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, diarrhea, adverse effects on gastrointestinal tract (GIT), indigestion, stomach cramping and pain compromised 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
Early development of pathogenic resistance.
Significant systemic absorption and consequent toxic effects.
Kidney failure.
Tetracyclines 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 microflora. 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, bioreabsorbable 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 liquefied 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. gingivalis, 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. gingivalis, 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.

\[
\text{Pyruvate by PFORs (Vitamin Co factor TPP)} \rightarrow \text{Targets Energy (Vitamin Co factor TPP)}
\]

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
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.
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 ≤ 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 ≤ 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 ≤ 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 ≤ 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 $3.30 \pm 0.47$ to $2.05 \pm 0.60$ at 3 months and $1.65 \pm 0.49$ 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 ($p \leq 0.05$). (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

<table>
<thead>
<tr>
<th></th>
<th>Tests (n = 20)</th>
<th>Control (n = 20)</th>
<th>U</th>
<th>p</th>
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<tbody>
<tr>
<td>Before</td>
<td></td>
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<tr>
<td>Mean ± SD.</td>
<td>2.6 ± 0.5</td>
<td>2.8 ± 0.4</td>
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<tr>
<td>Median (Min. – Max.)</td>
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<td>3 (2 – 3)</td>
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<td>3 months</td>
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<tr>
<td>Mean ± SD.</td>
<td>1.5 ± 0.5</td>
<td>1.9 ± 0.4</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>1.55 (1 – 2)</td>
<td>2 (1 – 2)</td>
<td>130.0</td>
<td>0.060</td>
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<td>6 months</td>
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<tr>
<td>Mean ± SD.</td>
<td>0.3 ± 0.4</td>
<td>1.2 ± 0.5</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>0 (0 – 1)</td>
<td>1 (0 – 2)</td>
<td>47.50*</td>
<td>&lt;0.001*</td>
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<td>Decrease in 6 months from before</td>
<td>2.3 ± 0.7</td>
<td>1.6 ± 0.7</td>
<td>100.0*</td>
<td>0.006*</td>
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<td>% decrease in 6 months from before</td>
<td>90 ± 18.3</td>
<td>55.8 ± 21.1</td>
<td>54.0*</td>
<td>&lt;0.001*</td>
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<tr>
<td>Before</td>
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<tr>
<td>Mean ± SD.</td>
<td>2 ± 0.4</td>
<td>2 ± 0.5</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>2 (1 – 2.8)</td>
<td>2 (1.1 – 2.8)</td>
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<td>3 months</td>
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<td>Mean ± SD.</td>
<td>0.7 ± 0.5</td>
<td>1.3 ± 0.4</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>0.55 (0 – 1.5)</td>
<td>1.2 (0.5 – 2)</td>
<td>65.00*</td>
<td>&lt;0.001*</td>
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<tr>
<td>6 months</td>
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<tr>
<td>Mean ± SD.</td>
<td>0.4 ± 0.4</td>
<td>1.1 ± 0.4</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>0.3 (0 – 1)</td>
<td>1.0 (0.5 – 2)</td>
<td>53.00*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Decrease in 6 months from before</td>
<td>1.6 ± 0.6</td>
<td>1 ± 0.5</td>
<td>85.50*</td>
<td>0.001*</td>
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<tr>
<td>% decrease in 6 months from before</td>
<td>82 ± 20</td>
<td>47.6 ± 20.2</td>
<td>51.0*</td>
<td>&lt;0.001*</td>
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<tr>
<td>Before</td>
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<tr>
<td>Mean ± SD.</td>
<td>5.7 ± 0.5</td>
<td>5.8 ± 0.4</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>6 (5 – 6)</td>
<td>6 (5 – 6)</td>
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<td>3 months</td>
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<td>Mean ± SD.</td>
<td>3.6 ± 0.9</td>
<td>4.6 ± 1.2</td>
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<td>Median (Min. – Max.)</td>
<td>3 (3 – 6)</td>
<td>5 (3 – 6)</td>
<td>110.50*</td>
<td>0.014*</td>
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<td>6 months</td>
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<tr>
<td>Mean ± SD.</td>
<td>2.7 ± 0.6</td>
<td>3.5 ± 0.6</td>
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<td>Median (IQR)</td>
<td>3 (2 – 4)</td>
<td>4 (2 – 4)</td>
<td>73.50*</td>
<td>&lt;0.001*</td>
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<td>Decrease in 6 months from before</td>
<td>3.1 ± 0.6</td>
<td>2.3 ± 0.5</td>
<td>78.0*</td>
<td>0.001*</td>
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<tr>
<td>% decrease in 6 months from before</td>
<td>53.5 ± 9.6</td>
<td>39.8 ± 8.6</td>
<td>63.0*</td>
<td>&lt;0.001*</td>
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<tr>
<td>Before</td>
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<tr>
<td>Mean ± SD.</td>
<td>3.5 ± 0.5</td>
<td>3.3 ± 0.5</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>3 (3 – 4)</td>
<td>3 (3 – 4)</td>
<td>170.0</td>
<td>0.429</td>
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<tr>
<td>Mean ± SD.</td>
<td>1.6 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td></td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>126.00*</td>
<td>0.046*</td>
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<td>6 months</td>
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<tr>
<td>Mean ± SD.</td>
<td>1.2 ± 0.5</td>
<td>1.7 ± 0.5</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>1 (0 – 2)</td>
<td>2 (1 – 2)</td>
<td>116.50*</td>
<td>0.023*</td>
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<tr>
<td>Decrease in 6 months from before</td>
<td>2.3 ± 0.6</td>
<td>1.7 ± 0.7</td>
<td>109.5*</td>
<td>0.013*</td>
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<td>% decrease in 6 months from before</td>
<td>65 ± 15.4</td>
<td>49.2 ± 16.4</td>
<td>100.0*</td>
<td>0.006*</td>
</tr>
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</table>

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 $p \leq 0.05$
**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 ecosystem 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 microbiota, 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 different traditional mechanical periodontal management are the best candidates for therapy by systemic antibiotic. The paper supports moderate systemic antibiotic usage with special attention to the patient, administered drug and microbial polysaccharides. This complicated ecosystem 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).

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 Acetyl-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 Clostridium 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
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 amoxicilce. 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 Amoxicilce 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 The authors received specific funding for this work. It was a generous gift of Tabuk Pharmaceuticals, Riyadh, Saudi Arabia.

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