The Impact of Topically Applied 1% Phenytoin Gel on Treatment of Periodontitis Stage II and III Grade A

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ABSTRACT

Aim: The aim of the present study was to evaluate the efficacy of topically applied 1% phenytoin as an adjunctive treatment in Stage II or III, Grade A periodontitis patients. Subjects and Methods: This study was designed as a split-mouth randomized controlled clinical, carried out on 20 patients of both sexes (12 female and 8 male), aged from (33-55) years with mean age (43.25± 6.64) with stage II or III, grade A periodontitis. Patients’ sides were classified randomly into the following groups: Group I: included 20 sides with Stage II or III, Grade A periodontitis patients treated by scaling and root planing alone. Group II: included 20 sides with Stage II or III, Grade A periodontitis patients treated by scaling and root planing combined with 1% phenytoin gel. All patients were evaluated clinically at; baseline, 1, 3 and 6 months using plaque index (PI), gingival index (GI), probing pocket depth (PPD), clinical attachment level (CAL) and radiographically by evaluation of the marginal bone level (MBL).

Results: Phenytoin group: showed reduction in PPD and CAL, as well as significant gain in MBL than group I at 6 months after treatment

Conclusion: The adjunctive use of 1% PHT in-situ gel exhibited an attractive effect on probing pocket depth reduction clinical attachment gain in non-surgical treatment of stage II and III grade A periodontitis. Phenytoin 1% in-situ gel seemed to have an osteogenic efficacy through the reported marginal bone gain in treatment of stage II and III grade A periodontitis patients.

INTRODUCTION

Periodontal diseases are multifactorial inflammatory diseases involving the supportive apparatus that investing and surrounding the tooth. Disease status ranges from gingivitis to periodontitis(1).

Periodontitis is a set of chronic inflammatory processes characterized by increased microbial aggression and increased activity of the host immune response. Yet, the complete pathophysiology of the condition remains unknown, dysbiosis in periodontal biofilms is included in the pathogenesis of periodontitis. This includes enhanced immune response
and the augmentation of inflammatory response through local or systemic inflammatory mediators(2).

The main goals of periodontal treatment are to eliminate bacterial deposits by removing the supragingival and subgingival biofilms and to restore the biological compatibility of periodontally diseased root surfaces for subsequent attachment of periodontal tissues to the treated root surface. Generally, these objectives are achieved by mechanical scaling and root planing (SRP). Although SRP produces significant clinical improvements in patients with periodontitis, the complete elimination of bacterial deposits can be difficult to accomplish(3).

Regeneration of the periodontal apparatus with the formation of the bone-periodontal ligaments-cementum complex is ultimate clinical goal in the management of advanced periodontal defects arising from periodontitis. Over the past 30 years, numerous techniques and materials have been introduced and evaluated clinically and have included guided tissue regeneration, bone grafting materials, growth, and other biological factors and gene therapy(4). The clinical benefits achievable with regenerative approaches characterized by additional clinical attachment gain, pocket probing depth reduction, and resolution or reduction of the intra-bony component or furcation defect(5).

Phenytoin (PHT) is an anti-seizure drug belongs to the hydantoin group of drugs that has been under clinical evaluation for around eight decades. It is primarily used for the treatment of tonic-clonic and partial seizures. The effects of oral phenytoin pre-treatment on the healing of surgically created gingival wounds in patients with periodontal disease were studied and an apparent stimulatory effect on connective tissue has prompted its use in wound healing(6).

The present study was designed to investigate the efficacy of topically applied 1% phenytoin following non-surgical periodontal therapy in periodontitis patients (Stage II and III, Grade A).

SUBJECTS AND METHODS

Study setting and population

The present study was designed as a split-mouth randomized controlled clinical, radiographic, and biochemical study, carried out on 20 patients with stage II or III, grade A periodontitis. All patients were selected from those attending the outpatient clinic, Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch.

Ethical issues

The study was approved by the ethical committee, Faculty of Dental medicine, Al-Azhar University (no; AUAREC20210721-11).

All patients were fully informed about the nature and the possible risks of the study procedures; they signed the consent form before the work.

Inclusion criteria:

1. All patients were free from any systemic diseases.
2. Patients with Stage II and III, Grade A periodontitis. Stage II has CAL 3 to 4mm with no tooth loss and probing pocket depth ≤5 mm. Stage III has CAL ≥5 mm, the potential for additional tooth loss, probing pocket depth ≥ 6mm with vertical bone loss ≥ 3mm. Grade A: no evidence of CAL or bone loss over 5 years, the patient is a nonsmoker and has no evidence of diabetes.

Exclusion criteria

1. Patients with previous periodontal treatment including scaling and root planing or periodontal surgery in the last 3 and 6 months, respectively.
2. Patients received antibiotics and non-steroidal anti-inflammatory for at least 3 months before sample collection.
3. Patients with sensitivity to the medication used in the study.
4. Patients under antihypertensive, immune suppressants and anticonvulsant drugs which could affect their periodontium
5. Pregnant or lactating women.

Patients grouping and randomization

Sample size calculation

A power calculation was performed to determine the sample size. The sample size was calculated using (α= 0.05) and 85% power. A value of 1 mm was used, with clinical attachment level (CAL) change defined as the primary outcome variable. The minimum clinically significant value considered was 1 mm. It was determined that a minimum sample of 18 sides per group (36 sides in total) would be required. To compensate for sample loss, 20 patients were enrolled in this study.

Patients’ sides were classified randomly into the following equal groups using a flip of a coin.

**Group I:** Consisted of 20 grade A periodontitis sides (10 stage II and 10 stage III) received scaling and root planing only.

**Group II:** Consisted of 20 grade A periodontitis sides (10 stage II and 10 stage III) received scaling and root planing combined with intra-pocket application of 1% phenytoin in-situ gel.

Preparation of 1% phenytoin in-situ gel:

The in-situ gel containing 1% phenytoin was prepared in the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Al-Azhar University.

For the preparation of 1% PTH in-situ gel 100ml cold distilled water was taken in a beaker. 15-20 % w/v of pluronic was dispersed to it with continuous stirring at 400 RPM for 1hour. The polymer dispersion was then stored in refrigerator at 4°C for 24 h to obtain a clear polymeric solution. A pre weighed amount of PTH*® was added to the above-mentioned homogeneous solution and dissolved completely to get a homogeneous phase of polymer, solvent, and drug. This homogenization was performed using a lab stirrer at 1300 rpm. Methyl paraben (as preservative) was added to the preparation. The prepared formulation was placed overnight in the refrigerator to allow the complete dissolution of the drug and polymer. The prepared formulations were transferred to 3ml syringes under strict sterile conditions and dispensed for clinical study.

At low temperature, the preparation was in a liquid form and after injection into the pocket, the preparation was converted to gel by the effect of body temperature (8).

Periodontal intervention:

All patients were received phase I periodontal therapy. Full-mouth scaling and root planing were performed without the use of adjunct disinfectants.

Intra-pocket application of 1% phenytoin in-situ gel:

Firstly, areas of application were isolated by the cotton roll. The application was accomplished by inserting the needle into the base of the periodontal pocket firstly and then injecting the gel while working the way up, until the gel appeared from gingival margin (fig 1). The treated sites were covered with periodontal dressing**® to achieve retention of the product into the pocket and avoid carry-across effects and the patient was scheduled for removal of periodontal dressing 3 days later (9). Patients were instructed to stop eating, spitting, and drinking for 1 hour after application, teeth

* (Global pharmaceutical industries company, Section 2, 6th of October, Giza, Egypt)
** (pericem, Parque Industrial Bandeirantes, Brazil )
brushing and flossing for 4 hours after application. Also were instructed for plaque control regimen, and the oral hygiene instructions were provided at each appointment. The application was repeated once weekly for one month.

Evaluation of periodontal status:

1- Clinical evaluation

The periodontal conditions were evaluated clinically for all patients at baseline, 1, 3 and 6 months after treatment using the following parameters:

- Plaque index\(^{(10)}\).
- Gingival index\(^{(11)}\).
- Probing pocket depth\(^{(12)}\) was measured by William's graduated periodontal probe as the distances from the free gingival margin to the base of the periodontal pocket at six sites around all the teeth at screening.
- Clinical attachment level\(^{(13)}\) was measured using William's graduated periodontal probe as the distance from the cemento-enamel junction to the base of the pocket.

2- Radiographic assessment:

The marginal bone level was assessed for all patients at baseline, 1, 3 and 6 months after treatment as the distance from the cementoenamel junction to the alveolar crest (fig 2). The gain or loss of MBL is calculated by subtraction or addition of MBL of certain interval to original MBL at baseline respectively, examination of alveolar bone loss was done by two inter-examiners. Each examiner performed two readings (intra-examiner), then the average value was calculated and recorded\(^{(14)}\).

Statistical analysis

Data analyzed by IBM® SPSS® Statistics Version 20 for Windows. The significance level was set at \(P \leq 0.05\). Paired sample t-test was used to compare between two groups. Spearman correlation was used to find the correlation between different parameters.

RESULTS

Clinical results:

Changes in plaque index

- A statistically significant differences in both groups at the different intervals when compared to the baseline.
- No statistically significant difference in group I when compared with group II at different intervals.
Changes in gingival index

- A statistically significant differences in all groups at the different intervals when compared to the baseline.
- No statistically significant difference in group I when compared with group II at different intervals.

Probing pocket depth measurements

- A statistically significant difference in both groups at the different intervals when compared to the baseline, except in group I, no statistically significant difference between was found 1 month and 6 months.
- There were significant differences in group II when compared with group I at 3 and 6 months after treatment.

Clinical attachment level measurements

- A statistically significant difference in both groups at the different intervals when compared to the baseline, except in group II, no statistically significant difference was found between 3 and 6 months.
- There were statistically significant differences in group II when compared with group I at 1, 3 and 6 months after treatment.

Radiographic results:

Marginal bone level assessment

- A statistically significant difference in both groups at the different intervals when compared to the baseline, except in group II, no statistically significant difference was found between baseline and 1 month.
- There was a statistically significant difference in group II when compared with group I at 6 months after treatment.

Table (1) Showing mean ± standard deviation (SD) of the clinical and radiographic parameters for both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>2.60</td>
<td>0.52</td>
<td>2.62</td>
</tr>
<tr>
<td>After 1m</td>
<td>0.66</td>
<td>0.19</td>
<td>0.61</td>
</tr>
<tr>
<td>After 3m</td>
<td>0.83</td>
<td>0.17</td>
<td>0.79</td>
</tr>
<tr>
<td>After 6m</td>
<td>1.15</td>
<td>0.21</td>
<td>1.04</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>2.54</td>
<td>0.32</td>
<td>2.61</td>
</tr>
<tr>
<td>After 1m</td>
<td>0.62</td>
<td>0.14</td>
<td>0.55</td>
</tr>
<tr>
<td>After 3m</td>
<td>0.84</td>
<td>0.13</td>
<td>0.78</td>
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<tr>
<td>After 6m</td>
<td>1.08</td>
<td>0.15</td>
<td>1.01</td>
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<tr>
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<tr>
<td>Baseline</td>
<td>5.90</td>
<td>0.85</td>
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<tr>
<td>After 1m</td>
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<tr>
<td>After 3m</td>
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<tr>
<td>After 6m</td>
<td>3.84</td>
<td>0.75</td>
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*; significant (p<0.05)  ns; non-significant (p>0.05)
DISCUSSION

Several treatment modalities were available for management of periodontitis depending on its stage, and they can be classified into either non-surgical or surgical approaches\(^{(15)}\). Unfortunately, no conventional treatments alone (including scaling and root planing, open flap debridement) aimed at root surface decontamination to halt the disease progression\(^{(16)}\).

Phenytoin is an anticonvulsant drug. It was found that phenytoin causes fibroblast proliferation, collagen synthesis, collagenase enzyme inhibition, increase in epidermal growth factor, induces new vessel formation, decrease the microbial colonies, reduces pain and inflammation and improves healing\(^{(17)}\).

In the present study, stage II and III grade A periodontitis patients were selected according to the criteria of the 2017 classification system of periodontal and peri-implant diseases and conditions\(^{(18)}\). The recommended treatment modality for management for stage II is non-surgical approach while the surgical approach is recommended for stage III\(^{(19)}\), this study was conducted to investigate the regenerative power of phenytoin as a non-surgical treatment for stage II and presurgical option to restore the lost and destructed tissues in treatment of stage III grade A periodontitis patients, as it was reported that; phenytoin alleviates the aging of gingival fibroblasts and has an anabolic action on bone cells and gingival fibroblasts\(^{(20)}\).

Subgingival injection technique for delivering PHT was used, as the local drug delivery systems offer the advantages of high concentrations at the target site with a reduced dosage, fewer applications, and high patient acceptability\(^{(21)}\). In the present study the in-situ gel was selected, as the formed in-situ gel increase the residence time in the periodontal pocket and controls the drug release which is expected to improve the therapeutic outcomes\(^{(22)}\).

Pluronic F-127 hydrogel has favorable properties such as enhancement of stability, lack of cytotoxicity, excellent biocompatibility, simple drug encapsulation in micellar cores and significant capacity to form a “depot” for in situ-controlled drug release\(^{(23)}\).

<table>
<thead>
<tr>
<th></th>
<th>PI</th>
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<th>PPD</th>
<th>CAL</th>
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<td>.503**</td>
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<td>0.000</td>
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<td>0.556</td>
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<td>.463**</td>
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<td>Spearman</td>
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Till now, no studies reported the use of 1% phenytoin in-situ gel as local drug delivery in the treatment of periodontitis stage II and III, grade A, except single clinical study which reported that; the application of PHT muco-adhesive paste following conventional therapy for periodontitis contributes to improve clinical parameters \(^1\)(24), and other in vivo study, which investigates the effect of PHT on the regeneration of murine periodontal tissue defect model and concluded that; Phenytoin appears to be a promising drug that promotes periodontal regeneration\(^2\)(25).

Regarding the plaque accumulation and degree of gingival inflammation, the results of the present study found statistically significant reduction in PI and GI scores of both groups at different intervals when compared to baseline without significant differences between both groups in the GI and PI at the observation period. These results may be explained by that, oral hygiene was maintained and reinforced in all patients during the observation period of the study. Also, attributed to the study design itself which eliminates inter-subject variance. This is in agreement to the findings of the study which concluded that, the application of PHT muco-adhesive paste following conventional therapy for periodontitis contributes to improve clinical parameters\(^2\)(23).

With regards to PPD, this study recorded a reduction in the mean probing pocket depth in both group with statistically significant at the different intervals when compared to the baseline.

The present study found no statistically significant differences between both groups at baseline and 1 month, but there is statistically significant difference in group II when compared to group I at 3 and 6 months. This may be attributed to the effect of topical phenytoin on in acceleration of the healing process with increase in production of fibroblasts, myofibroblasts, extracellular matrix, its proteins, and activity of growth factors\(^2\)(25).

The reduction in CAL was statistically significant at the different intervals when compared to the baseline in both groups, but in phenytoin group there is no statistically significance difference between 3 and 6 months which may attributed to, the last dose of the drug application was scheduled at 1 month and the release of drug from LDDs to GCF may last 3-5 days after its application maximally 7-10 days based one the used vehicle criteria\(^2\)(26), so the action can be reflected in 3 months and really not reflected in 6 months values.

In the relation between both group, there was statistically significant difference at 1 month, 3 months and 6 months, this is attributed to the direct action of PHT on gingival fibroblast which promote and accelerate collagen deposition, increases the density of the periodontal ligament, induces bone turnover and neovascularization with increased expression of growth factors\(^2\)(27).beside the effect of upregulated level of bFGF which induce angiogenesis, connective tissue formation on the root surface, formation of dense fibers bound to the alveolar bone and newly synthesized cementum in teeth\(^2\)(28).

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CONCLUSION

The adjunctive use of 1% PHT in-situ gel exhibited an attractive effect on probing pocket depth reduction clinical attachment gain in non-surgical treatment of stage II and III grade A periodontitis.

Phenytoin 1% in-situ gel seemed to have an osteogenic efficacy through the reported marginal bone gain in treatment of stage II and III grade A periodontitis patients.

REFERENCES


تأثير الفينيتوين جيل 1% المستخدم موضعياً في علاج التهاب الأنسجة حول السنية من الدرجة 2 و3 الفئة A (دراسة إكلينيكية)

عنوان الدراسة:

تعداد حالة غداة من أطباء الأسنان، جامعة الأزهر أسيوط، مصر

الاستطلاع:

1) المرضى الذين يعانون من التهاب الأنسجة حول السنية من الدرجة الثانية والثالثة الفئة A.
2) المرضى الذين يتم علاجهم من خلال استخدام الفينيتوين جيل 1% موضعياً والعلاج الخاص.

النتائج:

1) الفينيتوين جيل 1% علاج فعال في علاج التهاب الأنسجة حول السنية من الدرجة الثانية والثالثة الفئة A.
2) الفينيتوين جيل 1% يزيد من نقص عمق الجيوب اللثوية ومستوى اللثة الإكلينيكية في العلاج الغير الجراحي.

الخلاصة:

1) الفينيتوين جيل 1% علاج فعال للتهاب الأنسجة حول السنية من الدرجة الثانية والثالثة الفئة A.
2) الفينيتوين جيل 1% يزيد من التصاق اللثة والجنيب اللثوى الإكلينيكية.

الكلمات المفتاحية:

التهاب الأنسجة حول السنية من الدرجة 2 و3 الفئة A، علاج التهاب الأنسجة، الفينيتوين جيل 1%