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Topically Applied Phenytoin Gel as Adjunctive Treatment in Periodontitis Patients

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KEYWORDS

Periodontitis, Scaling and root planing, 1% Phenytoin gel, Platelet-derived growth factor-BB.

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ABSTRACT

Aim: The aim of this work was to evaluate efficacy of topically applied 1% phenytoin as an adjunctive treatment in stage II grade A periodontitis. **Subjects and methods:** The current study was designed as a randomized controlled clinical trial performed on 60 patients of both sexes, aged from (30-52) years with stage II grade A periodontitis. Patients sites were classified into the following groups: Group I: included 30 patients treated by scaling and root planning. Group II: included 30 patients treated by scaling and root planning combined with 1% phenytoin gel application. Clinical parameters were measured at baseline, 3 and 6 months. The effect of phenytoin on vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF-BB) expression in gingival crevicular fluid (GCF) was investigated at baseline, 1, 2, 3 and 4 weeks. **Results:** The clinical parameters PPD and CAL showed a significant reduction in phenytoin treated sites compared with control and this reduction was considered significant at 3 months. Although phenytoin (PHT) significantly upregulated levels of PDGF-BB and VEGF in GCF than control sites within the first and second week, growth factors level decreased to nearly the base line value at 3 weeks and this reduction still to 4 weeks**. Conclusion:** It can be concluded that adjunctive use of 1% phenytoin gel showed a positive impact on clinical periodontal parameters in the form of probing depth reduction and attachment level gain.

INTRODUCTION

Periodontal diseases are multifactorial inflammatory conditions that affect the bone and connective tissue supporting the tooth, gingivitis and periodontitis are among the disease states [(1)]. Although the whole pathophysiology of the disorder is yet unclear, dysbiosis in periodontal biofilms which trigger host immune response in the form of local or systemic inflammatory mediators explain a part of the etiology of periodontitis [(2)].

The ultimate therapeutic aim in the therapy of periodontal disease is a regeneration of the periodontal tissuesy. These goals are often

accomplished by mechanical scaling and root planing (SRP) which remove bacterial deposits by eliminating supragingival and subgingival biofilms. Although SRP generates considerable clinical benefits in individuals with periodontitis, the total removal of bacterial deposits might be challenging to accomplish [3].

Numerous methods and materials, such as grafting materials, growth and other biological factors and gene therapy, have been developed during the past 30 years[4]. Clinical advantages of these regenerative methods includes increased clinical attachment, decreased pocket probing depth (PPD) and elimination or reduction of the intra-bony component or furcation defect [5].

Phenytoin (PHT) has been the subject of clinical research for around eighty years. The main conditions it is used to treat includes tonic-clonic and partial seizures. Gingival hyperplasia which reported in 50% of patients with long-term phenytoin treatment has been reported as a common side-effect [6].

From periodontal point of view, the effects of phenytoin pre-treatment on the healing of surgically inflicted gingival wounds was investigated, and an evident of stimulatory effect on connective tissue was found [7].

Phenytoin is known to increase expression of various types of growth factors including PDGF, VEGF and fibroblast growth factor (FGF) in the wound tissue [8]. Platelet-derived growth factor-BB considered a major growth factor in serum, stored in blood platelets and released during blood clotting, mediates repair of tissue and stimulates soft tissues healing. Also, PDGF-BB has been shown to posses stimuatorye effect helps in periodontal tissues regeneration [9].

Vascular endothelial growth factor VEGF is released by many types of cells which respond to inflammation and leads to production of chemotactic factors, endothelial cell migration, proliferation, formation of granulation tissue, and angiogenesis [9] Which considered the main feature of the proliferative wound healing phase [10].

SUBJECTS AND METHODS

Study setting and population

The present study was designed as a randomized controlled clinical and biochemical study, carried out on 60 stage II, grade A periodontitis. patients were selected from those attending the outpatient clinic of Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch.

Ethical issues

This study was approved by the ethical committee, Faculty of Dental medicine, Al-Azhar University (approval no; AUAREC202300002-05).

All patients fully informed about the nature and the possible risks of the procedures and signed the consent before the work.

Inclusion criteria:

1. Patients diagnosed as Stage II, Grade A periodontitis according to the 2017 classification system criteria for periodontal diseases and conditions [11] .
2. The selected patients were free from systemic diseases.
3. Good patients compliance with oral hygiene instructions.

Exclusion criteria

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

Patients grouping

Calculation of sample size

The power calculation was performed to determine the size of the selected sample. The sample size calculated using (α= 0.05) and 85% power. A value of 1 mm was used, changes in clinical attachment level (CAL) which considered as the primary outcome variable. The minimum clinically significant value was 1 mm. A samples of 26 patients per group (52 patients in total) were determined as a minimum to be required. To compensate for sample loss, 60 patients were included.

Periodontitis patients were classified randomly into the following equal groups.

Group I (control): Consisted of 30 patents received scaling and root planing only.

Group II: Consisted of 30 patients received scaling and root planing combined with intra-pocket application of 1% phenytoin in-situ gel.

Preparation of 1% phenytoin gel:

The in-situ gel containing 1% phenytoin was formulated in the Pharmaceutics and Pharmaceutical Technology Department, Faculty of Pharmacy, Al-Azhar University as follows: 100 ml cold distilled water was taken in a beaker, pluronic with 15-20 % w/v concentration was dispersed to it with stirring for 1hour at 400 RPM then was stored at 4°C in refrigerator for 24h to obtain a polymeric clear solution. A pre weighed PTH amount (Global pharmaceutical industries company, Section 2, 6th of October, Giza, Egypt) added to the solution and completely dissolved to get a homogeneous of polymer, solvent and drug. This homogenization was performed at 1300 rpm by a lab stirrer. Methyl paraben (preservative) was added to the preparation. The prepared formulation was placed in the refrigerator overnight to allow the complete dissolution of the drug and polymer then transferred to 3ml syringes under completely sterile conditions. 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 [12].

Periodontal intervention:

Phase I therapy (full-mouth scaling and root planing) was received by all patients, a procedure was performed using a combination Gracey curettes (Hu-Friedy, Chicago, USA) and ultrasonic device (MiniPiezon, EMS, Electro Medical System, Le Sentier, Switzerland), underlocal anesthesia when necessary.

Intra-pocket application of 1% phenytoin gel:

In group II ,The regions of application carfully were isolated with cotton roll . The gel was applied by initially placing the tip of the needle into base of the pocket until it started to emerge from the gingival margin. (Figure 1-A). Following application, patients instructed not to rinse, drink or eat for 30 min at least. Also instructed not disturb the area by fingers, tongue or toothpick and avoid chewing any sticky or hard food for at least 1 week, postpone brushing and flossing on the treated areas for 1 week [13]

Clinical evaluation:

***1-* Clinical evaluation**

The periodontal status were evaluated clinically for all patients at baseline, 3 and 6 months after treatment using these periodontal parameters:

- Plaque index (PI) [14].
- Gingival index (GI) [15].
- Probing pocket depth (PPD) which measured by William's graduated periodontal probe (Hu-Friedy, Chicago, USA) from free gingival margin to the periodontal pocket base [16].
- Clinical attachment level (CAL) which measured from the cementoenamel junction to the base of the pocket [17] by William's graduated periodontal probe (Hu-Friedy, Chicago, USA).

Gingival crevicular fluid samples collection:

- The selected areas for sampling were isolated by a cotton roll, supra gingival plaque was removed, Isolated sites dried gently with an air syringe. A pre-adjusted microcapillary pipette was used to collect a standardized 1 µL volume of GCF [18] . Figure (1-B)
- Each one of the collected sample was allotted for 10 minutes, the contaminated micropipettes with blood and/or saliva were excluded. Samples were transferred to Eppendorf tube vials containing 100 µL phosphate buffer saline (PBS; 137 mm NaCl, 10 mm Na2HPO4 and 2.7 mm KCl; pH 7.3) then frozen at -80°C till they assayed for PDGF-BB and VEGF.

2- Biochemical evaluation:

- Platelet derived growth factor-BB level and VEGF in the GCF samples was measured at baseline and 1, 2, and 4 weeks in both groups. Using a human PDGF-BB and VEGF enzyme-linked immunosorbent assay kit (RayBio Human PDGF-BB ELISA assay kit, Ray Biotech, Norcross, GA) and (RayBio Human VEGF ELISA assay kit, Ray Biotech, Norcross, GA) respectively WHICH uses a specific antibody for human VEGF or PDGF-BB coated a 96 well plate. A highly sensitive reader was used to detect PDGF-BB and VEGF level in pg/ml. The assays conducted according to the manufacturer's guidlines.

Statistical analysis:

Data were analyzed by IBM® SPSS® Statistics version 20. The level of significance was at $P \leq 0.05$. Paired t-test which used to compare the two groups and spearman correlation was used to find the correlation between different parameters.

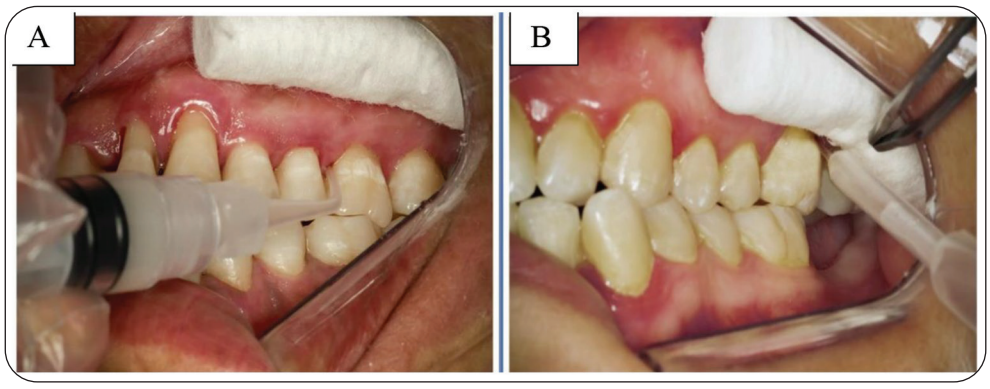

Fig. (1) 1-A Intra-pocket application of phenytoin gel 1-B Gingival crevicular fluid samples collection

RESULTS

1. Clinical results:

A. Changes in gingival and plaque indicese

- No statistically significant difference in group I compared with group II at different evaluation periods, table (1).

B. Probing pocket depth measurements

- There were significant differences in group II when compared with group I at 3 months after treatment, table (1).

C. Clinical attachment level measurements

- There were statistically significant differences in group II when compared with group I at 3, months after treatment, table (1).

2. Biochemical results:

a- Platelet-derived growth factor (PDGF-BB) assessment

- There was a statistically significant difference in group II when compared with group I at 1,2 and 3 week, table (2).

b- Vascular endothelial growth factor (VEGF) assessment

- There was a statistically significant difference in group II when compared with group I at 2 week, table (2).

Table (1) *Mean ± standard deviation (SD) of clinical and biochemical parameters for both groups*

	Group				p-value
	Group 1		Group 2		
	Mean	SD	Mean	SD	
PI (score)					
Base line	1.47	.52	1.47	.52	1.000
After 3 months	.27	.46	.33	.49	0.695
After 6 months	.53	.52	.33	.49	0.277
GI (score)					
Base line	1.53	.52	1.53	.52	1.000
After 3 months	.40	.51	.33	.49	0.710
After 6 months	.47	.52	.40	.51	0.717
PPD (mm)					
Base line	4.53	.52	4.53	.52	1.000
After 3 months	2.40	.63	1.67	.62	0.005*
After 6 months	1.93	.46	1.60	.51	0.073
CAL (mm)					
Base line	3.07	.80	3.07	.80	1.000
After 3 months	1.40	.99	.73	.70	0.054*
After 6 months	1.20	.77	.67	.72	0.061

	Group				p-value
	Group 1		Group 2		
	Mean	SD	Mean	SD	
PDGF-BB (pg/ml)					
Base line	890.27	118.71	893.99	113.22	0.931
After 1 week	1029.03	127.45	1356.81	190.62	<0.001*
After 2 weeks	1101.43	128.68	601.16	134.49	<0.001*
After 3 weeks	481.83	109.18	362.83	114.78	0.007*
After 1 month	241.45	71.36	224.22	49.07	0.447
VEGF(pg/ml)					
Base line	76.00	14.45	74.83	10.95	0.804
After 1 week	91.27	12.06	96.53	32.11	0.558
After 2 weeks	86.93	11.91	110.07	19.20	<0.001*
After 3 weeks	60.99	7.22	64.62	11.40	0.307
After 1 month	50.43	3.95	48.19	5.33	0.200

**; significant (p<0.05) ns; non-significant (p>0.05)*

Table (2) *Showing the correlation between the clinical and biochemical parameters*

		PI	GI	PPD	CAL	PDGF	VEGF
PI	**Spearman Correlation**	1.000	-.357	-.015	-.089	-.606**	-.082
	p-value		.052	.939	.641	.000	.668
GI	**Spearman Correlation**	-.357	1.000	.160	.216	.241	.124
	p-value	.052		.397	.252	.200	.513
PPD	**Spearman Correlation**	-.015	.160	1.000	-.228	.176	.095
	p-value	.939	.397		.225	.352	.616
CAL	**Spearman Correlation**	-.089	.216	-.228	1.000	-.124	.281
	p-value	.641	.252	.225		.515	.132
PDGF	**Spearman Correlation**	-.606**	.241	.176	-.124	1.000	.209
	p-value	.000	.200	.352	.515		.269
VEGF	**Spearman Correlation**	-.082	.124	.095	.281	.209	1.000
	p-value	.668	.513	.616	.132	.269	.

** *Correlation is significant at the 0.01 level (2-tailed).*

DISCUSSION

Periodontitis mainly treated by non surgical treatment combined with regular maintenance care however, debridement may be of little value in all cases and adjunctive therapy still the treatment of choice with SRP. Periodontal surgery indicated in some cases to gain access to the root surface [19].

It was shown that phenytoin increases expression of various growth factors, stimulates fibroblast proliferation, collagen production, collagenase enzyme inhibition, encourages new vascular formation, reduce inflammation and pain and promotes tissue healing capacity. According to reports, Scar tissue formation and wound contraction have also been shown to be reduced by phenytoin [20].

Phenytoin known to improve wound healing due to its proliferative and anti-inflammatory effects and the majority of earlier studies were focused on animal researches, human studies evaluated the effects of drug in the forms of cream or gel on skin wounds [21]. Althogh the effects of oral phenytoin on periodontal healing was assessed and a favorable outcomes was found [22], its application in periodontal disease not investigated. So, The present study was designed to evaluate changes in these clinical periodontal indices (PI, GI, PPD and CAL) following the use of topically applied 1% phenytoin as an adjunctive treatment in periodontitis patients. Also, the biochemical changes in GCF level of PDGF and PDGF-BB which considered a portent periodontal regenerative biomarker was also estimated .

Periodontitis is treated using a variety of local medication delivery formulations in adjunctive to SRP to overcome the systemic side effects and provide a higher concentrates of the material in periodontal tissues [23]. The current trial used o 1% phenytoin in-situ gel preparation to regulates and extends the period of medication release which are predicted to improve treatment results [24].

A significant reductions in all measured clinical parametrs were found in findings of the present research at different evaluation periods compared to

a baseline. This is consistent with the findings of another study used PHT in the form of mucoadhesive paste after SRP and improvment these clinical periodontal parameters were also found [21].

Regarding PPD and CAL, this study found a significance reduction in both parameters when compared to the baseline in both groups and maximum reduction was observed at 3 month. Also, when comparing both group, a significant difference between the phenytoin group at 3 month when compared with control was found. This might be explained by how topical phenytoin could accelerate wound early healing process by increasing fibroblasts and myofibroblasts proliferation, extracellular matrix and its proteins formation and growth factor activity [21]. Phenytoin also act as a potent chemoattractant and mitogenic factor for the cells recruitment and angiogenesis which has been proved in a histological study in which a phenytoin treated wounds biopsies showed a mononuclear cells, fibroblasts, collagen formations, neovascularization and re-epithelization were increased [25].

The effect of topically applied phenytoin loaded PLGA microspheres in periodontal diseases was studied and results provided an evidence that localized and controlled release phenytoin could provide a benefits in gingival recession and alveolar bone resorption and the research concluded that phenytoin considered to be a promising drug in periodontal tissue regeneration [26].

In terms of biochemistry, the present study found a significant rise in GCF PDGF-BB and VEGF levels in both group after one and two weeks when compared to base line value and the level was significantly higher in group II compared with control at 1 and 2 weeks in PDGF-BB and in 2 weeks in VEGF. Theses findings are in agreement with a reports of some studies which reported a higher levels of growth factors after early stages of tissue injury. [27-30] Also, the biochemical effect of topically applied phenytoin on tissue healing in animals was studied and results found that both PDGF and VEGF increased significantly based on time and dose factors in phenytoin concentrations of 1% and 3% in the 6- and 12-day protocols [31].

A reduction in the GCF level of these growth factors at 3 and 4 weeks which considered a statistically significant in PDGF-BB level at 3 week in phenytoin treated group was also observed, this is in agreement with another study which found that PDGF-BB and was upregulated with overexpression of VEGF in the early stages of phenytoin-treated wounds before regressing in later stages [32] also, the expression of growth factors in GCF of gingival enlargement positive patients treated with phenytoin was investigated and results found that the total amounts of transforming growth factor beta (TGF-b) and PDGF-BB in the enlargement positive groups was higher than the negative one [33].

CONCLUSIONS

Topically applied 1% PHT in-situ gel showed an attractive positive periodontal clinical effect in the form pocket depth reduction clinical attachment level gain. The level of GCF growth factor of both PDGF-BB and VEGF significantly increased before gradually declined at the end of evaluation periods.

Conflicts of interest

There are no conflicts of interest.

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جل الفينيتوين المستخدم موضعياً كعلاج مساعد في مرضى التهاب الأنسجة حول السنية

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الملخص :

الهدف: من المعروف أن الفينيتوين (PHT) يمتلك تأثيرات مضادة للالتهابات والتي تحفز التئام الجروح. ومع ذلك، فإن تطبيقاته خاصة في التركيبة الموضعية في أمراض اللثة لا تزال غير واضحة. كان الهدف من هذا العمل هو تقييم فعالية الفينيتوين المستخدم موضعياً بنسبة 1% كعلاج مساعد في المرحلة الثانية من التهاب الأنسجة حول السنية من الدرجة الأولى.

المواد والاساليب: صممت الدراسة الحالية كتجربة اكلينيكيه أجريت على 60 مريضا من كلا الجنسين، تتراوح أعمارهم بين (30-52) سنة مصابين بالتهاب الأنسجة حول السنية من الدرجة الثانية الفئة الأولى. تم تصنيف المرضى إلى المجموعات التالية: المجموعة الأولى: شملت 30 مريضاً تم علاجهم عن طريق العلاج الغير جراحي. المجموعة الثانية: شملت 30 مريضاً تم علاجهم عن طريق العلاج الغير جراحي مع استخدام جل الفينيتوين 1%. تم قياس عمق الجيوب اللثوية ومستوي التصاق اللثة الاكلينيكي قبل العلاج المبدئي مباشره وعند 3 و6 أشهر بعد العلاج. تم دراسة تأثير الفينيتوين على عامل نمو بطانة الأوعية الدموية (VEGF) وعامل النمو المشتق من الصفائح الدموية (PDGF-BB) في السائل اللثوي (GCF) قبل العلاج المبدئي مباشره وعند 1، 2، 3 و4 أسابيع بعد العلاج.

النتائج: أظهرت المجموعة الثانية تحسنا ملحوظا فيما يتعلق بقياس عمق الجيوب اللثوية ومستوي التصاق اللثة الاكلينيكي في المواضع المعالجة بالفينيتوين مقارنةً بالمجموعة الاولي. واعتبر هذا الانخفاض مهمًا إحصائيا عند 3 أشهر. على الرغم من أن الفينيتوين (PHT) قام بتنظيم مستويات PDGF-BB وVEGF بشكل ملحوظ في GCF مقارنة بالمجموعة الاولي خلال الأسبوعين الأول والثاني، إلا أن مستوى عوامل النمو انخفض إلى قيمة ما قبل العلاج تقريبًا عند 3 أسابيع واستمر هذا الانخفاض إلى 4 أسابيع.

الخلاصه: يمكن الاستنتاج أن الاستخدام المساعد لجل الفينيتوين 1% أظهر تأثيرًا إيجابيًا على عمق الجيوب اللثوية ومستوي التصاق اللثة الاكلينيكي.

الكلمات المفتاحية: التهاب الأنسجة حول السنية، العلاج الغير جراحي، جل الفينيتوين 1%، عامل النمو المشتق من الصفائح الدموية