, the combination of amoxicillin and MTZ are recommended only in stage III and IV periodontitis with grade B and C [38].

- Supports tissue healing: Periodontal infections often result in tissue inflammation and damage. By reducing bacterial load, local antimicrobial therapy creates a more favorable environment for tissue healing and regeneration.

- Research support: Multiple clinical studies and research trials have demonstrated the effectiveness of local antimicrobial therapy in improving periodontal health and reducing inflammation. These studies provide a strong foundation for the integration of this approach into comprehensive periodontal treatment protocols.

In summary, local antimicrobial therapy in periodontal treatment offers numerous advantages, including targeted action, reduced antibiotic resistance, minimized systemic side effects, and support for patient compliance. By combining local antibiotic therapy with traditional mechanical treatments, periodontal practitioners can offer a comprehensive and effective approach to managing PD [12].

While local antibiotic therapy in periodontal treatment offers several advantages, it has certain disadvantages and limitations that need to be considered. These disadvantages include [12]:

- Limited reach: Local antibiotics are primarily effective in treating infections within the immediate area of application. They may not effectively address deeper pockets or extensive bacterial colonization in more advanced cases of PD. The penetration of local antimicrobials into periodontal pockets can be inconsistent, especially in cases where the pockets are deep or anatomically complex. This can result in incomplete bacterial eradication and potential treatment failure.

- Narrow spectrum: Some local antimicrobials have a narrow spectrum of activity, meaning they are effective against a limited range of bacteria. This could result in incomplete eradication if the infection is caused by bacterial strains not targeted by the antimicrobial.

- Clinician skills: Local antibiotic therapy often involves the placement of antibiotic-containing materials or solutions within periodontal pockets. Proper placement requires skill, and patient compliance to avoid dislodgement or premature removal of these materials, which could compromise treatment effectiveness.

- Side effects: Local antibiotics can cause local side effects such as tissue irritation, burning sensations, or allergies. While these side effects are generally milder than systemic reactions, they can still impact patient comfort and treatment adherence.

- Cost: Some local antibiotic delivery systems can be more expensive than traditional systemic oral route therapy. The cost factor might limit their accessibility for certain patients or healthcare settings.

- Lack of long-term data: While there is some research supporting the benefits of local antimicrobial therapy, there might be limited long-term data available to demonstrate the sustained efficacy and stability of this approach over extended periods.

- Regulatory approvals: Some local antibiotic delivery systems might not be widely available due to differences in regulatory approvals across regions or countries.

Although local antimicrobial therapy can offer targeted treatment benefits in periodontal care, it has limitations and potential drawbacks that should be carefully considered when determining the most appropriate treatment approach for individual patients. In general, the antimicrobial drugs are inserted directly in the subgingival sites or the periodontal pocket, and then the drug will be released in either an immediate or controlled or sustained manner to eliminate the microbial insult [39]. Local drug delivery systems are available in the form of irrigating systems, fibers, gels, strips, films, microparticles and nanoparticles.

4. Common Local Antimicrobials in Periodontal Therapy

4.1. Chlorhexidine Gluconate

CHX is an antiseptic, antifungal, and bactericidal agent effective against Gram-positive and Gram-negative bacteria. Additionally, it has a bacteriostatic effect, which stops microbes from multiplying [40]. This antimicrobial is used topically as a gel-based, and strips drugs delivery system. A chemo-mechanical treatment notion has been established to increase the efficacy of non-surgical treatment [31].

Results from ten studies examining the qualitative and quantitative analysis of split mouth applications are presented in table 1. On the other hand, four studies compared full-mouth disinfection with subgingival use of CHX gel and full-mouth scaling with RSD, and four studies examined the application of CHX gel as an adjuvant to RSD at specific areas with a minimum PPD of 4 mm (Table 2).

In summary, it can be said that the reduction of PPD was significantly improved after local CHX gel application as an adjuvant to RSD in both split mouth and full mouth study designs. PPD and CAL are improved, and periodontal infections are significantly reduced. This can be related to the fact that CHX has significant substantivity, broad-spectrum antibacterial action, and use in sustained-release formulations, CHX showed its greatest clinical improvement.

Table 1: Clinical outcomes of split mouth studies comparing adjunctive use of CHX gel.

Split mouth applications studies										
Studies	**Patients**	**Methodology**	**Follow-up (month)**	**Results**						
	N (C/T)	**Description of Gel**		**Groups**	**PPD Base-line (mm)**	**PPD 3 months (mm)**	**PPD reduc-tion**	**CAL Baseline (mm)**	**CAL 3 months (mm)**	**CAL gain (mm)**
Unsal *et al.* (1994) [41]	15 (8/7)	1% CHX gel	3	Control	5.14±1.45	3.31±0.73	1.83±0.54	3.66±1.22	2.62±1.24	1.04±0.16
				Test	4.90±1.11	3.32±1.01	1.58±0.96	4.03±1.5	3.33±1.76	0.70±1.09
Gupta *et al.* (2008) [42]	30 (30/30)	CHX 1.5%	1,3	Control	6.03±1.15	4.30±0.87	1.73±0.94	6.00±1.11	5.13±0.86	0.86±0.68
				Test	6.40±0.89	3.63±1.29	2.76±1.25	6.53±1	4.50±1.30	2.03±1.22
Verma *et al.* (2012) [43]	46 (46/46)	CHX 1.5%	1,3	Control	6.39±0.95	5.17±1.12	N/A	6.65±1.12	5.76±1.21	N/A
				Test	6.41±0.96	4.26±1.00	N/A	6.70±1.21	5.17±1.18	N/A
Matesanz *et al.* (2013) [44]	22 (12/10)	CHX 1.5%	1,3,6	Control	3.73±0.45	3.54±0.45	0.17±0.38	4.72±1.25	4.6±1.25	0.14±0.45
				Test	3.58±0.47	3.32±0.47	0.29±0.38	4.31±0.98	4.12±0.98	0.16±0.47
Chauhan *et al.* (2013) [45]	40 (20/20)	CHX 1.5%	1,3	Control	5.90±0.27	4.30±0.33	1.60±0.27	6.10±0.38	5.55±0.37	0.55±0.16
				Test	5.95±0.31	3.48±0.34	2.48±0.32	6.15±0.36	5.03±0.36	1.13±0.27
Chitsazi *et al.* (2013) [46]	20 (20/20)	CHX 1.5%	1,3	Control	4.9±0.78	3.25±0.65	1.67	3.9±0.58	3.4±0.6	0.5
				Test	5.05±0.75	3.38±0.79	1.65	4.15±0.67	3.67±0.65	0.47
Jain *et al.* (2013) [47]	30 (30/30)	CHX 1.5%	1.5,3,6	Control	5.20±0.48	3.07±0.69	N/A	11.43±2.7	9.20±2.84	N/A
				Test	5.20±0.48	2.50±0.73	N/A	11.70±2.8	10.03±2.9	N/A
Phogat *et al.* (2014) [48]	30 (30/30)	CHX 1.5%	1,3	Control	N/A	N/A	2.264±0.03	N/A	N/A	2.405±0.079
				Test	N/A	N/A	3.764±0.01	N/A	N/A	2.913±0.051
Lecic *et al.* (2016) [49]	5 (5/5)	0.5% CHX gel	1,3	Control	5.25±0.55	3.25±0.55	N/A	4.05±1.35	3.20±0.76	N/A
				Test	5.05±1.00	2.95±0.75	N/A	3.75±1.2	3.40± 0.82	N/A
Faramarzi *et al.* (2017) [50]	68 (34/34)	CHX 1.5%	3,6	Control	5.41±0.76	3.67±0.83	1.74±0.14	4.67±0.54	3.90±0.74	0.77±0.09
				Test	5.41±0.8	3.48±0.56	1.93±0.33	5.06±0.67	4.19±0.79	0.87±0.1

C/T: Control/test, CAL: Clinical attachment loss, CHX: Chlorhexidine, N/A: Not available. PPD: Periodontal pocket depth.

Table 2: Full mouth application studies of CHX gel.

Full mouth application studies										
Studies	**Patients**	**Methodology**	**Follow-up (month)**	**Results**						
	N (C/T)	**Description of Gel**		**Groups**	**PPD Baseline (mm)**	**PPD 3 months (mm)**	**PPD reduction (mm)**	**CAL Baseline (mm)**	**CAL 3 months (mm)**	**CAL gain (mm)**
Quirynen *et al.* (2006) [51]	20 (10/10)	1% CHX gel	1,3	Control	4.9±0.78	3.25±0.65	1.67±0.63	3.9±0.58	3.4±0.60	0.5
				Test	5.05±0.75	3.75±0.79	1.65±0.48	4.15±0.67	3.67±0.65	0.47
Swierkot *et al.* (2009) [52]	18 (9/9)	1% CHX gel	1,2,4,	Control	3.20±0.57	2.39±0.35	2.44±0.35	3.68±0.93	3.13±1.09	3.15±0.85
				Test	3.55±0.88	2.67±0.80	2.73±0.74	4.20±0.69	3.37±0.67	3.35±0.67
Santos *et al.* (2013) [53]	37 (18/19)	1% CHX gel	3,6,1	Control	3.7±0.8	3.0±0.5	2.9±0.5	4.4±0.99	3.9±0.87	3.8±0.92
				Test	3.4±0.5	2.9±0.4	2.9±0.4	4.1±0.85	3.7±0.92	3.6±0.77
Fonseca *et al.* (2015) [54]	30 (15/15)	1% CHX gel	3,6	Control	2.27±0.60	2.09±0.52	2.08±0.52	2.39±0.99	2.17±0.77	2.20±0.74
				Test	2.10±0.50	1.50±0.38	1.53±0.41	2.84±0.95	2.48±0.81	2.41±0.80

C/T: Control/test, CAL: Clinical attachment loss, CHX: Chlorhexidine, PPD: Periodontal pocket dept.

4.2. Doxycycline Hyclate

DOX is a bacteriostatic antibiotic with broad spectrum activity against common periodotal pathogens, including *Aggregatibacter actinomycetemcomitans* [55], *Porphyromonas gingivalis*, *Prevotella intermedia, Fusobacterium nucleatum*, *Eikenella corrodens*, and *Spirochetes* [56]. Based on several clinical trials, individuals with PD gained more improvement from locally applied DOX when combined with nonsurgical therapy than when RSD was used alone [45, 46]. Table 3 summarizes five trials that demonstrated changes in PPD reduction and CAL gain at three months. Additionally, a number of studies have documented the effectiveness of 10% DOX hyclate as a local delivery antimicrobial for achieving PPD decrease and obtaining clinical attachment as a result of local application of DOX [57] (Table 3).

To sum up, DOX has shown to be useful in reducing PPD and improving CAL when used as adjunct to mechanical periodontal therapy. This could be associated to its dual role as both an antimicrobial and a matrix metalloproteinase inhibitor. Its local application via microspheres or gel formulations achieves high concentrations at the infection site, contributing to enhanced clinical outcomes by reducing inflammation and promoting tissue healing.

Table 3: Studies examining the effect of local Doxycycline hyclate application.

Author (year)	Product used	Pockets analyzed (mm)	PPD reduction after 3 months (mm)	CAL gained after 3 months (mm)
Ryder *et al.* (1999) [58]	Doxycycline hyclate gel	≥5, ≥7	1.83	1.52
Wennström *et al.* (2001) [59]	Doxycycline hyclate gel	≥5	1.3	0.5
Machion *et al.* (2004) [60]	Doxycycline hyclate gel	≥5	2.02	1.36
Tomasi and Wennstrom (2004) [61]	Doxycycline hyclate gel	≥5	1.53	1.69
Machion *et al.* (2006) [29]	Doxycycline hyclate	≥5	1.89	1.76
Bogren *et al.* (2008) [62]	Doxycycline hyclate	≥5	0.9	0.8
Tomasi *et al.* (2008) [63]	Doxycycline hyclate gel	≥5	1	0.6
Al Hulami *et al.* (2011) [64]	Doxycycline hyclate gel	≥5	2.07	0.52
Hulami *et al.* (2011) [64]	Doxycycline hyclate gel	5-6, ≥7	1.69	1.56
Sandhya *et al.* (2011) [65]	Doxycycline hyclate gel	≥6	1.31	1.68
Tomasi and Wennstrom (2011) [66]	Doxycycline hyclate gel	≥5	1.1	0.5
Rao *et al.* (2012) [67]	Doxycycline microspheres	4-6	1.4	0.9
Madi *et al.* (2018) [68]	Nano-doxycycline gel	4-6	1.31	1.02

CAL: Clinical attachment loss, PPD: Periodontal pocket depth.

4.3. Tetracycline

Tetracycline is a bacteriostatic antibiotic that inhibits tissue collagenase activity in addition to inhibiting bacterial protein synthesis. It has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, including the beta-lactamase-producing (penicillin-resistant) bacteria that are present in approximately 50% of PPD of 6-7 mm [69].

A study found that overall tetracycline fiber treatment substantially increased the therapeutic advantages acquired by scaling and RSD in individuals with periodontitis. The test group showed a greater decrease in plaque index, gingival index, and PPD than the control group [70] (Table 4).

Scaling and local medication administration has positive effects on the management of PD in conjunction with regular monitoring, which includes a full periodontal examination. Local tetracycline application might provide an additional method for dental practitioners to maintain significantly improved clinical health in patients with PD. Consequently, it enhances periodontal maintenance outcomes and aids in decreasing the patient visits [71].

The three periodontal local antimicrobial therapies of 2% minocycline gel, 25% MTZ gel, and 25% tetracycline fibers were found to be more beneficial than RSD alone over a six-month periodontal therapy comparison. Nonetheless, PPD was reduced more in the group that had 25% tetracycline fiber treatment. At six months, RSD with tetracycline reduced PPD by 1.38 mm, whereas scaling plus MTZ,

or minocycline resulted in 0.93 mm and 1.10 mm reduction, respectively, compared to RSD alone (0.71 mm) [72]. Since some of these materials are no longer in use, it makes sense to point out that the use of tetracycline fibers with non-resorbable carrier material was a limitation of this study.

Comparing to DOX, tetracycline has shown to be slightly less effective, however, it does still provide considerable clinical benefits, especially when used in sustained-release systems.

Table 4: Summary of studies examining the effect of local Tetracycline application.

Author (year)	Drug	Participants	Duration (month)	Outcome
Singh *et al.* (2009) [73]	Tetracycline hydro- chloride and metronidazole	120	3	Local tetracycline hydrochloride and metronidazole improved microbial indicators and the clinical parameters.
Sachdeva and Agarwal (2011) [74]	Tetracycline fibers	35	3	RSD + tetracycline fibers reduced pocket depth and clinical attachment loss by 2.69 mm and 1.89 mm, respectively. Whereas RSD alone achieved 1.57 mm and 1.03 mm, respectively.
Sadaf *et al.* (2012) [70]	Tetracycline fibers	30	3	Pocket depth decreased more than in the control group.
Khan *et al.* (2015) [75]	Tetracycline fibers	40	3	Adjunctive antimicrobial use of tetracycline fibers demonstrated better results compared to the control group.

RSD: Root surface debridement.

4.4. Metronidazole

Amongst the antibiotics that are used commonly for the treatment of periodontitis, MTZ is particularly suitable due to its broad spectrum of activity against obligate anaerobes [76]. MTZ is a synthetic, chemically derived antibiotic that inhibits the production of bacterial DNA, resulting in cell death [77]. It is an effective antibacterial medication used against anaerobic bacteria and protozoa, and is administered as a systemic or local adjunct to the traditional periodontal therapy [78].

A summary of 16 studies that investigated the effect of local MTZ alone or as an adjunct to RSD in the treatment of periodontitis is presented in table 5. All studies evaluated the effect on PPD and CAL reduction and CAL improvement and the results show that MTZ as adjunct to RSD was superior to RSD alone. However, the improvement of clinical periodontal parameters of PPD and CAL showed the lowest value among the agents reviewed, but it remains valuable due to its targeted action against anaerobic bacteria, which are prominent in periodontal infections. MTZ is most effective when combined with other antibiotics, demonstrating its role as an adjunctive rather than a primary treatment.

Table 5: Studies examining the effect of local metronidazole application.

Authors (year)	Study Design	Delivery Mode	Follow-Up (weeks)	Baseline PPD (mm)	Results			
					PPD		CAL	
					Reduction (mm)			
					MTZ + RSD	RSD alone	MTZ + RSD	RSD alone
Yeung *et al.* (1983) [79]	Split-mouth	Strips	4	≥5	1.1	1.2	N/A	N/A
			8		1.4	1.5	N/A	N/A
			12		1.6	1.8	N/A	N/A
Wan Yusof *et al.* (1984) [80]	Split-mouth	Irrigation	4	≥4	1.3	1.2	N/A	N/A
			8		1.2	1.1	N/A	N/A
			12		1.6	1.1	N/A	N/A
Aziz *et al.* (1986) [81]	Split-mouth	Irrigation	4	≥4	1.4	1.1	N/A	N/A
			8		1.5	1	N/A	N/A
			12		1.2	0.9	N/A	N/A
Hitzig *et al.* (1994) [82]	Split-mouth	Strips	4	>5	2	1.6	1.1	1
			12		2.1	1.4	2	2
Stelzel *et al.* (1997) [83]	Split-mouth	Irrigation	4	≥5	1.2	1.2	N/A	N/A
			12		1.4	1.4	N/A	N/A
			24		1.4	1.2	N/A	N/A
			36		1.2	1.1	N/A	N/A
Lie *et al.* (1998) [84]	Split-mouth	Irrigation	12	≥5	1.4	0.44	0.8	0.4
			24		1.2	0.2	1.2	0.2
Palmer *et al.* (2000) [85]	Parallel	Irrigation	8	>4	1.7	1.5	0.4	0.4
			24		0.5	0.5	0.5	0.5
Kinane and Radvar (2000) [72]	Parallel	Fibers + irrigation	6	≥5	0.8	0.6	0.4	0.3
			12		0.9	0.9	0.5	0.5
			24		0.9	0.7	0.5	0.5
Stelzel *et al.* (2000) [86]	Split-mouth	Fibers	36	≥5	1.4	1.2	N/A	N/A
Griffiths *et al.* (2000) [87]	Split-mouth	Irrigation	1	≥5	2.2	2.3	1.2	0.2
			3		1.4	1.4	1.3	0.3
			6		1.2	1.4	1.3	0.3
			9		0.5	1.5	1.4	0.4
Linden *et al.* (2001) [88]	Split-mouth	Irrigation	4	≥4	1.1	1	N/A	N/A
			8		1.1	0.8	N/A	N/A
			12		1	0.6	N/A	N/A
Akncbay *et al.* (2007) [89]	Parallel	gel	6	4-7	1.5	0.8	N/A	N/A
			12		1.4	1.2	N/A	N/A
			24		1.5	1.3	1	0.8
Leiknes *et al.* (2007) [90]	Split-mouth	gel	12	≥5	1.4	1.6	1.5	1
			24		1.9	1.8	1.6	1
Pandit *et al.* (2013) [91]	Split-mouth	gel	4	5-8	1.7	0.95	1.15	1.75
			12		2.7	1.65	2	1.7
Paul *et al.* (2014) [92]	Split-mouth	Strip	4		2.55	0.9	N/A	N/A
Bergamaschi *et al.* (2016) [93]	Parallel	gel	24	≥5	1.8	1.8	1.9	2

CAL: Clinical attachment loss, MTZ: Metronidazole, N/A: Not available, PPD: Periodontal pocket depth, RSD: Root surface debridement.

5. Conclusions

This review demonstrated that using the local antimicrobial as adjunct to the mechanical periodontal therapy has substantial clinical benefits when directly applied to the site of infection. This review looked at several studies that evaluated the effectiveness of different antimicrobial drugs used in local delivery systems, with CHX, DOX, tetracycline, and MTZ being the most frequently studied. Among these, CHX showed the most significant clinical improvement, followed by DOX, tetracycline, and MTZ, all of which helped reduce PD parameters and improve treatment outcome.

CHX demonstrated the greatest clinical improvement due to its broad-spectrum antimicrobial activity, strong substantivity, and its application in sustained-release formulations. The extended release of CHX allows for prolonged antimicrobial action, which leads to significant reductions in periodontal pathogens and improvements in PPD and CAL.

DOX followed closely in effectiveness, offering a unique advantage through its dual role as both an antimicrobial and a matrix metalloproteinase inhibitor. Its local application via microspheres or gel formulations achieves high concentrations at the infection site, contributing to enhanced clinical outcomes by reducing inflammation and promoting tissue healing.

Tetracycline, though slightly less effective than DOX, still provided considerable clinical benefits, especially when used in sustained-release systems, despite increasing bacterial resistance in some cases.

MTZ showed the lowest clinical improvement among the agents reviewed, but it remains valuable due to its targeted action against anaerobic bacteria, which are prominent in periodontal infections. MTZ is most effective when combined with other antibiotics, demonstrating its role as an adjunctive rather than a primary treatment. The findings may have implications for advancing targeted therapies in periodontal care and may guide future research towards developing more efficient and patient-friendly treatment modalities for PD.

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