



Clinical effectiveness of subgingival application of 25% metronidazole gel as a monotherapy & as adjunctive treatment of chronic periodontitis

Dr. Maha Abdul Aziz. B.D.S, M.Sc.*

Dr. Maha Shukri. B.D.S, M.Sc.**

Dr. Basima Ghafory B.D.S, M.Sc. ***

Abstract

Metronidazole has been used successfully as an adjunctive antimicrobial drug in the treatment of periodontal diseases. The aim of this study was to determine if two subgingival applications of 25% metronidazole (MET) gel of one week interval alone or adjunct to root planing (RP) have a significant effect on the following periodontal parameters: plaque index (PLI), bleeding on probing (BOP), Probing pocket depth (PPD), relative attachment level (RAL).

A metronidazole 25 % dental gel has been developed for application locally into the periodontal pocket, the gel disintegrates in the periodontal pocket and releases metronidazole. A total of 20 patients with an age range of (30-40) yr, each patient with at least 4 sites with PPD \geq 4mm and clinical attachment loss (1-2) mm participated in this study. The study protocol included a pretreatment phase of plaque control instructions followed by scaling and polishing until the oral hygiene status reached to mean PLI (0.4). An alginate impression was taken and an occlusal stent was constructed for each patient to measure the relative attachment level. A total of 270 sites were randomly assigned to receive either 25% MET gel alone (group 1) or root planing plus 25% MET gel (group 2). Clinical periodontal parameters which include: PLI, BOP, PPD and RAL were recorded at day zero, after 2 weeks, 4 weeks, 6 weeks and 8 weeks.

Statistical analysis of data of the two groups revealed significant improvements in all periodontal parameters (PPD, RAL, BOP) at all subsequent visits when compared with the base line, the same result was demonstrated when the two groups were compared with each other at week 8 except (group 1) which did not show a significant gain in RAL at week 2 only. Mean plaque scores were improved in the two groups at all visits and non significant differences were demonstrated when the two groups were compared with the baseline and at week 8.

In conclusion, double applications of 25% MET gel subgingivally have a positive effect on reducing the clinical signs of periodontal disease.

Keywords: Periodontal disease, 25 % metronidazole gel.

Introduction

Metronidazole is a

chemotherapeutic agent with a range of

* Assistant Professor, Department of Periodontics, College of dentistry, University of Baghdad

** Assistant Professor, Department of Periodontics, College of dentistry, University of Baghdad

***Assistant Professor, Department of Periodontics, College of dentistry, University of Baghdad

activity specifically directed against anaerobic bacteria which are believed to be the predominant causative factor in periodontitis ⁽¹⁾. The local administration of MET can accomplish higher concentrations in subgingival sites than those obtainable by systemic administration ⁽²⁾.

Stoltze⁽³⁾ found that after 1 application of 25% MET gel in periodontal pocket, which is a biodegradable controlled release local delivery system, MET concentrations in gingival crevicular fluid (GCF) were above minimal inhibitory concentration (MIC) for susceptible periopathogens 24 hours post-treatment period. In dose finding study ⁽⁴⁾, they revealed that the 25% MET gel applied once a week for 2 weeks was defined as the best candidate for periodontal therapy.

Several studies demonstrated that the use of local 25% MET gel seems to be as effective as subgingival mechanical therapy in the treatment of chronic periodontitis ⁽⁵⁻⁷⁾ furthermore, other studies ⁽⁸⁻¹⁰⁾ on recall patients showed an improvement in the investigated clinical and microbiological parameters of MET gel treated sites comparable with subgingival scaling (S), the same results were found when comparing sites receiving 25% MET gel as an adjunct to scaling & root planing (SRP) and subgingival debridement alone in the treatment of chronic periodontitis ⁽¹¹⁻¹⁴⁾ in maintenance patients ⁽¹⁵⁾ and in periodontal pockets associated with furcation ⁽¹⁶⁾ and intra osseous defects ⁽¹⁷⁾.

On the other hand, some studies ^(18, 19) showed that adjunctive local antimicrobial delivery systems (25% MET gel) seem to offer some benefit over root planing (RP) alone in the treatment of persistent periodontal pockets. Because the cost of the material is very high,

thus it was decided to prepare the material locally to reduce the cost and to test its effectiveness clinically alone & as adjunct to root planing, for this reason the present study was undertaken.

Materials and Method

MET gel (25%) was prepared by Iraqi Pharmaceutical industry containing 40.2% MET-benzoate corresponding to 25% MET (250 mg/g), Glycerylmono-stearate, Sesame oil (Triglyceride) ⁽²⁰⁾. The activity of the prepared MET gel was assessed microbiologically in-vitro by inoculation of MET gel on nutrient agar plates streaked with subgingival plaque. Then these plates were cultured anaerobically for 48 hours and a positive inhibition zone of 1mm or more was recorded ⁽²¹⁾.

Twenty patients, 10 females and 10 males with an age range of (30-40) years were participated in this study. All patients had no history of any systemic disease and had not taken any medication or received periodontal treatment for the past 3 months. Patients with known hypersensitivity to MET, smokers, pregnant women, and menopause or on contraception were excluded from the study. All subjects had at least 4 sites with probing pocket depth of 4mm or greater and clinical attachment loss of 1-2mm.

The study protocol included a pretreatment phase of plaque control instructions including daily correct use of tooth brush and dental floss followed by scaling and polishing, until the oral hygiene status reached to mean plaque index (0.4), this was considered to be the baseline. Periodontal parameters were registered using William's periodontal probe at 2 weekly intervals commencing on day 0 which is the baseline and terminated on

week 8. A total of 5 examinations for each patient were recorded.

Periodontal parameters included:

1. Plaque Index (PII)⁽²²⁾
Plaque index system in scale from (0-3)
2. Bleeding on probing (BOP):⁽²³⁾
Periodontal probe was gently inserted to the base of the pocket, if the bleeding occurs within 30 sec after probing, the site was given score 1. If the bleeding does not occur, score 0 was given.
3. Probing pocket depth(PPD):
The distance from gingival margin to the most apical extent of the probe without pressure.
4. Relative attachment level (RAL):
The distance from the base of the pocket to the lower periphery of the acrylic stent which was constructed for each patient.

Using systematic method of randomizing the selected sites from each patient assigned to receive one of the following treatments:

Group 1: 131 sites received 25% MET gel treatment on day 0 and day 7, which consisted of isolation of the sites with cotton pellets and dried, then MET gel was gently applied subgingivally with a 5ml disposable syringe with 23 G hypodermic needle until the gel was detected at the gingival margin.

Group 2: on day 0, 139 sites received subgingival root planing using (Gracey Curette) until all root surfaces became hard and smooth, then 25% MET gel was applied subgingivally. On day 7: the same sites received a second application of the gel.

The data was processed and analyzed using (SPSS). Means, standard deviation and percentage were assessed.

Results

At baseline mean PII for the two groups were very close. Both groups showed a gradual reduction plaque scores with time but this reduction did not reach a significant level when compared with the baseline (Table 1), as well as, at the termination of the study(week 8)when we compared group1 with group 2 (Table 5).Both groups showed a gradual reduction in percentage of sites with BOP during subsequent visits and this reduction was better in group 2 which received MET gel with SRP & reached a very highly significant level compared with the baseline (Table 2) and showed a better & significant difference when compared with group 1 at week 8 (Table 6).

(Table 3), showed reductions in mean PPD at the five examination intervals with a very highly significant level in the two groups when compared with the baseline, hence, more reduction was observed in group 2 with a significant difference when compared with group 1 at week 8 (Table 5).Both experimental groups demonstrated a gradual gain in mean RAL during the study period and this gain in RAL reached a very highly significant level at all recall visits when compared with the baseline data except group 1 which revealed a non-significant difference at week 2 and a highly significant difference at week 4 (Table 4) but, when group 1 was compared with group 2 at week 8, the difference was significant with a better improvement in group 2 (Table 5).

Discussion

Prior to baseline examination, all patients were subjected to supragingival scaling, polishing and received oral hygiene instructions which reinforced when necessary, also

professional teeth cleaning was carried out when needed, thus an optimal plaque control was maintained throughout the study with little variations which proved to be non-significant. These findings are in agreement with the results obtained by other studies^(11, 13, 16, 17).

The significant improvement that observed in both groups at the four visits regarding a decrease in percentage of sites with BOP might in fact be the effect of professional scaling, polishing and oral hygiene instructions, since a controlled oral hygiene program itself results in reduction of inflammation⁽²⁴⁾, in addition, to the effect of application of MET gel locally in pockets as this clearly demonstrated in group 1, this result agrees with other results⁽⁴⁻⁶⁾. This improvement in group 1 did not reach the same level as RP plus gel group so a highly significant difference was observed at week 8 when compared group 1 with group 2. Indeed this means that subgingival mechanical debridement is still necessary. This finding is in agreement with the results obtained by other study⁽¹¹⁾.

Analysis of data, showed a significant reduction in mean PPD in all sites as compared with the baseline values which persisted throughout the experimental period. These results are comparable with previous results of numerous studies^(5, 8, 10, 13). This reduction might in fact be the result of controlled oral hygiene program which itself leads to some shrinkage in the gingival tissues as a result of a reduction of inflammation⁽¹⁾. As well as, an effect gained by the pocket therapy. Another finding worth noting that the MET gel treated sites showed improved clinical effects although no subgingival mechanical treatment was performed, thus plaque retentive factors might have been present in

these sites, but MET gel may hence be able to disturb the existing ecological balance in the pocket changing the composition of subgingival microflora towards a composition more compatible with health and these have seemingly not led to a faster rate of recolonization^(6, 8).

At week 8, group 2 showed a significant difference with group 1 with better results in group 2. These findings are in agreement with other study⁽¹¹⁾. One explanation is that after removal of subgingival plaque, calculus and the endotoxin containing root cementum in order to resolve the inflammation, bacteria were organized into biofilms in periodontal pockets, so local delivery of the antimicrobial agent used as an adjunct to RP, disrupted the biofilm and enhanced the elimination of bacteria harbored at the bottom of the pocket⁽²⁵⁾. These findings are in contrast with other result⁽¹³⁾ since, they observed a non-significant difference between these two treatment modalities, this may be explained by the different methodologies which include a pretreatment scaling and oral hygiene instructions that affect the degree of gingival inflammation and will determine the degree of gingival shrinkage when the inflammatory process is resolved.

A significant gain in attachment level was observed mostly in both groups, these results are in agreement with previous studies^(10, 16, 17, 19). As a result of supra and subgingival instrumentation with oral hygiene instructions, the subgingival plaque, calculus and the endotoxin containing root cementum were removed, hence to establish a biologically acceptable surface that enables the periodontal cells to build up new tissues⁽²⁶⁾. In addition, it has been shown that after one application of MET gel in periodontal pockets, the concentration of MET in the GCF is generally above

the minimum inhibition concentration (MIC₅₀) for most susceptible periopathogens for 24-36 hours⁽³⁾, thus long lasting shift in the composition of the subgingival microflora which demonstrated by a significant increase in the proportions of streptococci and a decrease in the proportions of black pigmented gram-negative rods and spirochetes^(6,8).

The significant difference between group 1 and 2 at week 8 could be explained as the application of antimicrobial agent which does not react equally on all present bacterial species in periodontal pockets, in addition to the remaining plaque, endotoxin and calculus as a retentive factor on root surface at MET gel treated sites without any concomitant subgingival mechanical treatment. In conclusion, the double applications of 25% metronidazole gel sub gingivally have a positive effect on reducing the clinical signs of periodontal disease.

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Table (1) Distribution of mean plaque index for group 1 & 2 at different visits with comparison to baseline.

Type of treatment	Visits	Mean	S.D.	Significance
Group 1	Baseline	0.4274	0.4966	
	W2	0.3511	0.5251	NS
	W4	0.3587	0.4814	NS
	W6	0.3282	0.4713	NS
	W8	0.3511	0.4791	NS
Group 2	Baseline	0.3884	0.4891	
	W2	0.3525	0.4794	NS
	W4	0.3381	0.4747	NS
	W6	0.3453	0.4771	NS
	W8	0.3669	0.4837	NS

NS= not significant difference at $p > 0.05$

Table (2) Distribution of bleeding on probing expressed as a percentage for group 1 & 2 for each visit with comparison to baseline.

Type of treatment	Visits	Percentage	Significance
Group 1	Baseline	100	
	W2	77.099	VHS
	W4	67.176	VHS
	W6	42.748	VHS
	W8	34.351	VHS
Group 2	Baseline	100	
	W2	60.432	VHS
	W4	38.129	VHS
	W6	23.022	VHS
	W8	19.424	VHS

VHS= Very Highly Significant difference at $p < 0.001$

Table (3) Distribution of mean probing pocket depth for group 1 & 2 and visits with comparison to baseline.

Type of treatment	Visits	Mean	S.D.	Significance
Group 1	Baseline	5.2977	0.9173	
	W2	4.8626	1.2388	VHS
	W4	4.2290	1.3042	VHS
	W6	3.9618	1.3610	VHS
	W8	3.7862	1.4936	VHS
Group 2	Baseline	5.2733	0.9691	
	W2	4.4244	1.7403	VHS
	W4	3.6618	1.8710	VHS
	W6	3.4964	1.8742	VHS
	W8	3.2949	2.1177	VHS

VHS= Very Highly Significant difference at $p < 0.001$

Table (4) Distribution of mean relative attachment level for group 1 & 2 and visits with comparison to baseline .

Type of treatment	Visits	Mean	S.D.	Significance
Group 1	Baseline	10.3969	1.5426	
	W2	10.2366	1.4561	NS
	W4	10.0687	1.1779	HS
	W6	9.8549	1.3537	VHS
	W8	9.6412	1.4254	VHS
Group 2	Baseline	10.2374	2.4363	
	W2	9.7194	2.4993	VHS
	W4	9.5755	2.4781	VHS
	W6	9.3021	2.5782	VHS
	W8	9.1438	2.8144	VHS

NS= not significant difference at $p > 0.05$.

HS= highly significant difference at $p < 0.01$.

VHS= very highly significant difference at $p < 0.001$.

Table (5) Comparison of mean PII , PPD , RAL between group 1 and 2 at week 8

P.D. parameters	Group 1		Group 2		t-test	Significance
	Mean	SD	Mean	SD		
PLI	0.351	0.479	0.366	0.483	0.257	NS
PPD	3.786	1.493	3.294	2.117	2.201	S
RAL	9.641	1.425	9.143	2.814	1.822	S

NS= not significant difference at $p > 0.05$.

S= significant difference at $p < 0.05$.

Table (6) comparison of the percentages of sites with bleeding on probing between group1 &2 at week 8.

Periodontal parameter	Group1		Group 2		Z-test	Significance
	No	%	No	%		
BOP	45	34.351	27	19.424	2.854	S

S=significant difference at $p < 0.005$.