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Introduction

Periodontal infections tend to be site-specific, mostly confined to the periodontal pocket. Therefore, much attention has been directed towards the use of local drug delivery agents as adjuncts to avoid potential side effects and increased antibiotics resistance with systemic antimicrobials use. There has been an emergence of alternative pharmacologic therapies besides local antimicrobials in the form of photodynamic therapy, hyaluronic acid, probiotics, and other experimental non-antimicrobial drugs. However, the answer to the question of which is the most efficient local drug delivery or adjunctive agent for dental practitioners to utilize and provide the maximum benefit to their patients still remains doubtful.

Objectives

To review the efficacy of current commercially available local drug delivery and adjunctive agents used in non-surgical periodontal therapy in adults treated for periodontitis.

Methods

The PubMed/MEDLINE, EMBASE and CENTRAL databases were searched to identify any randomised controlled human intervention studies with professionally applied local subgingival drug delivery and adjunctive agents in the treatment of periodontitis. The search considered works published from 1979 until April 2019 using the keywords "periodont*", "antimicrobial", "photodynamic therapy", "hyaluron*", "chlorhexidine", "tetracycline", "minocycline", "metronidazole", "doxycycline", "non-surgical", "scaling and root planing", "adjunct", "subgingival", and "local delivery". Bibliographies from previous systematic reviews on the topic were scrutinised. Only relevant literature in the English language were selected, and the use of experimental or discontinued drugs was excluded.

Results

24 randomised controlled trials with the longest follow-up studies of each local delivery agent were identified. The details of each agent and their clinical results are summarised in Tables 1 and 2.

Table 1: Summary of clinically tested commercial local antimicrobial drug delivery used as adjuncts in non-surgical periodontal therapy.

Active agent	Brand	Content	Delivery vehicle	Longest follow-up study	Mean differences (SE)	
					PPD (mm)	CAL (mm)
Chlorhexidine	Chlo-Site® (Ghimas Company, Italy)	1.5% Chlorhexidine	Gel	6 months (Jain et al. 2013 ¹⁴)	0.60 (0.18)	-0.66 (0.81)
	Periochip® (Perio Products Ltd., Israel)	2.5mg Chlorhexidine gluconate	Chip	9 months (Carvalho et al. 2007 ⁵ ; Grisi et al. 2002 ¹³ ; Jeffcoat et al. 1998 ¹⁵)	0.10 (0.44) [#] , -0.20 (0.32) [#] , 0.26 (0.07) [#]	0.00 (0.62) [#] , -0.40 (0.26) [#] , 0.20 (0.06) [#]
	PerioCol®-CG (Eucare Pharmaceuticals Ltd., India)	2.5mg Chlorhexidine gluconate	Film	6 months (Singh et al. 2014 ²³)	0.91 (0.31) [#]	1.92 (0.30) [#]
	EC40® (Biodent BV, The Netherlands)	35% Chlorhexidine diacetate	Varnish	9 months (Cosyn et al. 2006 ⁷)	0.62 (0.25)	Not available
	Cervitec® (Ivoclar/Vivadent AG, Liechtenstein)	1% Chlorhexidine		3 months (Manikandan et al. 2016 ¹⁸)	1.11 (0.36) [#]	Not available
Metronidazole	Elyzol® (Dumex Denmark)	25% Metronidazole benzoate	Gel	9 months (Griffiths et al. 2000 ¹²)	0.50 (0.38) [#]	0.40 (0.38) [#]
Tetracycline	Periodontal Plus AB™ (Advanced Biotech Products, India)	2mg Tetracycline hydrochloride	Fibre	6 months (Singh et al. 2014 ²³)	1.25 (0.27) [#]	1.69 (0.26) [#]
Doxycycline	Atridox® (Atrix Laboratories, USA)	10% Doxycycline hyclate	Gel	36 months (Bogren et al. 2008 ⁴)	0.10 (0.16) [#]	0.20 (0.20) [#]
Minocycline	Arestin® (OraPharma, Inc., USA)	1mg Minocycline hydrochloride	Micro-spheres	24 months (Cortelli et al. 2008 ⁶ ; Killeen et al. 2018 ¹⁶)	0.41 (0.51) [#] , -0.37 (0.24) [#]	Not available; -0.51 (0.27) [#]
	Dentomycin® (Lederle Dental Division, UK)	2% Minocycline hydrochloride	Ointment	18 months (Timmerman et al. 1996 ²⁴)	0.05 (0.37) [#]	0.27 (0.45) [#]
	Periocline® (Sunstar Corp., Japan)					

Table 2: Summary of clinically tested commercial local subgingival adjunctive agents used in non-surgical periodontal therapy.

Active agent	Brand	Content	Delivery vehicle	Longest follow-up study	Mean differences (SE)	
					PPD (mm)	CAL (mm)
Enamel matrix derivative	Emdogain® (Institute Straumann AG, Switzerland)	30 mg/ml porcine enamel matrix derivative	Gel	12 months (Mombelli et al. 2005 ¹⁹)	0.20 (0.70)	0.70 (1.20)
Hyaluronic acid	Aftamed® (BioPlax Limited, UK)	240mg/100g Sodium hyaluronate	Gel	6 weeks (Omer et al. 2018 ²¹)	1.36 (0.41)	0.72 (0.31)
	Aminogam® (Errekappa Euroterapici, Italy)	Sodium hyaluronate, Amino acids		3 months (Bevilacqua et al. 2012 ²)	0.50 (0.79) [#]	0.19 (0.69) [#]
	Gengigel® (Ricerfarma, Italy)	0.2% & 0.8% Sodium hyaluronate		6 months (Eick et al. 2013 ⁹)	0.25 (0.12) [#]	-0.10 (0.20) [#]
	Healon GV® (Pharmacia & Upjohn, Sweden)	14mg/ml Sodium hyaluronate		12 months (Engström et al. 2001 ¹⁰)	-0.60 (0.83) [#]	Not available
Photo-sensitizer	EmunDo® (A.R.C. laser GmbH, Germany)	Indocyanine green (iodide-free)	Dye Solution	3 months (Birang et al. 2015 ³ ; Monzavi et al. 2016 ²⁰)	-0.30 (0.41); 1.91 (0.23) [#]	0.90 (0.44); -0.19 (0.27) [#]
	HELBO® (Bredent Medical, Germany)	Phenothiazine chloride		12 months (Alwaeli et al. 2015 ¹ ; Lulić et al. 2009 ¹⁷)	0.91 (0.57); 0.20 (0.33) [#]	1.35 (0.45); -0.11 (0.33) [#]
	Periowave™ (Periowave Dental Technologies Inc, Canada)	Methylene blue		25 weeks (Segarra-Vidal et al. 2017 ²²)	-0.17 (0.65)	-0.20 (0.47)
	Fotosan® (CMS Dental, Denmark)	Toluidine blue / Tolonium chloride		6 months (Goh et al. 2017 ¹¹)	0.26 (0.05)	0.05 (0.07)
Natural products	NBF Gingival Gel (NanoCureTech Co. Ltd, South Korea)	Vitamin C, E, Propolis extract, Aloe extract, Green tea extract	Gel	3 months (Debnath et al. 2016 ⁸)	0.71 (0.63)	0.74 (0.63)

PPD: probing pocket depth; CAL: clinical attachment level; [#]repeated application; negative value indicates result in favour of control (mechanical debridement alone)

Discussion & Conclusion

Overall, many commercial pharmacotherapeutic local drug delivery and adjunctive agents had been clinically tested in the non-surgical treatment of periodontitis. The adjuncts from the selected studies above had reported mean differences ranging from **-0.60 to 1.91 mm of mean PPD reduction** and **-0.66 to 1.92 mm of mean CAL gain**. In general, most of these adjunctive agents had shown minimal but positive clinical results compared with mechanical debridement alone. However, the methodologies and clinical results vary within and between each agent. Therefore, it is difficult to conclude and support the superiority of one local agent over another.

Clinical Implications & Future Research Recommendations

The application of local drug delivery and adjunctive agents could provide some benefits in treating periodontitis. Additional randomised controlled trials with medium- (at least 6 months) to long-term (at least 12 months) studies are needed to determine the efficacy of local agents as their usefulness in the long term is still debatable, taking into account the cost-benefit ratio with modest clinical results.

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