EFFECTIVENESS OF TOPICALLY APPLIED NITAZOXANIDE (NTZ) GEL IN THE MANAGEMENT OF MODERATE PERIODONTITIS (A RANDOMIZED, CONTROLLED CLINICAL TRIAL)

Sylvia F. Antoune[1*] BDS, Mohy A. El-Rashidy[2] PhD, Maha R. Taalab[3] PhD, Labiba K. El-Khordagui[4] PhD

ABSTRACT

INTRODUCTION: Previous studies indicate that topical application of antibiotic drugs has better clinical results with the conventional treatment. Many locally delivered chemotherapeutic agents are available such as tetracycline fibers chlorohexidine chips and doxycycline gel. Nowadays a local antimicrobial treatment for periodontal infection has been established by using a formula of nitazoxanide (NTZ) gel applied to the periodontal pocket.

AIM OF THE WORK: The study is established to evaluate the effectiveness of local application of nitazoxanide (NTZ) gel combined with conventional treatment in the management of moderate periodontal infection.

MATERIALS AND METHODS: A randomized, controlled clinical trial was performed, a whole including number of forty patients, in two groups with moderate periodontal infection. They were subdivided into two groups: (1) which was comprised of twenty patients who received the conventional treatment only and served as a control group, and group (2) which was comprised of twenty patients treated with conventional treatment and locally delivered sustained release NTZ gel and served as study group. Clinical parameters measured were pocket depth, clinical attachment level (CAL), modified gingival index and bleeding index, these parameters were assessed on day 0 and after 3 and 6 months.

RESULTS: The two groups had marked reduction in all clinical measurements after six months. However the NTZ gel group had better outcomes than control group.

CONCLUSION: Topical use of NTZ gel into SRP proved to be successful in the treatment of moderate periodontitis offered superior results when compared to the conventional treatment alone.

KEY WORDS: Moderate periodontitis, antimicrobial agents, nitazoxanide gel, local drug delivery, clinical attachment level.

RUNNING TITLE: Topical use of nitazoxanide gel in treatment of periodontitis

----

[1] Dentist at Ministry of Health, Alexandria, Egypt.

[2] Professor of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology, Faculty of Dentistry, Alexandria University, Alexandria, Egypt.

[3] Associate Professor of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology Faculty of Dentistry, Alexandria University, Alexandria, Egypt.

[4] Professor Emeritus Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University; Alexandria, Egypt.

Corresponding author:
E-mail: sandyfarid92@gmail.com

INTRODUCTION

The best therapeutic technique attributed to the effective management of periodontal infection is the capability to eradicate the bacteria causing the infection. Increasing knowledge of anaerobic bacteria as the main cause in the development of periodontitis has resulted in new management strategies, mainly in order to suppress specific periodontal bacteria. A minimal invasive technique in the treatment of periodontitis is applying an anti-infective drug into the pocket, which is biodegradable and gives adequate anti-infective cover for sustained duration.

A significant advantage of systemic antibiotic utilization is the concept that the active material arrives to all the pockets and other oral bacterial colonies. This application is particularly efficient for systemic periodontal infections in which affection reaches many or the whole teeth. The drawbacks of systemic antibiotic utilization consist of common side effects, which may range from minimal gastrointestinal upset to hypersensitivity reactions. The main contraindications for their use and their interactions with other materials should usually be considered. We must know more about this in the scope of suggested active materials for periodontal management. The increase in antimicrobial resistance and the spread of multidrug-resistant strains must be reduced by regulated, diagnostically established and reliable use.

There are many side effects of using systemic antibiotics including: nausea, vomiting, diarrehea, adverse effects on gastrointestinal tract (GIT), indigestion, stomach cramping and pain copromised gut health and the most important adverse effect is antibiotic resistance (1).

The disadvantages of systemic antibiotics include the following (2):
Reduced penetration in the infected area

42

Early development of pathogenic resistance.
Significant systemic absorption and consequent toxic effects.
Kidney failure.

Tertracyclines have been used for treatment of periodontal diseases, they are bacteriostatic. Side effects include gastrointestinal disturbances, hypersensitivity. In addition, tooth discoloration occurs when this agent is introduced to infants below twelve years old (3,4).

Metronidazole inhibits a great variety of suspected periodontal pathogens. Alcohol must be prevented during treatment and it also impairs warfarin metabolism. This agent has a metallic taste in the oral cavity (5).

Doxycycline is a known broad-spectrum antibiotic drug, with antibiotic action towards the sub-gingival micro-flora. One of its advantages is a noticeable capability to adhere to the dentin, keeping bacteriostatic concentration sufficient to antagonize for sometime the periodontal pathogens (6).

The topical application of antimicrobial agents provides a new strategy in the treatment of periodontal "localized" diseases. The essential benefit is that minimal doses of topical drugs might reach into the pocket, preventing the drawbacks of systemic antibiotics, in addition elevating the exposure of target bacteria to increased concentrations and also high therapeutic levels of the drug (7).

Research showed superior outcomes for many locally delivered drug systems such as tetracycline fibers, metronidazole gel, minocycline gel and minocycline microspheres, chlorhexidine chip, and doxycycline hyclate, without producing systemic side effects to the patient (8,9).

Metronidazole is one of the predominant broad-spectrum antibiotics and is effective against many periodontal bacteria (9). Anaerobic bacterial strains are considered to be the most common causative organism in periodontal infection. So, metronidazole which particularly hits anaerobic bacteria was commonly utilized in the management of chronic periodontitis (10).

Metronidazole gel is an antimicrobial agent available as an easily flowable, resorbable, bioresorbable drug delivery system containing 25% metronidazole-benzoate. Basically, it is a fluid, available with the help of a syringe and blunt cannula. The gel is applied to the pocket in viscous composition, where it is liquified by the body heat and after that it becomes hard, creating crystals in contact with water. The formulation contains metronidazole benzoate, which is readily transformed into active materials by the effect of esterases in gingival crevicular fluids (GCF). It assumes high concentration level in GCF four hours after application and stays above 100mg/ml for the first eight hours (11, 12).

Minocycline (MCL) is one of the topical antibiotics used in treatment of periodontal pockets, it can be loaded in situ as a hydrogel to be delivered into pockets. The drug is released for more than two days with a sustainable "burst release" and was found to have antibacterial actions and significant pharmacodynamics efficacy (13).

Garrett et al., (14) stated that when doxycycline treatment was compared to conventional treatment the result was equally effective in lowering clinical manifestations of moderate periodontal infection. Walker et al., (15) concluded that doxycycline use markedly decreased the anaerobic colonization in plaque and did not affect the number of resistant microorganism.

Nowadays, a topical antibacterial therapy for periodontitis has been established in the form of NTZ gel delivered to periodontal pockets in the form of a liquid polymer that becomes solid on contact with the gingival crevicular fluid.

Nitazoxanide gel is an important agent in decreasing the clinical manifestations of moderate periodontal inflammation. (16).

Nitazoxanide has a broad-spectrum action against anaerobic bacteria. NTZ is a noncompetitive inhibitor of the pyruvate (an output of metabolism of glucose) oxidation by ferredoxin/flavodoxin oxidoreductases (PFORs) enzyme to generate energy in anaerobic bacteria (17).

Ferredoxin/flavodoxin oxidoreductases (PFORs) is present in all obligate periodontal anaerobic bacteria, such as P. ginigvalis, P. intermedia (18). Nitazoxanide (NTZ) gel is a category of antibacterial that works by affecting the activated form of Thiamine pyrophosphate (TPP) (vitamin cofactor of PFOR and related enzymes) and not the enzymes itself (19).

Nitazoxanide may be the unique agent of an antibacterial that attacks the "activated cofactor" of an enzymatic reaction rather than its substrate or catalytic sites, a new technique that may prevent mutation-based drug resistance (17).

Thus nitazoxanide is very potent towards large numbers of species of anaerobic bacteria (P. ginigvalis, P. intermedia and C. Difficile), all of which contain PFOR and utilize pyruvate: for energy production by the interruption of the energy cascade in anaerobic bacteria by suppression of the pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR) cycle (20, 21).

Thus in this study, the clinical effect of using NTZ gel applied subgingivally combined to scaling and root planning in moderate periodontitis patients was evaluated.

$$Pyruvate \xrightarrow[\text{by PFORs (Vitamin Co factor TPP)}]{\text{Oxidation}} Energy$$

$$NTZ \xrightarrow{\text{Targets}} (\text{Vitamin Co factor TPP})$$

The null hypothesis of this research was that there is no superior benefit of topical application of Nitazoxanide gel in management of moderate periodontitis in non-surgical treatment of periodontal pockets.

MATERIALS AND METHODS

Study overview (design)

The current study is a randomized clinical trial conducted according the CONSORT guidelines (22). (Figure 1)

All patients were diagnosed from the outpatient clinic in Oral Medicine, Periodontology, Oral Diagnosis and Radiology Department, Faculty of Dentistry, Alexandria University, Egypt. All subjects approved to

43

Alexandria Dental Journal. Volume 47 Issue 1 Section A

participate in the clinical trial and signed a written informed consent. The study was accepted by the Research Ethics Committee of the faculty of Dentistry, Alexandria University. Ethics number: 0079-10/2020 (IRB no: 00010556, IORG: 0008839) (23,24).

A six-month randomized controlled clinical trial was conducted on forty patients (15 male and 25 female) diagnosed with mild to moderate periodontitis according to AAP/CDC criteria (25).

They were subdivided into group (1) which comprised twenty patients who received the conventional treatment only which served as a control group and group (2) comprised twenty patients who received the conventional treatment with topically delivered sustained release NTZ gel and served as study group six months duration.

The exclusion criteria were patients who had any systemic diseases like diabetes or were under medications, pregnancy or active lactation and those who received chemotherapy during 6 months.

Screening procedures

PICO do patients having moderate periodontitis: (P) treated with topically applied Nitazoxanide gel, (I) compared to those treated with conventional scaling and root planning, (C) show better periodontal health (O) outcome.

Eligibility was determined by conducting a periodontal evaluation at baseline screening visits to evaluate the disease status, periodontal and medical treatment history. Subjects were diagnosed as moderate periodontitis, if the periodontal pocket depth was from ≥5 mm and not more than ≤7 mm, and CAL was from (3-4 mm) and all cases showed bleeding on gentle probing according to the American Academy of Periodontology (AAP) classification (2017) (26).

MATERIALS

Nitazoxanide, (2-(acetyloxy)-N-(5-nitro-2-thiazolyl)-benzamide), Cayman Chemical Company, Ann Arbor, MI. Hyaluronic acid (Mw 1000-1500 kD Xi'an Natural Field Bio-Technique Co., Ltd., China). Poloxamer 407 average MW 13306 g/mol, oxyethylene 72.5% (Nantong Chenrun Chem, Jiangsu, China) (Figure 2).

Gel preparation

Nitazoxanide thermosensitive hydrogel

A- Preparation of the hydrogel

A thermoresponsive hydrogel containing 0.01% w/v nitazoxanide was prepared using a blend of hyaluronic acid (HA) and poloxamer 407 (P) as gelling agents (27). Briefly, a poloxamer 407 solution of different concentration (22.8, 30 and 37.8 % w/v) was prepared by dispersing the polymer in deionized water in an ice bath under magnetic stirring at 300 rpm. The dispersion was kept in a refrigerator at 4°C overnight to ensure complete P dissolution. A HA solution 1% w/v was prepared in deionized water. The P and HA solutions were physically mixed in the ratio of 2: 1 to obtain three gel formulations with different P concentrations (15, 20, and 25% w/v). Finally, nitazoxanide 0.01% w/v was added to the polymer blend solution which was maintained under magnetic stirring for 1h in an ice bath and stored at 4°C in a refrigerator for subsequent studies (Figure 2).

B- Characterization of the hydrogel

Hydrogel gelation

A simple vial-inverting method was applied to measure the onset of the sol-gel transition in the three gel formulations. Upon inversion of the vial, the sol behaved as an easily flowable liquid and the gel was a non-flowing gel. The thermo-sensitive behavior of the gel (0.33 wt % HA and 15 – 25 % w/v P) was established as a function of temperature, 10–45°C at an equilibrium time 5oC/10 min using a water bath (Figure 2).

METHODS

Treatment procedure

Clinical evaluation included probing depth, bleeding index (28), modified gingival index (29), and clinical attachment level.

At the baseline and follow up, the clinical evaluations were done at day 0 and after 3 and 6 months for probing depth, bleeding index and modified gingival index. Since clinical attachment level recording was measured at baseline and at 6 months only. All periodontal clinical parameters were done using Williams' calibration periodontal probe graduated in 1 mm increment. (Figure 2)

After tracing the clinical measurements at each site in studied patients, thorough scaling and root planning were applied via hand instruments and ultrasonic scalers for both groups.

Coronoplasty was done when required.

Only patients who could maintain an O'Leary plaque index ≤10 proceeded into the study, drying and isolation of the site by cotton rolls and suction was performed before applying the gel.

Only test group received the NTZ gel after SRP and the other group had SRP only without application of a gel. The gel was applied via a syringe with a bent, blunt-end needle. The needle was gently introduced inside the periodontal pocket and the gel was administered in the test sites in a careful probing method, aiming to fill the whole pocket capacity. The gel was used up to the gingival margin and the extra amount was wiped with sterile gauze (Figure 3).

The procedures were repeated after one week.

Patient instructions

After gel administration, patients were ordered to follow strict oral hygiene protocol. They were also asked not to chew hard or sticky foods at the gel placement sites and not to eat for three hours.

On the follow up visits, the clinical measurements and any side effects were noticed.

Statistical method

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

The Kolmogorov-Smirnov test was used to measure the distribution and normality.
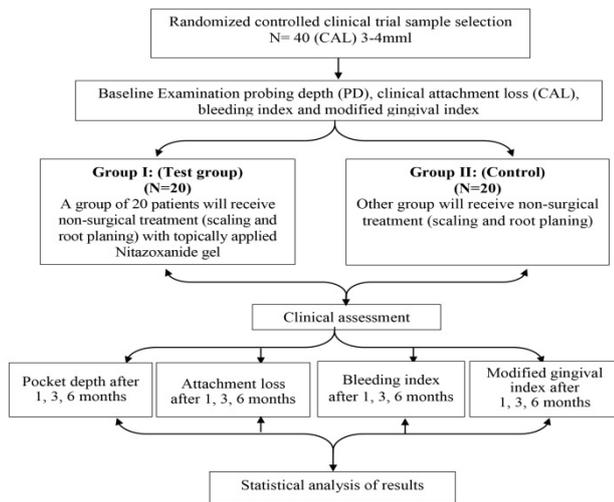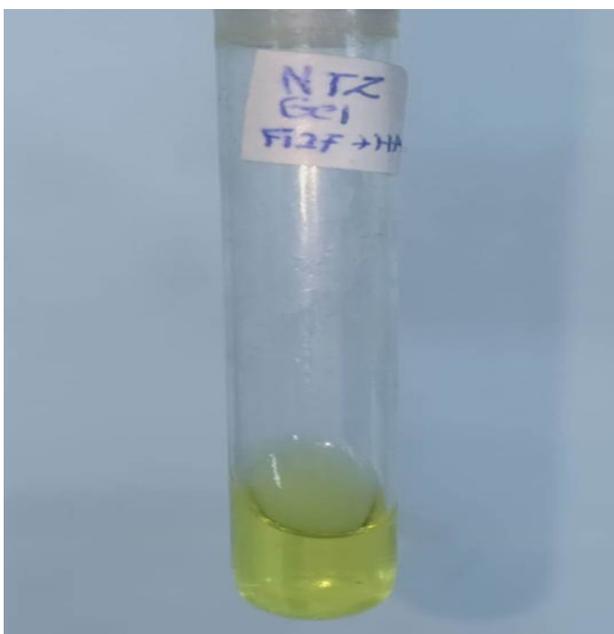
44

Figure 1: Gel formulation

Figure 2: Topical application of NTZ gel

Figure 3: Clinical attachment loss shows 3 to 4 mm with bleeding on probing

RESULTS

All the clinical parameters, i.e., modified gingival index, pocket depth and clinical attachment level revealed decrease in the whole study period in both groups.

All clinical examinations were performed by a blinded clinician who was unaware of the treatment protocol.

Modified Gingival Index (MGI)

The test group revealed a decrease in the mean of MGI, which was decreased from 2.55 ± 0.51 at baseline to 1.50 ± 0.51 at three months and 0.25 ± 0.44 at six months after treatment. While control group revealed decrease in the mean of MGI from 2.80 ± 0.41 at baseline to 1.85 ± 0.37 at three months and 1.20 ± 0.52 at six months after management. (Figure 4, 5)

So, there was no statistically marked difference between two groups at baseline and after three months, while at six months follow up duration there was statistically potential difference in MGI between the two groups (at $p \leq 0.05$). Moreover there was statistically marked difference in decrease in MGI from baseline to six months among the two groups as test group revealed more decrease than the control group ($p \leq 0.05$). (Figure 6)

Bleeding index (BI)

The test group revealed a decrease in the mean of bleeding on probing (BOP), which was decreased from 1.95 ± 0.43 at baseline to 0.72 ± 0.47 at three months and 0.35 ± 0.40 at six months after treatment. While, the control group revealed a decrease in the mean of bleeding on probing (BOP) from $2.0 (1.65 – 2.50)$ to $1.0 (0.75 – 1.50)$ at six months after therapy.

So, there was no statistically potential difference among the two groups at baseline, while at three and six months follow up period there was statistically marked difference in BOP among both groups (at $p \leq 0.05$). Moreover there were statistically marked difference in decrease in BOP from baseline to six months among both groups as test group showed more decrease than the control group. (Figure 4, 5)

Probing pocket depth (PPD) in mm

The test group revealed a decrease in the mean of probing pocket depth from 5.70 ± 0.47 at baseline to 3.55 ± 0.94 at 3 months and 2.65 ± 0.59 at 6 months after treatment. While the control group revealed a decrease in the mean of probing pocket depth from 5.80 ± 0.41 to 4.55 ± 1.23 at 3 months and 3.50 ± 0.61 at 6 months after treatment. (Figure 4, 5)

So, there was no statistically potential difference among the two groups at baseline, while at three and six months follow up period there was statistically marked difference in PPD among both groups ($p \leq 0.05$). Moreover there were statistically marked difference in decrease in PPD from baseline to six months among both groups as test group revealed more decrease than the control group ($p<0.05$). (Figure 5, 6)

Clinical attachment level (CAL) in mm

The studied group had a reduction in the mean of CAL from 3.45 ± 0.51 at baseline to 1.60 ± 0.50 at 3 months and 1.20 ± 0.52 at 6 months after treatment. While the control group had a decrease in the mean of

CAL from 3.30 ± 0.47 to 2.05 ± 0.60 at 3 months and 1.65 ± 0.49 at 6 months after treatment. (Figure 4, 5)

So, there was no statistically significant difference among the two groups at baseline, while at three and six months follow up period there was statistically significant difference in CAL among both groups ($p \leq 0.05$). Moreover there was statistically significant difference in decrease in CAL from baseline to six months among both groups as test group revealed more decrease than the control group (p≤0.05). (Figure 5, 6)

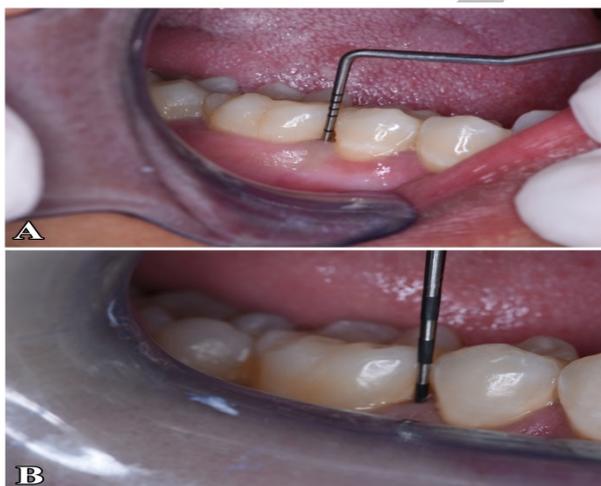**Figure 4:** Reduction of CAL with reduction of PD with no signs of bleeding.

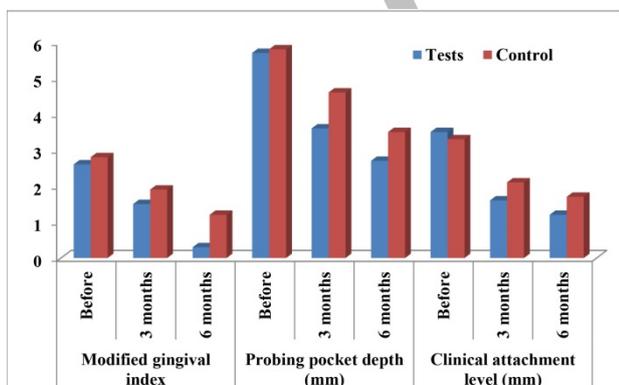**Figure 5:** After 6 months of topical application of NTZ gel show reduction in PD, CAL and MGI.

Figure 6: Figure showing comparison between the test and control group in different clinical parameters.

Table 1: Comparison between the two studied groups according to different parameters

		Tests (n = 20)	Control (n = 20)	U	p
Modified gingival index	Before Mean ± SD. Median (Min. – Max.)	2.6 ± 0.5 3ᵃ (2 – 3)	2.8 ± 0.4 3ᵃ (2 – 3)	150.0	0.183
	3 months Mean ± SD. Median (Min. – Max.)	1.5 ± 0.5 1.5ᵇ (1 – 2)	1.9 ± 0.4 2ᵇ (1 – 2)	130.0	0.060
	6 months Mean ± SD. Median (Min. – Max.)	0.3 ± 0.4 0ᶜ (0 – 1)	1.2 ± 0.5 1ᵇ (0 – 2)	47.50*	<0.001*
	Decrease in 6 months from before	2.3 ± 0.7	1.6 ± 0.7	100.0*	0.006*
	% of decrease in 6 months from before	90 ± 18.3	55.8 ± 21.1	54.0*	<0.001*
Bleeding index	Before Mean ± SD. Median (Min. – Max.)	2 ± 0.4 2ᵃ (1 – 2.8)	2 ± 0.5 2ᵃ (1.1 – 2.8)	177.50	0.547
	3 months Mean ± SD. Median (Min. – Max.)	0.7 ± 0.5 0.5ᵇ (0 – 1.5)	1.3 ± 0.4 1.2ᵇ (0.5 – 2)	65.00*	<0.001*
	6 months Mean ± SD. Median (Min. – Max.)	0.4 ± 0.4 0.3ᶜ (0 – 1)	1.1 ± 0.4 1ᵇ (0.5 – 2)	53.00*	<0.001*
	Decrease in 6 months from before	1.6 ± 0.6	1 ± 0.5	85.50*	0.001*
	% dec. in 6 months from before	82 ± 20	47.6 ± 20.2	51.0*	<0.001*
Probing pocket depth	Before Mean ± SD. Median (Min. – Max.)	5.7 ± 0.5 6ᵃ (5 – 6)	5.8 ± 0.4 6ᵃ (5 – 6)	180.0	0.602
	3 months Mean ± SD. Median (Min. – Max.)	3.6 ± 0.9 3ᵇ (3 – 6)	4.6 ± 1.2 5ᵇ (3 – 6)	110.50*	0.014*
	6 months Mean ± SD. Median (IQR)	2.7 ± 0.6 3ᶜ (2 – 4)	3.5 ± 0.6 4ᶜ (2 – 4)	73.50*	<0.001*
	Decrease in 6 months from before	3.1 ± 0.6	2.3 ± 0.5	78.0*	0.001*
	% of decrease in 6 months from before	53.5 ± 9.6	39.8 ± 8.6	63.0*	<0.001*
Clinical attachment level	Before Mean ± SD. Median (Min. – Max.)	3.5 ± 0.5 3ᵃ (3 – 4)	3.3 ± 0.5 3ᵃ (3 – 4)	170.0	0.429
	3 months Mean ± SD. Median (Min. – Max.)	1.6 ± 0.5 2ᵇ (1 – 2)	2.1 ± 0.6 2ᵇ (1 – 3)	126.0*	0.046*
	6 months Mean ± SD. Median (Min. – Max.)	1.2 ± 0.5 1ᵇ (0 – 2)	1.7 ± 0.5 2ᵇ (1 – 2)	116.50*	0.023*
	Decrease in 6 months from before	2.3 ± 0.6	1.7 ± 0.7	109.5*	0.013*
	% of decrease in 6 months from before	65 ± 15.4	49.2 ± 16.4	100.0*	0.006*

Medians of periods in the **column** with **common small letters** are not significant (i.e. Medians with **Different letters** are significant)

U: Mann Whitney test   p: p value for comparing between the studied groups
*: Statistically significant at p ≤ 0.05

Alexandria Dental Journal. Volume 47 Issue 1 Section A

46

DISCUSSION

Chronic periodontitis is a chronic inflammatory condition caused by a sub-gingival biofilm usually combined with gram negative anaerobic bacteria like, Treponema denticola, Tannerella forsythia and Porphyromonas gingivalis. The sub-gingival biofilm enables to grow bacteria in an encrusted ecosystem which includes attaching to the tooth (a solid surface), enveloped by protein matrix and microbial polysaccharides. This complicated eco-system offers the bacteria several advantages including accessibility and uptake of nutrients, elimination of possibly dangerous products of metabolism, avoidance of the immune system of the host and capability to genes sharing mainly the ones that offer antibiotics resistance (30).

Periodontal infection management is established essentially on mechanical techniques like root planning and scaling in order to decrease the microbial burden. Antibiotics are typically utilized as subordinate treatment in more serious cases because of the risk for development of antibiotic resistance as well as their impact on the total patient microbial flora. The antibiotics utilized are generally broad-spectrum, subsequently influencing the total microbioma, both the pathogenic anaerobic bacteria as well as the aerobic health-promoting bacteria. Using metronidazole is as efficient as mechanical methods (root planning and scaling) in periodontal disease management as shown in many studies (31). Moreover, we can decrease the necessary of periodontal surgery by using metronidazole (32). The toxic nature of metronidazole, along with antibiotic resistance concerns halted these encouraging outcomes of using of antibiotic management in treating periodontal disease (32).

The American Academy of Periodontology's position paper on using systemic antibiotics in periodontics indicates that patients who show continuing periodontal attachment loss in spite of diligent traditional mechanical periodontal management are the best canditates for therapy by systemic antibiotic. The paper supports moderate systemic antibiotic usage with special attention to the patient, administered drug and pathogenic microbiota (33). According to these suggestions, it is recommended to pursue an antimicrobial agent, that can precisely aim for "keystone" pathogens, prevent resistance and does not endanger the patient.

Amixicile is recently detected potent inhibitor of Clostridium difficile, a gram-positive anaerobe which is correlated with pseudomembranous colitis in patients receiving broad-spectrum long-term antibiotics. Its mechanism of action is by pyruvate inhibition: ferredoxin oxidoreductase, a vital enzyme that is involved in the pathway of synthesizing vitamins a lot of anaerobes share. Because this pathway is highly preserved and important, this new therapeutic agent resistance is not consistent with life. Consequently, amixicile shows great hopes to pseudomembranous colitis patients unable to get other antibiotics (34).

Similar to metronidazole, amixicile focus on certain anaerobic bacteria, though it varies in its mechanism. Amixicile aims and reduces the pyruvate:

ferredoxin oxidoreductase (PFOR), a vital enzyme for central metabolism. PFOR speeds the transformation of Coenzyme A (CoA) and pyruvate to Acetyl-CoA and carbon dioxide. Once Acetly-CoA has been formed, it is then turned in the process to Acetate producing ATP. Amixicile attacks the TPP (thiamine pyrophosphate) vitamin cofactor of PFOR by overcoming the substrate pyruvate by two close orders of magnitude (35,36).

Models of animal examination have calculated the impacts when managing systemic Amixicile in the management of a Clostriudum difficile infection and associated it to Vancomycin. Scientists found Amixicile was effective in eliminating the infection, but also showed a nonappearance of mutation-based drug resistance, outstanding drug metabolism, and lower toxicity (34). They determined Amixicile can be a possible new treatment for infections triggered by PFOR-expressing bacteria. P. gingivalis, P. intermedia, F. nucleatum and T. forsythia are all periodontal pathogens that convey the PFOR enzyme, and are consequently new amixicile targets.

In the present study, an effort was made to calculate the efficacy of nitazoxanide (NTZ) gel in the management of periodontal pockets with or without root planning and scaling in patients suffering from moderate periodontitis.

In another meta-analysis and systematic review which meant to assess the clinical effectiveness of the local antimicrobial agent tetracycline in the treatment of chronic periodontitis, all involved researches reported gain in attachment specified in tetracycline local drug delivery (LDD) which varied from 1.73 ± 0.9 mm to 3.4 ± 0.7 mm at three months and 3.2 ± 0.9 mm to 4.06 ± 0.67 mm at six months. Attachment gain was significant in all tetracycline groups after 3 months (37).

All studies involved in this meta-analysis had shown a marked decrease in PD at 3, 6, and 9 months in favor of tetracycline as LDD. Decrease in PD showed in tetracycline varied from 1.01 ± 0.71 mm to 3.29 ± 0.63 mm at 3 months, 1.67 ± 0.96 mm to 3.88 ± 0.64 mm at 6 months, and 1.20 ± 0.79 mm to 4.08 ± 0.79 mm at 9 months (37).

Modified gingival index (MGI) was evaluated at 3 months, and significant improvement is observed in both group, but noteworthy variance between the groups was not observed. Similarly at six months, three studies evaluated MGI and no substantial change between the groups was observed. Modified gingival index was not showing considerable change between the groups and even at six months (37).

Another study evaluated the effect of subgingivally applied minocycline microspheres and 25.0% metronidazole gel when utilized as a co-factor to scaling and root planning (SRP) in the management of periodontitis. The study denoted that management with metronidazole gel and minocycline microspheres enhance probing pocket depth (PPD) reduction, and clinical attachment level gain (CAL) in periodontitis patients in comparison to only SRP (38).

Another study had compared the effect of Metronidazole applied systemically as tablet or locally as gel as combined treatment with full mouth periodontal

47

Alexandria Dental Journal. Volume 47 Issue 1 Section A

cleaning (1 h of ultrasonic calculus/removing plaque) in smokers suffering chronic periodontitis. They concluded that supplementary Metronidazole use (tablet or gel) to periodontal debridement had the equivalent microbiological and medical impact equal to the use of placebo + periodontal debridement in smokers suffering chronic periodontitis till six months post-treatment (38).

Previous studies show Nitazoxanide to be efficient at preventing growth of P. gingivalis, F. nucleatum, and T. forsythia at 1.0 µg/mL. A greater dose, 5.0 µg/mL, was needed to prevent P. intermedia growth. Though, it is noteworthy that even at 10.0 µg/mL, no repression of S. gordonii is noticed. This bacterium depends on no anaerobic pyruvate: ferredoxin oxidoreductase (PFOR) energy production enzyme and therefore was likely to have a reliable rate of growth dependent from amixicile. A. actinomycetemcomitans also does not encode PFOR and was not predicted to be inhibited by Nitazoxanide. Though, about a 10.0% decrease in rate of growth was observed with 10.0 µg/mL signifying that Nitazoxanide could probably have an effect on the bacterium growth by a non-PFOR-related mechanism. A minor result of NTZ and Amixicile on bacteria not expressing PFOR was stated before (39,40).

CONCLUSION

This study proved that the adjunctive use of Nitazoxanide (NTZ) gel is as efficient in decreasing the clinical signs of moderate periodontitis.

Additional studies are necessary to establish which type of periodontitis lesions will benefit most from the incorporation of locally delivered controlled release NTZ gel as an accessory to non-surgical periodontal treatment.

Gain in CAL and reduction in PD are the main clinical outcomes to decide the achievement of local drug delivery system.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

REFERENCES

1. Pankuch GA, Appelbaum PC. Activities of tizoxanide and nitazoxanide compared to those of five other thiazolides and three other agents against anaerobic species. Antimicrob Agents Chemother. 2006;50:1112-7.
2. Gelmetti C. Local antibiotics in dermatology. Dermator Ther. 2008;21:187-95.
3. Ciancio SG. Antiseptics and antibiotics as chemotherapeutic agents for periodontitis management. Compend Contin Educ Dent. 2000;21:59-66.
4. Ciancio SG, Slots J, Reynolds HS, Zambon JJ, McKenna JD. The effect of short-term administration of minocycline HCl on gingival inflammation and subgingival microflora. J Periodontol. 1982;53:557-61.
5. Jorgensen MG, Slots J. Responsible use of antimicrobials in periodontics. J Calif Dent Assoc. 2000;28:185-93.
6. Christersson LA, Norderyd OM, Puchalsky CS. Topical application of tetracycline-HCl in human periodontitis. J Clin Periodontol. 1993;20:88-95.
7. Moreira RM, Feres-Filho EJ. Comparison between full-mouth scaling and root planing and quadrant-wise basic therapy of aggressive periodontitis: 6-month clinical results. J Periodontol. 2007;78:1683-8.
8. Mohamed Haris PM, Panickal DM. Role of metronidazole as a local drug delivery in the treatment of periodontitis: A review. Int J Oral Health Med Res. 2017;3:141-5.
9. Jeffcoat MK, Bray KS, Ciancio SG, Dentino AR, Fine DH, Gordon JM et al. Adjunctive use of subgingival controlled- release chlorhexidine chip reduces the probing depth and improves attachment level compared with scaling and root planing alone. J Periodontol. 1998;69:989-97.
10. Umeda M, Takeuchi Y, Noguchi K, Huang Y, Koshy G, Ishikawa I. Effects of nonsurgical periodontal therapy on the microbiota. Periodontol 2000. 2004;36:98-120.
11. Carranza FA, Newman MG, Takei HH, Klokkevold PR. Carranza's clinical periodontology.10th ed. México: McGraw-Hill; 2010.
12. Leonard M, Walsh DM. Dental hygiene –theory and practice. 3rd ed. St. Louis, Mo.: Saunders/Elsevier; 2009.
13. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169:337-52.
14. Garrett S, Johnson L, Drisko CH, Adams DF, Bandt C, Beiswanger B, et al. Two 9 Months multicenter studies evaluating locally delivered doxycycline hyclate 8.5%, placebo control oral hygiene and scaling and root planing in the treatment of periodontitis. J Periodontol. 1999;70:490-503.
15. Walker KC, Godowski L, Borden L, Lennon J, Nangó S, Stone C, et al. The effects of sustained release doxycycline on the anaerobic flora and antibiotic resistant patterns in subgingival plaque and saliva. J Periodontol. 2000;71:768-74.
16. Stoller NH, Johnson LK, Trapnell S, Harrold CQ, Garrett S. The pharmacokinetic profile of a biodegradable controlled release delivery system containing doxycycline compared to systemically delivered doxycycline in gingival crevicular fluid, saliva and serum. J Periodontol. 1998;69:1085-91.
17. Hutcherson JA, Sinclair KM, Belvin BR, Gui Q, Hoffman PS, Lewis JP. Amixicile, a novel strategy for targeting oral anaerobic pathogens. Sci Rep. 2017;7:10474. doi: 10.1038/s41598-017-09616-0.
18. Hoffman PS, Sisson G, Croxen MA, Welch K, Harman WD, Cremades N, et al. Antiparasitic drug nitazoxanide inhibits the pyruvate oxidoreductases of helicobacter pylori, selected anaerobic bacteria and parasites, and campylobacter jejuni. Antimicrob Agents Chemother. 2007;51:868-76.
19. Goldstein EJ, Citron DM, Sears P, Babakhani F, Sambol SP, Gerding DN. Comparative susceptibilities to

48

fidaxomicin (OPT-80) of isolates collected at baseline, recurrence, and failure from patients in two phase III trials of fidaxomicin against Clostridium difficile infection. Antimicrob Agents Chemother. 2011;55:5194-9.

20. Pankuch GA, Appelbaum PC. Activities of tizoxanide and nitazoxanide compared to those of five other thiazolides and three other agents against anaerobic species. Antimicrob Agents Chemother. 2006;50:1112-7.

21. Broekhuysen J, Stockis A, Lins RL, De Graeve J, Rossignol JF. Nitazoxanide: pharmacokinetics and metabolism in man. Int J Clin Pharmacol Ther. 2000;38:387-94.

22. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials. 2010;11:32.

23. World Medical A. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310:2191-4.

24. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8:18.

25. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78:1387-99.

26. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Clin Periodontol. 2018;45:149-61.

27. Jung YS, Park W, Park H, Lee DK, Na K. Thermo-sensitive injectable hydrogel based on the physical mixing of hyaluronic acid and Pluronic F-127 for sustained NSAID delivery. Carbohydr Polym. 2017;156:403-8.

28. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. Int Dent J. 1975;25:229-35.

29. Lobene RR, Weatherford T, Rose NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clin Prev Dent. 1986;8:3-6.

30. Hoare A, Soto C, Rojas-Celis V, Bravo D. Chronic inflammation as a link between periodontitis and carcinogenesis. Mediators Inflamm. 2019;2019:1029857. doi: 10.1155/2019/1029857.

31. Stelzel M, Flores-de-Jacoby L. Topical metronidazole application compared with subgingival scaling. A clinical and microbiological study on recall patients. J Clin Periodontol. 1996;23:24–9.

32. Loesche WJ, Giordano JR, Hujoel P, Schwarcz J, Smith BA. Metronidazole in periodontitis: reduced need for surgery. J Clin Periodontol. 1992;19:103–12.

33. Slots J. Systemic antibiotics in periodontics. Science. 2005;76:1237-47.

34. Warren CA, van Opstal E, Ballard TE, Kennedy A, Wang X, Riggins M, et al. Amixicile, a novel inhibitor of pyruvate: ferredoxin oxidoreductase, shows efficacy against Clostridium difficile in a mouse infection model. Antimicrob Agents Chemother. 2012;56:4103-11.

35. Kennedy AJ, Bruce AM, Gineste C, Ballard TE, Olekhnovich IN, Macdonald TL, et al. Synthesis and antimicrobial evaluation of amixicile-based inhibitors of the pyruvateferredoxin oxidoreductases of anaerobic bacteria and Epsilonproteobacte. Antimicrob Agents Chemother. 2016;60:3980–7.

36. Ballard TE, Wang X, Olekhnovich I, Koerner T, Seymour C, Salamoun J, et al. Synthesis and antimicrobial evaluation of nitazoxanide-based analogues: identification of selective and broad spectrum activity. ChemMedChem. 2011;6:362–77.

37. Nadig PS, Shah MA. Tetracycline as local drug delivery in treatment of chronic periodontitis: A systematic review and meta-analysis. J Indian Soc Periodontol. 2016;20:576-83.

38. Haris M, Panickal DM. Role of metronidazole as a local drug delivery in the treatment of periodontitis: A review. Int J Oral Health Med Res. 2017;3:141-5.

39. Chahales P, Hofman PS, Tanassi DG. Nitazoxanide inhibits pilus biogenesis by interfering with folding of the usher protein in the outer membrane. Antimicrob Agents Chemother. 2016;60:2028–38.

40. Tchouaffi-Nana F, Ballard TE, Cary CH, Macdonald TL, Sifri CD, Hoffman PS. Nitazoxanide inhibits biofilm formation by Staphylococcus epidermidis by blocking accumulation on surfaces. Antimicrob Agents Chemother. 2010;54:2767-74.

49

Alexandria Dental Journal. Volume 47 Issue 1 Section A