OXYGENE GEL® AS AN ADJUNCT TO TREATMENT OF PERIODONTAL POCKETS

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Original Article

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ABSTRACT

Objective: Present clinical trial was designed to study effect of Oxygene Gel® Aloe enriched on healing of periodontal pockets following mechanical non-surgical therapy. **Methods:** Sample included 16 patients, with chronic adult periodontitis. These patients had paired teeth with pockets ≥6 mm in opposing sides of the mouth in this crossover design study. Fifty-eight teeth with pockets measuring 6-9 mm were alternately assigned to 2 treatment groups: scaling and root planing as well as application of test gel versus scaling and root planing alone. Root planing was performed at baseline for test and control teeth. The test gel was injected into pockets of test teeth at baseline, 1-week and 2-weeks intervals. One of the control teeth was extracted during the study eventually leaving 28 control teeth which were evaluated against the paired 28 test teeth. The trial extended over an 8-week period and assessments of probing pocket depth (PPD), loss of attachment (LOA), mobility, bleeding on probing (BOP) and plaque indices were made at baseline, 4th and 8th week intervals following therapy. Statistical analysis using Wilcoxon Matched-Paired Signed Rank test was performed. **Results:** The test gel as an adjunct to mechanical therapy significantly decreased PPD ($p<0.05 - <0.001$) on all 5 surfaces except on the midbuccal; reduced LOA ($p<0.05 - <0.01$) on the midlingual and distolingual surfaces; decreased BOP scores ($p<0.05 - <0.001$) on the mesial, distal and lingual sites and decreased mobility scores ($p<0.05$) of test teeth at the 8th week interval as compared to control group. **Conclusion:** Results of this study conducted on patients with teeth having deep periodontal pockets of ≥6 mm suggests a possible role for this gel of Chlorine dioxide Aloe enriched in the treatment of chronic adult periodontitis compared to nonsurgical treatment alone.

Key words: chlorine dioxide; aloe vera; periodontal pockets

INTRODUCTION

Chronic Periodontitis (CP) is one of the most common oral diseases which progresses over an indefinite period of time, affecting the supporting tissues of a tooth namely the periodontal ligament, alveolar bone and cementum, resulting in loss of the alveolar bone and apical migration of epithelium (1). The implication of dental deposits primarily plaque and calculus in the initiation and development of periodontal diseases (PD) has been well documented from epidemiological, animal, clinical and microbiological studies (2-9). The resultant inflammation in the gingival tissues is supported to some extent by the host response to the consistent existence of various bacterial products and bacterial antigenic factors (10-12). This inflammatory process related to the host responses, involve immune complexes, complements, cytokines, prostaglandin, histamines, kinins, polymorphonuclear leukocytes, macrophages and lymphocytes (13-18).

Up to the present, the prevention and treatment of PD greatly involve the mechanical removal of plaque such as by tooth brushing and interdental cleaning by the patient (6, 19-21); scaling, root planning (22-24) and subgingival curettage by the professional. However, the difficulty in patient compliance and education in maintaining their oral hygiene as well as the time consuming nature and possible incomplete deposits removal by mechanical procedures by the professionals have, therefore, led to alternative plaque control methods and treatment modalities, to control and treat PD.

Systemic administration of drugs particularly antibiotics may have undesirable side effects but are indicated in some situations (25-28). On the other hand, the local administration or delivery of therapeutic agents, incorporated into gels, strips, films, fibres and chips for local drug release into periodontal pockets, acting either on the bacteria or on the inflammatory pathways of the host response may have considerable advantage (29-34). The results suggest that some agents may be of benefit.

Among the antimicrobial agents experimented, chlorhexidine has been found to be the most effective (35-37) and non-steroidal anti-inflammatory agents have been shown to have a beneficial effect (38-41).

The antimicrobial effect of chlorine dioxide (ClO_2) and the potential therapeutic effects of Aloe Vera (AV) mainly its anti-inflammatory and immune stimulating effects as well as the search for local delivery agents in the treatment of PD propagated this clinical trial.

The objective of this study was to investigate the efficacy of Oxygene gel® (containing chlorine dioxide enriched with Aloe Vera) as an adjunct to conventional therapy on the resolution of inflammation and healing of pathologically deepened periodontal pockets.

MATERIALS AND METHODS

Study sample included 16 patients, with chronic periodontitis who expressed informed consent to participate. The subjects with ages ranging from 34 - 72 years were selected in this split-mouth design study according to the following criteria: They have: 1) no systemic diseases and none of the female patients are pregnant; 2) not been on any medication/antibiotic therapy in the past 6 months, neither have they been using any form of chemical agent for oral hygiene; 3) not undergone scaling nor other periodontal treatment for the past six months; 4) the designated teeth, with pockets 6-9mm, both test and control teeth present in separate quadrants on contralateral sides.

Fifty-eight teeth with pockets measuring 6-9 mm were alternately assigned to 2 treatment groups: scaling and root planing as well as application of test gel (Oxygene® - Figure 1) versus scaling and root planing alone. Root planing was performed at baseline for test and control teeth. The test teeth were isolated with cotton rolls for about 5 minutes. The test gel was then injected into pockets of test teeth with no. 16 gauge needle, attached to a 2.5 ml syringe (Figure 2), at baseline, 1-week and 2-weeks intervals. Gel completely filled all pockets in the tooth and excess was removed with a cotton bud. One of the control teeth was extracted during the study eventually leaving 28 control teeth which were evaluated against the paired 28 test teeth. The trial extended over an 8-week period and assessments of probing pocket depth (PPD), loss of attachment (LOA) with Williams probe, bleeding on probing (BOP) (42), mobility and plaque (43) indices were made at baseline, 4th and 8th week intervals following therapy. Data was evaluated using the SPSS package and statistical analysis was performed using Wilcoxon Matched-Paired Signed Rank test.

OXYGENE® GEL

Oxygene® gel is a viscous thixotropic syringeable gel manufactured by Oxyfresh (USA) and packed in a tube. Its components include stabilized Chlorine dioxide mainly, with Aloe vera, Carrageenan, Chamomile extract, Methyl and Prophyl parabens.

Figure 1. Oxygene gel tube with the clinical tray.

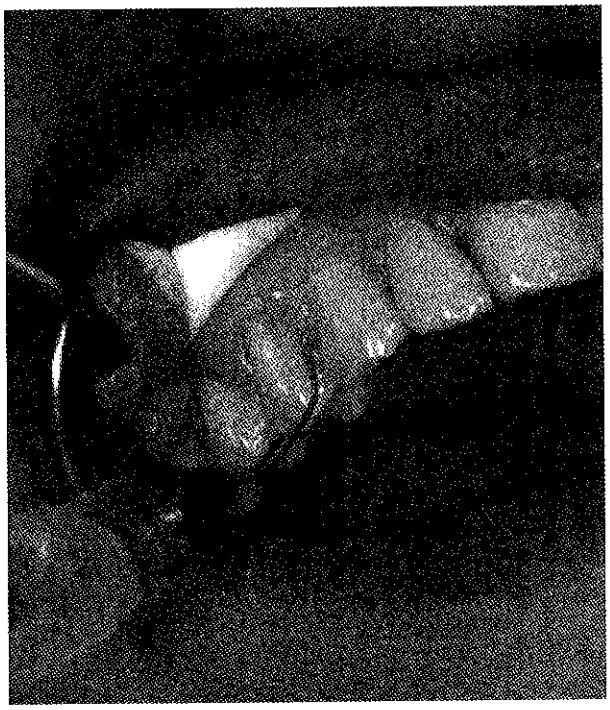

Figure 2. Local delivery of Oxygene gel into the periodontal pocket of test tooth.

Chlorine dioxide is a powerful oxidizing and germicidal agent with the ability to eliminate a wide range of bacteria, viruses and fungi in vitro within 1 minute (44). Aloe Vera is derived from the tropical cactus of the genus aloe, a plant having toothed fleshy leaves. A mucilaginous clear aloe gel from the leaves has been used for the treatment of skin burns and wounds (45). The composition of aloe vera is wide of which many components e.g. acemannan, carboxypeptidase, lectins, gibberelline, emodin and resins contribute to enhanced tissue healing.

RESULTS

The purpose of the comparison of all variables between test and control groups at baseline (Table 1) was to determine if there were significant differences between the control and test group in the indices selected. There were no significant differences in the variables analyzed by Wilcoxon Matched-Paired Signed Rank Test.

Table 2 shows the mean values for plaque levels for the test and control groups at the 4th and 8th week post treatment assessments which were subjected to statistical analysis. There were no statistically significant differences between the results for the test and control groups, using the Wilcoxon Matched-Paired Signed-Rank Test at both intervals.

Table 3 shows the 4th week and 8th week post-treatment results of the means for BOP scores. These values were subjected to statistical analysis using the Wilcoxon Matched-Paired Signed-Rank Test. During the 8th week post treatment assessment, the mesial, distal and lingual surfaces of the test teeth demonstrated significant improvements ($p<0.05$ – $p=0.001$)

Table 4 summarizes the mean values for PPD obtained at the 4th and 8th week intervals for control and test sites. These values between the test and control groups were subjected to statistical analysis. At the 4th week interval, the differences in mean PPD in the control and test groups were not significant for all surfaces but were statistically significant during the 8th

Table 1. Baseline Comparisons of All Variables for Test and Control Teeth

Variables	Surfaces	Control		Test		Wilcoxon Signed Rank Test	
		Mean ± S.D		Mean ± S.D		Z-Test	p-value
Plaque	Distal	1.413	0.501	1.448	0.5006	-1.000	0.317
	Buccal	1.207	0.559	1.207	0.559	0.000	1.000
	Mesial	1.310	0.541	1.379	0.494	-1.414	0.157
	Lin-pal	1.310	0.541	1.276	0.528	-1.000	0.317
Bleeding on Probing	Distal	1.759	0.690	1.759	0.690	-0.000	1.000
	Buccal	1.070	0.799	1.241	0.831	-1.299	0.194
	Mesial	1.793	0.675	1.828	0.711	-0.333	0.739
	Lin-pal	1.345	0.814	1.138	0.693	-1.633	0.102
Probing Pocket Depth	Distobuccal	5.07	2.10	4.72	2.07	0.680	0.497
	Mid buccal	3.97	1.90	4.45	2.10	1.164	0.245
	Mesiobuccal	5.00	1.56	5.14	2.49	0.312	0.755
	Mesiopal/lin	4.72	1.81	5.66	1.88	1.841	0.066
	Mid pal/lin	4.03	1.78	4.00	1.93	0.350	0.726
	Distopal/lin	4.86	1.75	5.03	1.74	0.404	0.686
Loss of Attachment	Distobuccal	6.34	2.47	5.90	2.11	0.769	0.442
	Mid buccal	5.48	1.98	6.00	2.45	1.401	0.161
	Mesiobuccal	6.21	1.59	6.45	2.41	0.338	0.735
	Mesiopal/lin	5.93	2.19	6.76	2.10	1.891	0.059
	Mid pal/lin	5.69	2.56	5.66	2.30	0.142	0.887
	Distopal/lin	6.38	2.34	6.21	1.61	0.494	0.621
Mobility	By tooth	1.310	0.604	1.448	0.686	-0.915	0.360

Table 2. Mean values for Plaque levels for the test and control teeth with statistical analysis Using Wilcoxon Matched-Paired Signed-Rank (WMPSR) Test

Surfaces	Week 4 (n=28)						Surfaces	Week 8 (n=28)					
	Test		Control					Test		Control			
	Mean	S.D.	Mean	S.D.	Z Test	P-Value		Mean	S.D.	Mean	S.D.	Z Test	P-Value
Distal	0.828	0.384	0.862	0.516	0.302	0.763	Distal	0.828	0.468	0.821	0.476	0.577	0.564
Buccal	0.379	0.494	0.414	0;501	0.302	0.763	Buccal	0.172	0.468	0.214	0.418	0.447	0.655
Mesial	0.897	0.409	0.862	0.441	0.333	0.739	Mesial	0.793	0.412	0.821	0.390	0.000	1.000
Lingual	0.724	0.455	0.655	0.484	0.816	0.414	Lingual	0.448	0.632	0.393	0.497	0.000	1.000

Table 3. Mean values for Bleeding on Probing Scores for the test and control teeth with statistical analysis (WMPSR Test)

Surfaces	Week 4 (n=28)						Surfaces	Week 8 (n=28)					
	Test		Control					Test		Control			
	Mean	S.D.	Mean	S.D.	Z Test	P-Value		Mean	S.D.	Mean	S.D.	Z Test	P-Value
Distal	0.655	0.670	0.862	0.639	1.386	0.166	Distal	0.345	0.553	0.714	0.713	2.230	0.026*
Buccal	0.379	0.622	0.586	0.780	1.604	0.109	Buccal	0.207	0.412	0.321	0.548	1.134	0.257
Mesial	0.828	0.602	0.828	0.602	0.000	1.000	Mesial	0.241	0.511	0.714	0.659	3.276	0.001*
Lingual	0.310	0.471	0.552	0.736	1.811	0.070	Lingual	0.103	0.320	0.357	0.622	2.070	0.038*

Table 4. Mean values for Pocket Depth for the test and control teeth at 4th and 8th weeks interval with statistical analysis using WMPSR Test

Surfaces	Week 4 (n=28)						Surfaces	Week 8 (n=28)					
	Test Mean ± S.D. (mm)		Control Mean ± S.D. (mm)		Wilcoxon Signed Rank			Test Mean ± SD (mm)		Control Mean ± S.D. (mm)		Wilcoxon Signed Rank	
					Z-Test	P-Value						Z-Test	P-value
Distobuccal	3.90	1.68	3.83	1.71	0.122	0.903	Distobuccal	2.41	1.27	3.54	2.08	2.554	0.011*
Midbuccal	3.10	2.20	3.62	2.44	1.110	0.267	Midbuccal	2.27	1.58	3.00	2.58	1.406	0.160
Mesiobuccal	3.86	2.07	4.14	2.34	0.444	0.657	Mesiobuccal	2.38	1.47	4.07	2.19	3.350	0.001*
Mesionlingual	4.03	1.57	3.93	1.56	0.540	0.587	Mesionlingual	2.38	1.01	3.50	1.53	2.237	0.025*
Midlingual	3.31	1.39	3.72	1.36	1.395	0.163	Midlingual	2.00	0.96	2.86	1.69	2.792	0.005*
Distolingual	3.79	1.54	4.00	1.73	0.564	0.573	Distolingual	2.31	1.04	3.76	1.64	3.566	<0.001*

Table 5. Mean value for Loss of Attachment for the test and control teeth at 4th and 8th weeks interval with statistical analysis using WMPSR Test

Surfaces	Week 4 (n=28)						Surfaces	Week 8 (n=28)					
	Test Mean ± S.D. (mm)		Control Mean ± S.D. (mm)		Wilcoxon Signed Rank			Test Mean ± SD (mm)		Control Mean ± S.D. (mm)		Wilcoxon Signed Rank	
					Z-Test	P-Value						Z-Test	P-value
Distobuccal	4.97	1.70	5.21	2.18	0.720	0.471	Distobuccal	2.86	1.94	3.25	2.37	1.274	0.203
Midbuccal	4.52	2.53	4.79	2.48	0.479	0.632	Midbuccal	3.48	2.46	3.89	3.05	0.626	0.531
Mesiobuccal	5.14	2.29	5.41	2.68	0.219	0.827	Mesiobuccal	3.14	2.05	3.75	2.74	0.557	0.578
Mesiolingual	4.97	1.82	5.38	2.16	0.978	0.328	Mesiolingual	2.93	1.71	3.86	2.22	1.858	0.063
Midlingual	4.51	1.62	5.31	1.81	1.876	0.610	Midlingual	2.93	1.60	3.96	2.20	2.537	0.011*
Distolingual	4.62	1.86	5.21	2.06	1.153	0.249	Distolingual	3.03	1.61	3.64	2.11	3.578	<0.001*

Table 6. Mean values for Mobility for the test and control teeth at 4th and 8th weeks interval using Wilcoxon Matched-Paired Signed-Rank Test

Week	Test		Control			
	Mean	S.D.	Mean	S.D.	Z Test	P-Value
4th	.552	.632	.655	.814	.796	.426
8th	.310	.471	.643	.911	.2.157	.031*

* – significant

week interval on all the surfaces except the mid-buccal surface ($p<0.05$-$p<0.001$).

Table 5 presents the mean values for LOA at 4th week and 8th week intervals between the test and control groups showing significant differences at the 8th week on the midlingual ($p<0.05$) and distolingual ($p<0.001$) surfaces.

Table 6 presents the mean values and standard deviations for mobility in the test and control groups which were subjected to statistical analysis using the Wilcoxon Matched-Paired Signed-Rank Test. The comparison showed that the difference between the test and control groups was statistically significant at the 8th week period.

DISCUSSION

The split-mouth design, used in this study has been the predominant design in many studies (46-50), and has

been widely used in the study of subgingival delivery of therapeutic agents (51-55). It allows smaller variability since patients served as their own control, but possibility of crossover effects could make clear interpretation of similarity between treatments difficult. These crossover effects may be a consequence of salivary contamination or they may arise from patient bias in the variation in patient's oral hygiene, mastication or other behaviour for the sites (56). These effects are a higher concern when multiple sites are treated as opposed to single sites with a chemotherapeutic agent because of the increase quantity of agent available to other sites in the mouth. Hence in this study only one or a maximum of 2 test and 2 control teeth per subject were included and excess gel was swapped from the site to eliminate possible crossover effects to the control teeth.

The systemically delivered antimicrobials may be better for infection of the oral cavity, but the aim of periodontal therapy is to control or to shift the organisms and/or to modify the host response to the action of these organisms in the periodontal pocket. Hence locally delivered agents into the periodontal pocket may be appropriate to apply.

The range of 6-9mm pocket depth was selected to allow sufficient dynamic range to accommodate a change of 2-3 mm. Deep periodontal pockets which harbour anaerobic organisms were selected as ClO2 the test gel is an oxidizing agent.

The oral hygiene instructions and scaling given to each subject by itself might have resulted in reduced gingival inflammation and theoretically also in the subgingival microflora. However, Lavanchy et al. (57) demonstrated that these procedures do not influence the subgingival microbiota following scaling.

Oxygene® is an over-the-counter-gel made up of the active ingredients, stabilized ClO2 and AV. Due to the antimicrobial effect of stabilized ClO2 and the healing effect of AV gel and chamomile extract as well as the anti-inflammatory and antimicrobial effect of AV, the effects of Oxygene® gel was tested in deep periodontal pockets. Local delivery may also offer important benefits in terms of patient compliance compared to systemic regimens. Hence due to these and other factors, a variety of local delivery systems are being developed. Syringeable gels may offer greater ease of use but they may also be relatively rapidly lost from the pockets. Hence this gel could be tested further, to evaluate its sustained delivery drug retention and antimicrobial activity, to establish a possible basis for further development, as this study looked only into the clinical outcomes towards investigating its efficacy.

Recordings of plaque scores, BOP scores, PPD measurements, clinical attachment levels and mobility evaluated the clinical outcomes. All parameters improved in both test and control sites at subsequent assessments with mechanical treatment as has been noted in other studies (58-62).

Reductions in plaque were seen in the teeth of both the control and the test groups but there were no statistically significant differences at both time intervals. These findings were mainly attributable to the mechanical debridement as the test gel may probably not affect the quantity of plaque accumulation. Since ClO2 is an oxidizing and germicidal agent, it would be of interest to investigate its effect on plaque microorganisms, particularly in the deep pockets where they are mainly anaerobes (63-66). There was also greater reduction in the BOP scores in the test group as compared to the control group which was significant on some surfaces during the 8th week. As with other parameters, there was PPD reduction in both test and control teeth throughout the study. The differences between the means were statistically significant at 5 out of 6 test surfaces at the 8th week assessments. Improvements in clinical attachment levels were statistically significant at 2 of the surfaces on the test teeth as compared to the control teeth again at the 8th week interval.

After three applications of the gel and at the end of the 8th week assessment period, it was found that most of the treated sites responded more favourably than others. This was illustrated by the relatively high standard deviations for the probing depth reductions and changes of attachment level. In individual sites, attachment level changes of more than 3 mm were occasionally observed. However, prolonged observation times are needed to evaluate the persistence or possible relapse of the clinical improvements at the test sites (67).

The greater improvement in gingival inflammation may be attributed to the germicidal property of ClO2 (44) and the anti-inflammatory activity of the extracts of AV gel with its inhibitory action on the arachidonic acid pathway via cyclooxygenase (68). ClO2 is a strong oxidizing agent which may assist in suppressing the anaerobic organisms predominant in the deep periodontal pockets where treatment was rendered. Salicylates shown to be by-products of emodin, aloe emodin and aloin from AV (69) act as analgesic and anti-inflammatory, inhibiting the production of prostaglandins from arachidonic acid (70). In this study, we are assuming that these potential properties were in effect during the time course of the drug regime. The anti-inflammatory properties can further be explained by the fact that a carboxypeptidase in Aloe could inactivate bradykinin (71), and magnesium lactate in AV inhibits histidine decarboxylase, thereby preventing the formation of histamine from histidine (72-74). Lectins found in high levels in commercial AV preparations are hemagglutinating proteins that bind to glycoproteins and decrease inflammation (75). Acemannan, a major carbohydrate derived from the gel of the leaf of AV, has significant beneficial therapeutic effects including acceleration of wound healing, immune stimulation, anti cancer and anti viral effects (76). The ability of acemannan to induce macrophage activation directly has important implications in the physiologic mechanisms of host defence against invading bacteria, virus and may explain accelerated

wound healing effects (77). In addition, Gibberellin from AV acts as a growth hormone and decreases inflammation by stimulating protein synthesis (78). These modes of action could account for the enhanced degree of resolution of gingival inflammation observed in the test group.

To our knowledge, this is the first report in literature investigating the efficacy of a gel of ClO2 and AV in the treatment of advanced CP. There were no manifestations of any side effects with this gel during the 8 weeks clinical trial as queried from the patients and no pathoses were detected during subsequent examinations of the patients indicating its safety during the short term usage.

This study of locally delivering the gel of ClO2 and AV in the deep periodontal pockets was to obtain heightened clinical resolution and possibly avoid surgery particularly in localized deep periodontal pockets.

CONCLUSIONS

1) Statistically significant clinical improvement was observed at many sites in the test teeth compared to control teeth at the 8th week interval. 2) Oxygene® gel, a topical medication could be utilized as an adjunct in the treatment of CP.

REFERENCES

1. Yuodelis. Basic Phenomena, clinical management, occlusal and restoration. In: Periodontal Diseases, ed. *Yuodelis. Philadelphia: Lea & Febiger* 1977; pp. 77.

2. Greene JC, Vermillion JR. The oral hygiene index: a method for classifying oral hygiene status. J Am Dent Assoc 1960; 61: 172.

3. Greene JC, Vermillion JR. The simplified Oral Hygiene Index. J Am Dent Assoc 1963; 68: 71.

4. Ramfjord SP. The periodontal status of boys 11-17 years old in Bombay, India. J Periodontol 1961; 32: 237.

5. Loë H, Silness J. Periodontal Disease in Pregnancy. I- Prevalence and severity. Acta Odontol Scandinavia 1963; 21: 533-51.

6. Loë H, Theilade E, Jensen SB. Experimental gingivitis in man. J Periodontol 1965; 48: 497-504.

7. Waerhaug J. Epidemiology of periodontal disease. In: The prevention of periodontal disease, eds. Eastoe J.E., Picton D.C.A., Alexander A.G. p.1 London: Kimpton publishers 1971.

8. Socransky SS. Microbiology of periodontal disease: Present status and future considerations. J Periodontol 1977; 48: 497-504.

9. Slots J. Subgingival microflora and priodontal disease. J Clin Periodontol 1979; 6: 351-82.

10. Page RC, Schroeder HE. Current status of the host response in chronic marginal periodontitis. J Clin Periodontol 1981; 52: 477-91.

11. Nisengard RJ. Immediate hypersensitivity and periodontal disease. J Periodontol 1974; 45: 344.

12. Nisengard RJ. The role of immunology in periodontal disease. J Periodontol 1977; 48: 505.

13. Ohm K, Albers H, Lisboa B. Measurement of eight prostaglandins in human gingival and periodontal disease using high pressure liquid chromatography and radioimmunoassay. J Perio Res 1984; 19: 501-11.

14. Gowen M. Immune cells and bone resorption. Adv Exp Med Biol 1986; 208: 261-73.

15. Seymour RA. Drugs and the periodontium. J Clin Periodontol 1988; 15: 1-16.

16. Lowik CW. Parathyroid hormone (PTH) and PTH-like protein (PLP stimulate interleukin-6 production by osteogenic cells: a possible role of interleukin-6 in osteoclastogenesis. Biochem Biophys Res Commun 1989; 162(3): 1546-52.

17. Leknes KN. The influence of anatomic and iatrogenic root surface characteristics on bacterial colonization and periodontal destruction: a review. J Periodontol 1997; 68(6): 507-16.

18. Tonetti MS. Neutrophil migration into the gingival sulcus is associated with transepithelial gradients of interleukin-8 and ICAM-1. J Periodontol 1998; 69(10): 1139-47.

19. Suomi JD, Greene JC, Vermillion JR, Doyle J, Chang JJ, Leatherwood EC. The effect of controlled oral hygiene procedures on the progression of periodontal disease in adults. Results after third and final year. J Periodontol 1971; 42: 152-60.

20. Lindhe J, Socransky SS, Nyman S, Haffajee A, Westfelt E. Critical probing depths in periodontal therapy. J Clin Periodontol 1982; 9: 323-36.

21. Bruun C, Ekstrand KR, Andreasen KB. A new in vitro method for testing the interproximal cleaning potential of toothbrushing. J Clin Dent 1998; 9(1): 11-5.

22. Baderstein A, Nilveus R, Egelberg J. Effect of non-surgical periodontal therapy. I- Moderately advanced periodontitis. J Clin Periodontol 1991; 8: 57-72.

23. Ramfjord S, Caffesse R, Morrison E. Four modalities of periodontal treatment compared over 5 years. J Clin Periodontol 1987; 14: 445-52.

24. Drisko CH. Root instrumentation. Power-driven versus manual scalers, which one? Dent Clin North Am 1998; 42(2): 229-44.

25. Newman HN. The approximal apical border of plaque on children's tooth. I- Morphology, structure and cell content. J Periodontol 1979; 50: 561.

26. Genco RJ. Antibiotics in the treatment of human periodontal disease. J Periodontol 1981; 52: 545-58.

27. Loesche WJ, Schmidt E, Smith A. Effects of metronidazole on periodontal treatment needs. J Periodontol 1991; 62: 247-57.

28. Loesche WJ, Giordano JR, Hujoel P. Metronidazole in periodontitis: Reduced need for surgery. J Clin Periodontol 1992; 19: 103-12.

29. Rosling BG, Slots J, Webber RL, Christersson LA, Genco RJ. Microbiological and clinical effects of topical subgingival antimicrobial treatment on human periodontal disease. J Clin Periodontol 1983; 10: 487-514.

30. Drisko CH. Non-surgical therapy: Pharmaco-therapeutics. Annl Periodontol 1996; 1: 491-518.

31. Rams TE, Slots J. Local delivery of antimicrobial agents in the periodontal pockets. Periodontol 2000 1996; 10: 139-59.

32. Soskolne WA, Heasman PA, Stabholz A, Smart GJ, Palmer M, Flashner M, Newman HN. Sustained local delivery of chlorhexidine in the treatment of periodontitis: a multi-center study. J Periodontol 1997; 68 (1): 32-8.

33. Killoy WJ. Assessing the effectiveness of locally delivered chlorhexidine in the treatment of periodontitis. J Am Dent Assoc 1998; 130(4): 567-70.

34. Kinane DF. A six-month comparison of three periodontal local antimicrobial therapies in persistent periodontal pockets. J Periodontol 1999; 70(1): 1-7.

35. Loë H, Schiott CR. The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. J Perio Res 1970; 5: 79-83.

36. Lindhe J. The effect of topical application of fluorides on the gingival tissues. J Perio Res 1971; 6(3): 211-7.

37. Schiott CR. Effects of chlorhexidine on the microflora of the oral cavity. J Dent Res 1973; 8: 7-10.

38. Nyman S, Schroeder HE, Lindhe J. Suppression of inflammation and bone resorption by indomethacin during experimental periodontitis in dogs. J Periodontol 1979; 50: 450-61.

39. Waite IM, Saxton CA, Young A, Wagg BJ, Corbett M. The periodontal status of subjects receiving non-steroidal anti-inflammatory drugs. J Periodontal Res 1981; 16(1): 100-8.

40. Weaks-Dybvig M, Sanavi F, Zander H, Rifkin B. The effect of indomethacin on alveolar bone loss in experimental periodontitis. J Perio Res 1982; 17: 90.

41. Taiyeb Ali TB, Waite IM. The effect of systemic ibuprofen on gingival inflammation in humans. J Clin Periodontol 1993; 20: 723-8.

42. Cowell CR, Saxton CA, Sheiham A, Wagg BJ. Testing therapeutic measures for controlling chronic gingivitis in man: a suggested protocol. J Clin Periodontol 1975; 2(4): 231-40.

43. Waite IM, Jalil R, Cornick DER. A probe for plaque measurement. In: "Dental Practice" 1983; 21(22): 1.

44. Scantina J, Abdel-Rahman MS, Gerges SE, Khan MY, Gona O. Pharmacodynamics of alcide, a new antimicrobial compound. Fundam Appl Toxicol 1985; 4(3): 479-84.

45. Rovatti B, Brennam RJ. Experimental thermal burns. Industrial Medicine and Surgery 1959; 28: 364-8.

46. Goodson JM, Tanner A, McArdle S, Dix K, Watanabe SM. Multicenter evaluation of tetracycline fiber therapy: III. Microbiological Response. J Perio Res 1991; 26: 440-51.

47. Murayama Y, Nomura Y, Yamoaka A. Local administration of minocycline for periodontitis. Double-blind, comparative study of LS-007. J Japan Assoc Periodontol 1988; 30: 206-22.

48. Eckles TA, Reinhardt RA, Dyer JK. Intracrevicular application of tetracycline in white petrolatum for the treatment of periodontal disease. J Clin Periodontol 1990; 17: 454-62.

49. Ainamo J, Lie T, Ellingsen BH. Clinical responses to subgingival application of a metronidazole 25% gel compared to the effects of subgingival scaling in adult periodontitis. J Clin Periodontol 1992; 19: 723-9.

50. Heijl L, Dahlen G, Sundin Y, Wenander A, Goodson JM. A 4 quadrant comparative study of periodontal treatment using tetracycline containing drug delivery fibers and scaling. J Clin Periodontol 1991; 18: 111-6.

51. Van Steenberghe D, Bercy P, Kohl J, De Bouver J, Adriaens P, Vanderfaeillie A, Adriaenssen C, Rampen E, De Vree H, Mc Carthy FE, Vandenhoven G. Subgingival minocycline hydrochloride ointment in moderate to severe chronic adult periodontitis: A randomized, double-blind, vehicle-controlled, multicenter study. J Periodontol 1993; 64: 637-44.

52. Murayama Y. The current concept of crevicular minocycline therapy for periodontal disease. Int Acad Periodontol 1991; 1(1): 5-8.

53. Minabe M, Uematsu A, Nishijima K. Application of a local drug delivery system to periodontal therapy. I. Development of collagen preparations with immobilized tetracycline. J Periodontol 1989; 60: 113-7.

54. Stabholz A, Kettering J, Aprecio R, Zimmerman G, Baker PJ, Wikesjö UM. Retention of antimicrobial activity by human root surfaces after in situ subgingival irrigation with tetracycline HCL or chlorhexidine. J Periodontol 1993; 64: 137-41.

55. Newman MG, Kornman.KS, Dohert FM. A 6-month multi-center evaluation of adjunctive tetracycline fiber therapy used in conjunction with scaling and root planing in maintenance patients: Clinical results. J Periodontol 1994; 65: 685-91.

56. Koch GG, Paquette. Design principles and statistical considerations in periodontal clinical trials. Annals of Periodontol 1997; 2: 42.

57. Lavanchy DL, Bicket M, Baehni PC. The effect of plaque control after scaling and root planing on the subgingival microflora in human periodontitis. J Clin Periodontol 1987; 14: 295-9.

58. Baderstein A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy. I. Moderately advanced periodontitis. J Clin Periodontol 1981 Feb; 8(1): 57-72.

59. Baderstein A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy. II. Severely advanced periodontitis. J Clin Periodontol 1984 Jan; 11(1): 63-76.

60. Lindhe J, Socransky S, Nyman S, Westfelt E, Haffajee A. Effect of age on healing following periodontal therapy. J Clin Periodontol 1985; 12(9): 774-87.

61. Oosterwaal PJM, Matee MI, Mikx FHM, van Hof MA, Renggli HH. The effect of subgingival debridement with hand and ultrasonic instruments on the subgingival microflora. J Clin Periodontol 1987; 14: 528-33.

62. Loos B, Claffey N, Egelberg J. Clinical and microbiological effects of root debridement in periodontal furcation pockets. J Clin Periodontol 1988; 15: 453-63.

63. Lynch E, Sheerin A, Claxson AW, Atherton MD, Rhodes CJ, Silwood CJ, Naughton DP. Multicomponent spectroscopic investigations of salivary antioxidant consumption by an oral rinse preparation containing the stable free radical species chlorine dioxide. Free Radic Res 1997; 26(3): 209-34.

64. Redding WR. Effects of chlorhexidine gluconate and chlorous acid-chlorine dioxide on equine fibroblasts and Staphylococcus aureus. Vet Surg 1991; 20(5): 306-10.

65. Berg JD. Effect of chlorine dioxide on selected membrane functions of Escherichia coli. J Appl Bacteriol 1986; 60(3): 213-20.

66. Moore GS, Calabrese EJ, Ho SC. Groups of potentially high risk from chlorine dioxide treated water. J Environ Pathol Toxicol 1980; 4(2-3): 465-70.

67. Lie T, Bruun G, Boe OE. Effects of Topical Metronidazole and Tetracycline in the Treatment of Adult Periodontitis. J Periodontol 1998; 69: 819-27.

68. Vazquez B, Avilla G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe Vera gel. J Ethnopharmacol 1996; 55: 69-75.

69. Robson MC, Heggers JP, Hagstrom WJ. Myth, magic, witchcraft or fact? Aloe vera revisited. J Burn Care Rehab 1982; 3: 157-62.

70. Penneys NS. Inhibition of arachidonic acid oxidation in vitro by vehicle components. Acta Derm Venereol 1982; 62: 59-61.

71. Fujita K, Teradaira R. Bradykinase activity of aloe extract. Biochem Pharmacol 1976; 25(2): 205.

72. Klein AD, Penneys NS. Aloe Vera. J Am Academ Dermatol 1988; 18: 714-20.

73. Hirata T, Suga. Biology active constituents of leaves and roots of Aloe Arborescens var. natalensis. Z Naturforsch 1977; 32(9-10): 731-4.

74. Lehninger A. *Biochemistry*, 2nd ed. New York: Worth 578. 1981.

75. Dunhof IE, Mc Anally BH. Stabilized Aloe Vera: Effect on human cells. Drug Cosmet Ind 1983; 133: 52-106.

76. Reynolds T. The compounds in aloe vera leaf exudates: A review. Bot J Linn Soc 1985; 90: 157-9.

77. Zhang L, Tizard IR. Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from Aloe Vera gel. Immunopharmacol 1996; 35: 119-28.

78. Davis RH, Maro NP. Aloe Vera and gibberellin: Antiinflammatory activity in diabetes. J Am Podiatr Med Assoc 1989; 79: 24-6.