

Local drug delivery in periodontitis treatment: A review of contemporary literature

Miejscowe dokieszonkowe podawanie leków w zapaleniu przęsbia – przegląd współczesnego piśmiennictwa

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Abstract

Traditional methods of non-surgical treatment of periodontitis, including mechanical scaling/root planing (SRP), do not guarantee remission of the disease. Local delivery of antimicrobial agents in periodontitis entails antimicrobial therapy placed directly in periodontal pockets. The advantage of this form of treatment is that the concentration of the drug after application significantly exceeds the minimum inhibitory concentration (MIC) and persists for up to several weeks. Therefore, many systems of locally applied devices, using a variety of antibiotics or antiseptics have been developed. There is continuous research aimed at introducing new forms of locally administered drugs, some of which have not proved to be effective, while others are promising. For almost 30 years such systems have been used for treatment as an adjuvant to SRP, and their efficacy has been evaluated. The aim of this article is to systematically review the contemporary literature regarding the currently available chemotherapeutics locally administered in the treatment of periodontitis.

Key words: periodontitis, local drug delivery, chlorhexidine chip

Słowa kluczowe: zapalenie przęsbia, miejscowe dokieszonkowe podawanie leków, listek chlorheksydynowy

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According to epidemiological studies conducted in Poland in 2012, 51.1% of people aged 35–44 years suffer from chronic periodontitis.¹ Deep periodontal pockets (>6 mm) were found in 16.4% of people in this age group.¹ Traditional methods of non-surgical treatment, including mechanical scaling/root planing (SRP), do not guarantee remission of the disease. The additional use of antibiotics systemically in the treatment of periodontitis is limited, due to the need for high doses to achieve the appropriate concentration of the drug in the gingival fluid, rapidly growing resistance of the bacteria, and side effects of the drugs. In addition, due to the advanced organization of the structure and function of the subgingival biofilm, antibiotics may not be effective or can be inactivated.

Therefore, for almost 30 years, drug systems (antibiotics and antiseptics) have been developed in the form of direct subgingival administration.^{2,3} The advantage of this form of treatment that the concentration of the drug after application significantly exceeds the minimum inhibitory concentration (MIC) and persists for up to several weeks. With this form of application, many side effects that are associated with general antibiotic therapy can be avoided. However, it is always possible to use multi-drug systems as an add-on to non-surgical treatment of the periodontium and not as an independent form of therapy. The first papers evaluating such drugs showed high efficiency of the evaluated systems and recommended them as a valuable auxiliary element in the treatment of deep pockets in periodontitis.⁴

The aim of this article is to present a systematic review of the literature regarding the currently available chemotherapeutics locally administered in the treatment of periodontitis.

To assess the efficacy of medications used in the treatment of periodontitis, studies published since 2010, available in the MEDLINE and Scopus databases, were qualified. The key words used for searching were: "chlorhexidine chip", "PerioChip®", "chlorhexidine xanthan gel", "metronidazole gel", "Elyzol®", "Periodontal Plus® AB", "tetracycline fiber", "subgingival antibiotic therapy", "local drug delivery", "doxycycline hydiate", "Arestin®", "and Atridox®". In all of the studies considered, the efficacy of administering the drug carrier to periodontal pockets after the SRP procedure was compared to a control group that was treated only by SRP. In all of these studies, the effects of the treatment on the periodontal pocket depth (PD) and on the level of the connective tissue attachment – clinical attachment level (CAL) were evaluated. The minimum follow-up period in the selected studies was 3 months.

All the key words in the search strategy were defined based on the following focus question and the population, intervention, comparison, and outcome (PICO) framework: "Does local drug delivery (LDD) significantly improve the clinical parameters in comparison with the tra-

ditional protocol for the treatment of periodontitis?" This question is addressed according to the following criteria:

- population: humans presenting periodontitis;
- intervention: usage of LLD after SRP in the treatment of periodontal pockets;
- control: periodontal pockets after SRP alone;
- outcome: improvement of periodontal condition evaluated with PD and CAL measurements.

Chlorhexidine

The antibacterial activity of chlorhexidine (CHX) results from the fact that its molecules have a positive charge. Therefore, it has a strong affinity with negatively charged ions or molecules of microorganisms, salivary glycoproteins and salivary phosphoproteins, and their acquired casings, oral mucosa epithelial cells.^{3,5} By binding to negatively charged cell walls of microorganisms, CHX changes the osmotic balance of cells, leading to leakage or precipitation of elements of the cytoplasm, which causes their death or significant limitation of function. By binding to the anionic acid groups of salivary glycoproteins, CHX inhibits the formation of acquired casings and the colonization of plaque.³ It also binds to salivary bacteria, disrupting their adsorption on the tooth surface.

Binding of CHX molecules to the surface of the teeth and mucous membranes results in the release of the anti-septic from these reservoirs for a long time, so the effect of CHX substantively lasts for several hours after its application. Chlorhexidine retains its properties in an alkaline environment (which prevails in periodontal pockets); at pH < 7, it works less effectively. It is inactivated by plasma proteins, so it is not used in the decontamination of open wounds.⁶ Studies have shown very low CHX toxicity and no bacterial resistance. However, in recent years there have been reports in the literature of the emergence of CHX-resistant bacterial strains, including multi-drug-resistant strains that can survive in the biofilm, especially when CHX is used for too long.⁷

Preparations containing chlorhexidine

In the treatment of periodontitis, a 4 × 5 mm film, of a thickness of approx. 350 µm and weighing approx. 7 mg, containing 2.5 mg CHX gluconate is used – PerioChip (Dexcel Pharma, Or Akiva, Israel) or PerioCol®-CG (Eucare Pharmaceuticals Ltd., Chennai, India). The matrix is formed by transversely cross-linked hydrolyzed gelatin and glycerol or type I collagen of fish origin. The advantage of chitosan films is their bioadhesive, antibacterial and wound-healing properties. After administration, gradual release of CHX takes about 7–9 days. The highest concentration of the drug in the gingival fluid is maintained for about 72 h (1400–1900 µg/mL, with 125 µg/mL being considered the concentration elimi-

nating 99% of bacteria).⁸ After this time, the concentration decreases gradually. Another application of the film is recommended after 3–4 weeks.

A second form of CHX used in intra-pocket applications in the treatment of periodontitis is a plastic gel containing 1.5% CHX in 2 forms: 0.5% chlorhexidine digluconate and 1% chlorhexidine dihydrochloride – Chlosite® (Ghimis S.p.A., Casalecchio di Reno, Italy). These active substances are suspended in xanthan – a saccharide polymer that forms a 3-dimensional pseudo-plastic mesh with water, which maintains and slowly releases the compounds contained therein. According to the manufacturer's information, chlorhexidine digluconate is rapidly released during the first 24 h. About 34% of the total amount of CHX is released from the gel at a fast and constant rate, reaching a concentration greater than 100 µg/mL, which allows the destruction of pathogenic bacteria.⁹ This process takes on average 6–9 days and releases 85% of the total amount of CHX contained in the gel. At the same time, chlorhexidine dihydrochloride is released slowly and, by maintaining a concentration with bacteriostatic and bactericidal action, prevents recolonization of the pockets by

pathogenic bacteria. After 9 days, when chlorhexidine digluconate is completely released, the presence of dihydrochloride ensures the efficacy and microbiological activity of the drug for another 6 days.⁹

Tables 1 and 2 present the results of studies on subgingival forms of drugs containing CHX. In the majority of studies published in 2010–2016, evaluating the effectiveness of the CHX film, there was no improvement in the clinical status of periodontal tissues after the treatment. Two publications confirm a statistically significant improvement in the parameters evaluated after using a CHX chip in comparison with traditional treatment. In a study by Pattnaik et al.¹³, after a 3-month observation, PD was reduced by $2.36 \text{ mm} \pm 0.84$ and CAL was improved by $2.29 \text{ mm} \pm 0.5$ ($p < 0.001$). In a study by Lecic et al., after 3 months of observation, periodontal pockets were 3.41 mm shallower and CAL improved by 1 mm ($p < 0.001$).¹⁴ Among the studies evaluating the efficacy of a gel containing 2 CHX compounds, only 2 show no statistically significant improvement in the parameters evaluated. In 5 articles, CAL was improved and periodon-

Table 1. List of studies using chlorhexidine (CHX) in the form of a film (PerioChip, PerioCol-CG)

Author	Assessed groups	Time of observation	Results		p-value
			test group	control group	
Sakellaris et al. 2010 ¹⁰	50 patients (4 pockets $>5 \text{ mm}$, $<7 \text{ mm}$) 25 patients – SRP 25 patients – SRP and CHX assessed: PD, CAL 8 bacteria, DNA-DNA hybridization	6 months	no statistically significant differences between assessed clinical and microbiological parameters		–
Medaiah et al. 2014 ¹¹	15 patients (3 pockets $>5 \text{ mm}$) 15 pockets – SRP 15 pockets – SRP and CHX 15 pockets – CHX assessed: PD, CAL	3 months	no statistically significant differences between assessed clinical parameters		–
Kumar et al. 2014 ¹²	30 patients 10 patients – SRP 10 patients – SRP and CHX 10 patients – PerioChip® assessed: PD, CAL, BANA	3 months	no statistically significant differences between assessed clinical and biochemical parameters		–
Pattnaik et al. 2015 ¹³	20 patients, split mouth 20 pockets – SRP and CHX 20 pockets – SRP assessed: PD, CAL	1 month 3 months	PD [mm] baseline: 6.42 ± 1.04 change after 1 month: 1.45 ± 0.59 change after 3 months: 2.36 ± 0.84 CAL [mm] baseline: 6.28 ± 1.01 change after 1 month: 1.23 ± 0.42 change after 3 months: 2.29 ± 0.50	6.52 ± 1.15 0.87 ± 0.34 1.59 ± 0.53 6.27 ± 1.22 0.77 ± 0.36 1.50 ± 0.47	– <0.001 <0.001 – <0.001 <0.001
Lecic et al. 2016 ¹⁴	40 pockets, split mouth 20 pockets – SRP and CHX 20 pockets – SRP assessed: PD, CAL	1 month 3 months	PD [mm] baseline: 5.70 ± 0.97 after 1 month: 2.80 ± 1.28 after 3 months: 2.75 ± 0.96 CAL [mm] baseline: 3.70 ± 1.41 after 1 month: 2.65 ± 1.69 after 3 months: 2.70 ± 1.75	5.25 ± 1.01 3.10 ± 0.71 3.40 ± 0.75 3.90 ± 1.02 2.85 ± 1.13 2.95 ± 1.05	– NS <0.050 – NS NS

Data presented as mean \pm standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; BANA – referring to the enzymatic breakdown of N-benzoyl-dL-arginine-2-naphthylamide; NS – nonsignificant.

Table 2. List of studies using chlorhexidine (CHX) in the form of a gel (Chlosite)

Author	Assessed groups	Time of observation	Results			p-value			
				test group	control group				
Kranti et al. 2010 ¹⁵	10 patients (60 pockets) 30 pockets – SRP and placebo 30 pockets – SRP and CHX assessed: PD, CAL	3 months 6 months	PD [mm]	reduction after 3 months: 2.25 ± 0.58	1.68 ± 0.50	<0.001			
	reduction after 6 months: 3.11 ± 0.47			2.44 ± 0.55	<0.001				
	1 month 3 months	CAL [mm]	gain after 3 months: 2.24 ± 0.62	1.69 ± 1.03	<0.001				
			gain after 6 months: 3.11 ± 0.65	2.44 ± 0.98	<0.001				
Verma et al. 2012 ⁹	46 patients (92 pockets) 46 pockets – SRP 46 pockets – SRP and CHX assessed: PD, CAL	1 month 3 months	PD [mm]	difference between 1 month and 3 months: 1.24 ± 0.82		0.35 ± 0.67	<0.001		
	difference between 1 month and 3 months: 0.85 ± 0.63			0.22 ± 0.42	<0.001				
Matesanz et al. 2013 ¹⁶	21 patients (4–10 pockets >4mm) SRP and placebo SRP and CHX assessed: PD, CAL	1 month 3 months 6 months		no statistically significant improvement of assessed parameters					
Chauhan et al. 2013 ¹⁷	40 patients 20 patients [pockets?] – SRP 20 patients – SRP and CHX assessed: PD, CAL	3 months	PD [mm]	baseline: 5.95 ± 0.31	5.90 ± 0.27	–			
	after 3 months: 3.48 ± 0.34			4.30 ± 0.33	<0.001				
		CAL [mm]	baseline: 6.15 ± 0.36	6.10 ± 0.38	–				
			after 3 months: 5.03 ± 0.36	5.55 ± 0.37	NS				
Chitsazi et al. 2013 ¹⁸	20 patients, split mouth 20 patients [pockets?] – SRP 20 patients – SRP and CHX assessed: PD, CAL	1 month 3 months		no statistically significant improvement of assessed parameters					
	6 weeks 3 months 6 months	PD [mm]	baseline: 5.20 ± 0.48	5.20 ± 0.48	–				
Jain et al. 2013 ¹⁹			30 patients, split mouth 30 pockets – SRP 30 pockets – SRP and CHX assessed: PD, CAL			after 6 weeks: 2.60 ± 0.81	3.00 ± 0.91	0.083	
						after 3 months: 2.50 ± 0.73	3.07 ± 0.69	0.002	
						after 6 months: 2.40 ± 0.68	3.00 ± 0.91	0.002	
		CAL [mm]	baseline: 11.70 ± 2.81	11.43 ± 2.75					
			after 6 weeks: 10.37 ± 3.11	9.30 ± 2.96	<0.001				
			after 3 months: 10.03 ± 2.98	9.20 ± 2.85	0.006				
Phogat et al. 2014 ²⁰	10 patients SRP SRP and CHX assessed: PD, CAL	1 month 3 months	PD [mm]	change after 1 month: 2.14 ± 0.01	1.16 ± 0.06	<0.001			
				change after 3 months: 3.76 ± 0.01	2.26 ± 0.03	<0.001			
			CAL [mm]	change after 1 month: 2.41 ± 0.01	2.04 ± 0.09	<0.001			
				change after 3 months: 2.91 ± 0.05	2.41 ± 0.08	<0.001			

Data presented as mean \pm standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; NS – nonsignificant.

tal pockets became shallower compared to the control group, and the results were statistically significant.

In both the CHX film and xanthan gel studies, the short follow-up periods are worth noting – the maximum time observation period is 6 months – as are the small study groups. In addition, it should be emphasized that in the period after 2010, fewer works evaluate the additional use of CHX carriers as adjunctive treatment in periodontitis. In a systematic review of LDD methods published in 2005, 17 reviews of CHX chips were collected.²¹ A statistically significant improvement in PD was observed in 2 studies, and in CAL – in 3 works. Taking this into account, it seems that CHX on a xanthan carrier may prove to be a valuable addition to traditional treatment.

Tetracycline

Tetracyclines are broad-spectrum bacteriostatic antibiotics for Gram-positive and Gram-negative bacteria, *Rickettsia* sp., *Mycoplasma* sp., *Chlamydia* sp., and *Spirochaeta* sp.²² They do not act in viral or fungal infections. The basis of the chemical structure of this group of antibiotics is the 4-membered tetracycline ring, which affects their physicochemical properties, such as alkaline nature, poor solubility in water and durability. The mechanism of action of tetracyclines consists in inhibiting protein biosynthesis and phosphorylation processes in bacterial cells. Tetracyclines are teratogenic and embryotoxic. They should not be used in pregnant women or in children un-

der 12 years due to the accumulation of tetracycline-calcium-phosphate complexes in the shafts of long bones.

In the last 2 decades, the use of tetracyclines in many bacterial infections has been limited due to the widespread development of bacteria resistant to the antibiotics of this group. Two types of tetracycline resistance are known: nonspecific and specific.^{23,24} The former is low-grade resistance and results from the reduction of tetracycline transport through purine channels in the outer membrane to the interior of the cell. Specific resistance can be associated with one of the 3 mechanisms: enzymatic inactivation of drug molecules; removal of tetracyclines from the inside of bacterial cells by means of active pumps; or protection of the ribosome against tetracyclines.

Minocycline is the most lipid-soluble and most active semi-synthetic tetracycline antibiotic. It affects both Gram-positive and Gram-negative bacteria as well as bacteria that do not have a cell wall. The action of minocycline is related to the inhibition of protein synthesis. Minocycline pass-

es directly through the lipid bilayer or passively diffuses through the porous channels in the bacterial membrane. It binds to the 30S ribosomal subunit, which prevents the binding of tRNA to the mRNA-ribosomal complex, as a result of which protein translation is stopped.²³ The weakness and impaired function of the bacteria leads to their destruction by the body's natural defense mechanisms.

A periodontics preparation containing minocycline is Arestin (OraPharma Inc., Warminster, USA). It contains 1 mg of minocycline in the form of microspheres. Arestin has an application system constructed in such a way that the microspheres are administered in the form of a powder to allow easy, targeted placement at the base of the periodontal pocket. After placing the preparation in the pocket, the microspheres instantly aggregate into the surrounding surfaces, providing a prolonged release of minocycline at the site of active infection.

In the majority of the studies reviewed (Table 3), statistically significant effects were found between the study

Table 3. List of studies evaluating the efficacy of subgingival minocycline

Author	Assessed groups	Time of observation	Results		p-value	
			test group	control group		
Tabenski et al. 2017 ²⁵	30 patients 15 [pockets?] – SRP 15 – SRP+minocycline assessed: PD, CAL	3 months 6 months 12 months		no statistically significant improvement of assessed parameters		
Killeen et al. 2016 ²⁶	27 patients – SRP 24 patients – SRP+minocycline assessed: PD, CAL	6 months 12 months	PD [mm]	baseline: 5.30 ± 0.60 after 6 months: 0.92 ± 0.83	5.50 ± 0.80	–
				after 12 months: 1.00 ± 0.95	0.62 ± 1.02	<0.001
			CAL [mm]	baseline: 5.40 ± 0.70 after 6 months: 0.92 ± 0.83	5.80 ± 0.90	–
				after 12 months: 0.70 ± 0.88	1.22 ± 0.93	0.006
Aboelsaad et al. 2014 ²⁷	20 patients 20 pockets – SRP 20 pockets – SRP+minocycline assessed: PD, CAL	3months 6 months	PD [mm]	baseline: 6.28 ± 0.50 after 3 months: 4.80 ± 0.70	6.53 ± 0.43	–
				after 6 months: 4.40 ± 0.40	5.90 ± 0.60	<0.05
			CAL [mm]	baseline: 6.80 ± 0.20 after 3 months: 5.75 ± 0.35	5.58 ± 0.60	<0.05
				after 6 months: 5.75 ± 0.15	6.90 ± 0.40	–
Pandit et al. 2013 ²⁸	20 patients 20 pockets – SRP 20 pockets – SRP+minocycline assessed: PD, CAL	1 month 3 months	PD [mm]	baseline: 6.85 ± 0.81 after 1 month: 4.75 ± 0.72	6.25 ± 0.91	–
				after 3 months: 3.75 ± 0.79	5.30 ± 0.80	0.020
			CAL [mm]	baseline: 7.05 ± 1.65 after 1 month: 5.30 ± 1.31	4.60 ± 0.82	<0.001
				after 3 months: 4.45 ± 1.20	6.65 ± 1.75	–
Sweatha et al. 2015 ²⁹	18 patients (72 pockets) SRP+minocycline assessed: PD, CAL	3 months 6 months	PD [mm]	baseline: 6.13 ± 0.79 after 3 months: 2.84 ± 0.44	5.82 ± 0.48	–
				after 6 months: 2.25 ± 0.46	3.36 ± 0.37	<0.001
			CAL [mm]	baseline: 6.19 ± 0.85 after 3 months: 2.79 ± 0.53	2.60 ± 0.47	<0.001
				after 6 months: 2.31 ± 0.42	5.97 ± 0.68	–

Data presented as mean \pm standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; NS – nonsignificant.

groups. In the group where minocycline was used in addition to standard SRP therapy, better PD and CAL values were found in comparison with the control group. The results obtained depended to a large extent on the time in which the assessment was conducted, and it is worth noting that the research cohorts were not very large. The observation periods lasted up to 12 months. In research carried out between 1993 and 2002, statistically significant reduction in PD in comparison with traditional non-surgical treatment was achieved in 4 of the 8 works reviewed.²²

Doxycycline is a long-acting tetracycline antibiotic. Its antibacterial spectrum is *Brucella* sp., *Mycoplasma* sp., *Pasteurella tularensis*, *Chlamydia* sp., *Ureaplasma* sp., *Neisseria gonorrhoeae*, *Leptospira* sp., *Actinomyces* sp., *Haemophilus* sp., *Rickettsia* sp., *Borrelia* sp. (*B. burgdorferi*), *Treponema* sp., *Yersinia* sp., *Legionella* sp., *Campylobacter* sp., *Vibrio* sp., *Listeria* sp., *Moraxella catarrhalis*, streptococci, including *Streptococcus pneumoniae* (resistant strains are present), Gram-negative rods from the Enterobacteriaceae family (resistant strains), with the exception of *Proteus* sp., *Providencia* sp., *Serratia* sp., staphylococci, anaerobes *Propionibacterium* sp., *Clostridium* sp. as well as *Bacteroides fragilis* (resistant strains).^{23,24} Tetracyclines are inactive against *Pseudomonas aeruginosa*. The mechanism of resistance of bacterial strains is associated with reduction in the ability to penetrate the inside

of the bacterial cell or with active removal of the antibiotic from the bacterial cell.^{23,24} The antibacterial spectrum is very wide, but the long-term use of tetracyclines in clinical practice has led to the selection of a high percentage of resistant strains both among Gram-positive cocci and Gram-negative bacilli.

Atridox (DenMat, Lompoc, USA) is a preparation that releases subgingival doxycycline. Before use, one should mix the contents of the 2 syringes in which the product is delivered. Syringe A contains 450 mg of Atrigel, which is a bioabsorbable, liquid polymer preparation of poly(DL-lactide) (PDLA), dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains 42.5 mg of active doxycycline. The product thus formed is a light yellow viscous liquid with a concentration of 10%. The preparation is inserted into the periodontal pocket using a bent needle, filling the pocket to the edge of the gum. The filled pocket should be covered with surgical cement. The dressing is left for 7 days, and then Atridox can be removed or allowed to biodegrade.

In 3 out of the 5 studies evaluated (Table 4), statistically significant differences were found between the study groups.^{30,33,34} In the group where doxycycline was used in addition to standard SRP therapy, better PD and CAL values were obtained in comparison with the control group. In the remaining 2 studies, no statistical differences were

Table 4. List of studies evaluating the efficacy of intra-pocket doxycycline (Atridox)

Author	Assessed groups	Time of observation	Results		p-value
			test group	control group	
Ahamed et al. 2013 ³⁰	12 patients 30 pockets – SRP 30 pockets – SRP+doxycycline assessed: PD, CAL	6 months	PD [mm] baseline: 6.40 ± 0.20	6.60 ± 0.30	–
			gain after 6 months: 4.50 ± 1.10	5.80 ± 1.10	<0.040
			CAL [mm] gain after 6 months: 1.00 ± 0.70	0.36 ± 0.40	<0.050
Javali and Vandana 2012 ³¹	4 patients 130 pockets SRP SRP+doxycycline assessed: PD, CAL	3 months	no statistically significant difference between groups in assessed parameters		
Al Hulami et al. 2011 ³²	12 patients 12 pockets – SRP 12 pockets – SRP+doxycycline assessed: PD, CAL	3 months	no statistically significant difference between groups in assessed parameters		
Deo et al. 2011 ³³	60 patients 30 patients – SRP 30 patients – SRP+doxycycline assessed: PD, CAL	6 months	PD [mm] baseline: 5.83 ± 0.53	5.70 ± 0.65	–
			after 6 months: 2.80 ± 0.76	3.40 ± 0.49	<0.001
			CAL [mm] baseline: 6.50 ± 0.50	6.53 ± 0.68	0.830
Sandhya et al. 2011 ³⁴	45 patients 45 pockets – SRP 45 pockets – SRP+doxycycline assessed: PD, CAL	1 month 6 months	PD [mm] baseline: 6.40 ± 1.03	6.27 ± 1.07	–
			after 1 month: 4.93 ± 0.94	5.20 ± 1.06	0.209
			after 6 months: 3.47 ± 0.63	4.53 ± 0.73	<0.001
			CAL [mm] baseline: 5.60 ± 0.96	5.47 ± 1.04	–
			after 1 month: 4.20 ± 0.92	4.40 ± 1.03	0.334
			after 1 month: 4.20 ± 0.92	3.73 ± 0.86	<0.001

Data presented as mean \pm standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; NS – nonsignificant.

found between the groups. The periods of observation were short (3–6 months) and the number of participants was small (4–12 patients). However, it is worth noting that in studies conducted on a larger number of patients (45–60 people), a statistically significant improvement in the clinical parameters evaluated was achieved.^{33,34}

Tetracycline fibers

Periodontal Plus AB (Advanced Biotech Products (P) Ltd., Chennai, India) is a biodegradable collagen fiber soaked with 8% tetracycline, releasing the drug in the dental pocket for a period of 10–14 days.³⁵ A collagen tow containing 25 mg of pure filamentous type I collagen provides a carrier for about 1.7 mg of tetracycline hydrochloride. This collagen strand is not transversely cross-linked, which results in systematic release of the drug according to how the collagen fibers are degraded. The advantages of this product are easy placement and good retention in the gingival pocket.³⁶

A study assessing the therapeutic effects resulting from the use of additional tetracycline fibers over longer periods clearly shows greater reduction in PD and a greater improvement in CAL (Table 5).^{37–40} The results of the test group, where a combined therapy in the form of SRP and Periodontal Plus AB was used, and the results of the control group, where only SRP was used, were significantly better at the end of the therapy than at the beginning, but they were comparable between the 2 groups, without significant statistical differences ($p = 0.288$, $p = 0.0530$, respectively).³⁹ However, in all the works with follow-up periods longer than 3 months^{37–40} as well as in the review by Nadig and Shah,⁴¹ the improvement of the PD and CAL parameters was significant ($p < 0.05$), which clearly indicates that the use of fibers saturated with tetracycline in addition to mechanical cleansing favorably improves the effects of treatment and enhances tissue healing. The benefits of using tetracycline threads observed over a period of 90 days are undoubtedly as-

Table 5. List of studies evaluating the efficacy of tetracycline fibers (Periodontal Plus AB)

Author	Assessed groups	Time of observation	Results		p-value
			test group	control group	
Sachdeva and Agarwal 2011 ³⁷	35 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	1 month 2 months 3 months	baseline: 6.83 ± 0.85	6.71 ± 0.93	0.001
			PD [mm] after 1 month: 5.23 ± 1.00	5.69 ± 0.99	
			after 2 months: 4.29 ± 1.04	5.29 ± 0.78	
	40 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	1 month 3 months	baseline: 7.31 ± 1.10	7.29 ± 1.04	0.001
			CAL [mm] after 1 month: 6.20 ± 1.23	6.49 ± 0.88	
			after 2 months: 5.69 ± 1.32	6.29 ± 1.10	
Dodwad et al. 2012 ³⁸	100 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	15 days 45 days 90 days	after 3 months: 5.43 ± 1.21	6.26 ± 1.06	0.288
			PD [mm] baseline: 3.55 ± 0.81	3.27 ± 0.88	
			after 1 month: 2.53 ± 0.59	2.92 ± 0.97	
		3 months	after 3 months: 2.14 ± 0.54	2.78 ± 0.96	0.015
			CAL [mm] baseline: 13.80 ± 0.83	13.10 ± 1.97	0.156
			after 1 month: 11.35 ± 0.67	12.40 ± 2.09	0.043
Sinha et al. 2014 ³⁹	40 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	15 days 45 days 90 days	after 3 months: 10.70 ± 0.87	12.15 ± 2.28	0.014
			PD [mm] baseline: 5.80 ± 0.65	5.61 ± 0.51	0.000
			after 15 days: 4.66 ± 0.64	5.38 ± 0.69	
	100 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	15 days 45 days 90 days	after 45 days: 4.16 ± 0.76	5.14 ± 0.64	
			after 90 days: 3.42 ± 0.79	4.44 ± 0.75	0.000
			CAL [mm] baseline: 3.67 ± 1.63	3.55 ± 0.56	
Khan et al. 2015 ⁴⁰	40 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	3 months	after 15 days: 2.81 ± 0.61	3.36 ± 0.69	<0.001
			PD [mm] after 45 days: 2.22 ± 0.71	3.14 ± 0.63	
			after 90 days: 1.45 ± 0.65	2.54 ± 0.65	
	40 patients test group – SRP+Periodontal Plus AB® control group – SRP assessed: PD, CAL	3 months	CAL [mm] baseline: 10.70 ± 0.61	10.48 ± 0.64	<0.001
			after 3 months: 8.03 ± 0.55	9.01 ± 0.64	

Data presented as mean ± standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; NS – nonsignificant.

sociated with the adhesive properties of tetracyclines in relation to root cement and the inhibitory effects on collagenase and matrix metalloproteinase.^{39,40}

Metronidazole

Metronidazole is a chemotherapeutic active against most Gram-positive and Gram-negative anaerobic bacteria and protozoa. It easily penetrates into single-cell organisms and bacteria. Metronidazole oxidase reduction potential is lower than in the case of ferredoxin – an electron-transporting protein found in anaerobic and oxygen-poor organisms. The potential difference causes the reduction of the 5-nitro group of metronidazole, and the compound makes the DNA chain break in these organisms.⁴²

In periodontology, metronidazole is administered in the form of Elyzol Dentagel (A. L. Pharma, Englewood, USA), with a 25% concentration corresponding to 1 g of metronidazole benzoate encapsulated in a glycerol matrix and sesame oil.³⁵ Concentrations of approx. 120 µg/mL are measurable for at least 8 h and concentrations over 1 µg/mL have been found at 36 h. Applied to the periodontal pocket twice a week, it tightens in contact with the gum fluid, precipitating crystals.³⁵

In one of the studies reviewed, the reduction of PD during the 3-month follow-up period was statistically significant in both the test group, which combined SRP and a metronidazole gel, and the SRP-only control group.²⁸ The reduction of PD by an additional 0.5 mm in the test group in comparison with the control group was non-significant, as was the improvement in CAL by an additional 0.25 mm. In the second of the studies evaluated, the reduction of PD in both groups was statistically significant, especially in the first 6 weeks of observation ($p < 0.001$).⁴³

However, there were no statistically significant differences in the improvement of CAL between the test and control group (Table 6). In a review by Bonito et al., ambiguous results were observed. Out of 11 studies reviewed, statistically significant improvement in CAL was observed in only 2 – 0.66 mm after 6 weeks ($p < 0.001$) and 0.4 mm after 39 weeks ($p < 0.001$).²¹

Conclusions

The review of the literature presented here does not give a definite answer to the question of whether LDD significantly improves the effectiveness of non-surgical treatment of periodontitis. It can be noted that the statistical significance of improvements in the clinical parameters was more often obtained using antibiotics compared to CHX. However, most of the current treatment systems are imperfect, due to the form of administration, and the mode and time of drug release. One of the disadvantages is also the price of preparations, which in the absence of high predictability of treatment is a problem for both the patient and the doctor.

Locally delivered drugs seem to be a good solution for the causal treatment of periodontitis, and work on improving carriers and the use of medicinal substances should be continued. Bisphosphonates have been tested as osteoclasts and binding calcium inhibitors,⁴⁴ probiotics as organisms that restore bacterial balance in periodontal pockets,⁴⁵ as well as new carriers based on liotropic liquid crystal systems that persist in pockets for over a week.⁴⁶ Drugs used in periodontal pockets in many cases help to avoid the general antibiotic therapy with its side effects. At the same time, there is no risk of overdose or overuse, as the concept of a subgingival application is still only a supplement to traditional non-surgical treatment.

Table 6. List of studies evaluating the efficacy of 25% metronidazole gel (Elyzol)

Author	Assessed groups	Time of observation	Results		p-value
			test group	control group	
Kadkhoda et al. 2012 ⁴³	20 patients test group – SRP+Elysol® control group – SRP assessed: PD, CAL	6 weeks 12 weeks	PD [mm] baseline: 6.09 ± 1.13	6.30 ± 1.55	0.580
			after 6 weeks: 3.39 ± 0.98	4.04 ± 1.21	0.002
			after 12 weeks: 3.02 ± 0.91	3.76 ± 1.21	0.001
	20 patients test group – SRP+Elysol® control group – SRP assessed: PD, CAL	1 month 3 months	CAL [mm] baseline: 5.17 ± 1.43	5.61 ± 2.02	
			after 6 weeks: 7.20 ± 1.75	7.43 ± 2.44	0.078
			after 12 weeks: 7.72 ± 1.89	7.83 ± 2.51	
Pandit et al. 2013 ²⁸	20 patients test group – SRP+Elysol® control group – SRP assessed: PD, CAL	1 month 3 months	PD [mm] baseline: 6.80 ± 1.00	6.25 ± 0.91	0.200
			after 1 month: 5.10 ± 1.02	5.30 ± 0.80	0.490
			after 3 months: 4.10 ± 0.91	4.60 ± 0.82	0.070
	20 patients test group – SRP+Elysol® control group – SRP assessed: PD, CAL	1 month 3 months	CAL [mm] baseline: 6.60 ± 1.99	6.65 ± 1.75	0.860
			after 1 month: 5.45 ± 1.65	5.90 ± 1.43	0.070
			after 3 months: 4.60 ± 1.76	4.95 ± 1.65	0.200

Data presented as mean ± standard deviation (SD). SRP – scaling/root planing; PD – pocket depth; CAL – clinical attachment level; NS – nonsignificant.

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