

Re-Evaluation of the First Phenytoin Paste Healing Effects on Oral Biopsy Ulcers

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Abstract

Background: Until now, several formulations of topical phenytoin have been used to promote wound healing. **Aim:** This study was aimed at re-evaluating the effects of a newly formulated phenytoin mucoadhesive paste on wound healing after oral biopsy. **Subjects and Methods:** In a double-blind clinical trial, 35 consecutive patients with oral lichenoid or lichen planus lesions were randomized into two groups. After incisional biopsy, patients applied simple, or 1% phenytoin paste at least three times a day (after each meal), for 4 days. They were evaluated every other day for size of wound closure, severity of pain, and diameter of the inflammatory halo. This study was approved by Medical Ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Statistical analysis was performed using Mann-Whitney U test and Ordinal Logistic Regression. **Results:** Of 35 patients, 17 (10 [10/17, 59%]) men, 7 (7/17, 41%) women, mean age: 40 (4.11) were in phenytoin group, and 18 (9 [9/9, 50%]) men, 9 (9/9, 50%) women, mean age: 43.1 (5.15) were in placebo group. There were no significant differences between both study groups in terms of age and sex (male/female ratio) ($P = 0.76$, $P = 0.88$). As all biopsies were done by means of punch number 8, the incisions were of 10 mm length. After second and third appointments, it was observed that patients in the treatment group showed quicker wound closure and less pain compared to control group significantly ($P < 0.05$). Although not significant, patients treated with phenytoin paste had smaller inflammatory halo than controls. **Conclusion:** Applying 1% phenytoin mucoadhesive paste on oral biopsy incisions resulted in accelerated wound healing and decrease in pain.

Keywords: Biopsy, Mucoadhesive, Oral, Paste, Phenytoin

Introduction

For more than 60 years, investigators have shown an interest in how topical phenytoin may be used to promote wound healing in acute or chronic ulcers.^[1]

Phenytoin (5,5-diphenyl-2,2-imidazolidione, sodium) was first synthesized in 1908, and has been used as an anti-seizure in 1937.^[2] Kimball and Horan, in 1939, first described the gingival hyperplasia occurred in some patients treated with phenytoin.^[3] This apparent stimulatory effect of phenytoin

suggested a possibility for its use in wound healing.^[4] Shapiro carried out the first controlled clinical trial on phenytoin and found out that periodontal patients with surgical wounds who were pretreated with phenytoin had less pain, inflammation, and accelerated healing as compared to controls.^[5]

Until now, several studies have demonstrated the healing effects of phenytoin on various kinds of wound such as leprosy, burns, diabetic foot, war wounds, excisional biopsies, and pressure sores.^[1,6-9] Topical phenytoin has been documented to promote wound healing and improve the quality and vascularity of granulation tissue due to enhancing fibroblast proliferation, maturation of collagen content, and decreasing collagen activity.^[9]

Review of literature revealed that there was no study using topical phenytoin as a mucoadhesive paste for treatment of human oral mucosal lesions. For this reason, we formulated a new phenytoin-containing mucoadhesive paste and used it

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for better healing of oral biopsy wounds.^[10] However, in the present study we re-evaluated the healing effects of phenytoin mucoadhesive paste with a larger sample size and more matching between case (phenytoin group) and control (placebo group) in terms of age, sex, site of the biopsy, and type of biopsied lesions.

Subjects and Methods

This double-blind, randomized, placebo-controlled clinical trial has been done on patients attending Ghazi Tabatabaei Dental Clinic, Shahid Beheshti University of Medical Sciences, who were candidate for oral biopsy. Thirty-five consecutive patients who met the inclusion criteria were randomly classified into two groups of treatment and placebo (containing all of the paste ingredients without the phenytoin in the form of paste).

According to a previous study by Hasamnis *et al.*, the paste contained 1% phenytoin powder (Merck Group, Frankfurt, Germany).^[4] Other ingredients were plant heteropolysaccharides (Sigma Pharmaceuticals Limited, Victoria, Australia), hydrolyzed collagen (Merck Group, Frankfurt, Germany), Vaseline (Merck Group, Frankfurt, Germany), 1, 2-Propanediol (Merck Group, Frankfurt, Germany), cellulose (Sigma Pharmaceuticals Limited, Victoria, Australia), and strawberry essence (Darou-Pakhsh Pharmaceuticals Mfg. Co, Tehran, Iran). The paste was formulated in School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

The inclusion criteria in the trial were as follows: (1) All patients had tentative diagnosis of oral lichenoid or lichen planus, (2) buccal mucosa was involved and biopsy was taken from this site in all participants, (3) age range between 30 and– 50, (4) no history of systemic diseases at the time, of study (5) not using any topical or systemic medications, (6) being non-smoker and non-alcoholic, and (7) willing to participate in the study. Meanwhile, malignant-looking oral lesions, necrotic lesions, pemphigus-like lesions, and pregnant patients were excluded from the study.

After taking a written consent from all patients lesions were biopsied under local anesthesia using punch biopsy number 8 (Kia Medical Company, Japan), so that the size of all incisions was almost 10 mm. After incisional biopsy, patients were instructed to apply simple, or 1% phenytoin - containing mucoadhesive paste at least three times a day (after each meal), for 4 days. The patient and the researcher who gave the paste to them were unaware of the paste constituents, and allocation of patients to study or control group was done randomly. Phenytoin and placebo paste were packed in similar tubes.

Patients were evaluated every other day for size of wound closure, severity of pain, and diameter of the inflammatory

halo. The inflammatory halo, as well as the degree of wound closure, were measured by Williams probe (Hu-Friedy Mfg. Co., Chicago, USA) at the day of the biopsy, and then on days 2 and 4 after biopsy.

The degree of pain was evaluated by patients' self-report using a 10-cm visual analog scale (VAS) at the day of biopsy, and then every other day till day 4 post biopsy.

The patients in both placebo and phenytoin-treated groups were instructed to apply the paste at least three times a day and preferably after meals on their incision site.

All study procedures were accomplished according to Helsinki Declaration after being approved by Medical Ethics committee session number 132, and research council number 330 of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Statistical analysis was done using Mann-Whitney U Test and Ordinal Logistic Regression by means of SPSS software, version 17 (Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Out of 35 patients, 17 were in the phenytoin group including 59% men (10) and 41% women (7) with the mean age of 40 (4.11). In the placebo group, 18 patients were enrolled consisting of 50% men (9) and 50% women (9) with the mean age of 43.1 (5.15). There were no significant differences between both study groups in terms of age and sex (male/female ratio) ($P = 0.76$, $P = 0.88$).

At the beginning of the study, two groups did not have significant differences in terms of size of incisions, size of inflammatory halo, and intensity of pain (VAS) as measured by Man-Whitney U Test [Table 1]. Then we used Ordinal Logistic Regression, which was adjusted for baseline effect to detect any differences between case and control groups in various intervals.

Table 1: Changes of incision size, IHS, and pain intensity (VAS) in different intervals in two groups

Variable	Recall	Treatment		Control		P
		Median	IQR	Median	IQR	
IS	1	10	10-10	10	10-10	1.00*
	2	6.5	5-7	8	7-8	0.03†
	3	2	0-3	4	3-5	0.10†
IHS	1	3	2-3	3	2-3	0.77*
	2	1	0-2	2	2-2	0.02†
	3	0	0-1	1	0-1	0.06†
VAS	1	3	2-4	4	3-4	0.43*
	2	1	0-2	2	0-2	0.53†
	3	0	0-0	0	0-1	0.27†

*Based on Mann-Whitney U Test, †Adjusted for the baseline values, based on Ordinal Regression. IS: Incision size, IHS: Inflammatory halo size, VAS: Visual analog scale, IQR: Inter quartile range

Regarding size of incisions, all patients in both groups had a similar incision size (10 mm) on the first visit. On the second recall, the median size of biopsy incisions was 6.5 mm in the treatment group with the interquartile range (IQR) of 5–7, while median size of biopsy incisions in the placebo group was 8 mm with the IQR of 7–8 mm, and the difference between two groups was statistically significant ($P = 0.03$). The median size of incisions reduced to 2 mm (IQR: 0–3) and 4 mm (IQR: 3–5) in treatment and placebo groups, respectively, on the third visit without any significant difference ($P = 0.10$) [Table 1].

The median size of inflammatory halo in the case group was 1 mm (IQR: 0–2), which was significantly smaller ($P = 0.028$) than that of the control group (2 mm, IQR: 2–2) on the second visit. However, no significant difference was found between two groups on the third visit [Table 1].

In regard with pain intensity, the median of VAS was reported as 1 cm (IQR: 1–2) in case group and 2 cm (IQR: 0–2) in the control group on the second visit without any significant difference between groups ($P = 0.53$). On the third visit, median of VAS was 0 in both groups ($P = 0.27$) [Table 1].

During the study period, patients in phenytoin group reported no side effects.

Discussion

Wound healing is a significant health-care problem in today's medical practice. Various methods and medications have been used so far to alleviate the symptoms and improve the healing process of wounds; however, the outcomes of existing methods are still far from optimal.^[11,12] The main mechanism by which phenytoin accelerates wound healing is still unclear. Clinical studies suggest that stimulation of fibroblastic proliferation, enhancing the formation of granulation tissue, decreasing bacterial contamination, decreasing collagenase activity (by reducing its production or secretion, or both), promoting deposition of collagen and other connective tissue components, and decreasing the formation of wound exudate might be implicated in the healing process.^[4]

In addition, biopsies of phenytoin-treated open wounds showed neovascularization and collagenization.^[13] The analgesic effect of phenytoin may be more complex. Local pain relief due to blocking the sodium channels and membrane-stabilizing action of topical phenytoin therapy has been observed in several studies.^[14,15]

In our study, we did not analyze the relation between age and sex with healing effects of pastes, but Makrantonaki and Zouboulis indicated that there was a sex divergence in the healing of acute wounds, and the healing process occurred more slowly in elderly men than in age-matched women.^[16]

Rhodes *et al.* found that topical phenytoin therapy resulted in a shorter time to complete healing and formation of granulation tissue when compared with DuoDerm dressings or triple antibiotic ointment applications.^[4]

Fonseka *et al.* found that phenytoin sodium 2% solution was beneficial for pyoderma gangrenosum with various etiologies, and it enhanced ulcer healing especially when the patient had refractory diseases.^[8]

Pereira assessed the therapeutic effect of topical phenytoin 0.5% on cutaneous healing from excision of melanocytic nevi on the face and found that patients who treated with phenytoin had significantly more profound epithelialization with smaller wounded area and shorter healing time than controls.^[2]

Hasamnis *et al.* studied the wound healing effect of 1% phenytoin cream in the wounds of rats. In their study, 20 male Wistar albino rats were subjected to excisional wounds measuring 500 mm² on the back and then randomized to control and treatment groups. The control group received no drug treatment till the end of the study. One percent phenytoin cream was applied to the wounds of rats in the treatment group and continued till the 16th day of the study. They calculated the percentage of wound healing by Walker formula after measurement of the wound area. They found statistically significant reduction in average wound area in the phenytoin group on days 4, 8, 12, and 16 of the experiment in comparison to control group.^[4]

Yadav *et al.* studied the effect of topical phenytoin in the treatment of split-thickness skin graft. Within the phenytoin group, all 30 wounds had healed compared with three of the antibiotic group. Pain level was also reported to be lower in the phenytoin group, and there were a higher number of negative bacterial cultures in this group as well.^[17] Kadhodazadeh *et al.* accomplished a similar study on the oral mucosa that noticed phenytoin suspension could effectively accelerate the process of healing at the donor site and reduce pain following periodontal surgeries. In their study, those patients treated with phenytoin suspension showed significantly faster healing at days 14 and 28 with significantly lower pain intensities.^[18]

Baharvand *et al.* administered 10 ml of 0.5% phenytoin mouthwash in patients with oral mucositis under chemotherapy four times a day. Their study failed to show any advantage of using 0.5% phenytoin mouthwash to reduce pain and discomfort, but it was effective in mucositis healing and improving life quality.^[19]

Applying the drug in the form of paste, when compared to cream or elixir, can avoid washing out the drug by saliva and prolongs contact of the formulation with the oral mucosa and allowing a longer duration for absorption. Besides, this formulation can act as a wound dressing, which can further ameliorate patients' pain and discomfort.^[6,20-22]

Baharvand *et al.* first described healing effect of phenytoin mucoadhesive paste after oral biopsy on humans in 2013. She found that the rate of wound healing and decrease in the size of ulcers were significantly quicker in the phenytoin group, and the patients in this group reported less pain than those in the placebo group. However, the diameter of the inflammatory halo was not significantly different between two groups.^[10] In their study, patients had different types of lesions with different entities of inflammatory, neoplastic, autoimmune-mediated, origin, etc., Moreover, biopsies were taken from different sites of keratinized and nonkeratinized epithelium. It seems that various nature and location of lesions with different microstructures might affect the healing process of the tissue and thereby therapeutic effects of phenytoin somehow. Therefore, in the present study, we modified the methodology and found some different results, which are discussed as follows.

In our study, it was shown that applying 1% phenytoin-containing mucoadhesive paste on biopsy incisions on the buccal mucosa can accelerate wound closure and help in reducing the size of incisions up to 3 days after surgery compared with control group, but after 5 days the difference between two groups was not significant. All incisions were of 1 cm length, of an acute nature, and expected to be healed up to 7 days after surgery. That is why phenytoin paste had a better effect in a short time, because as time passes the tissue healing process closes the wound through its natural mechanisms. Our results were in accordance with Chan *et al.*, Jarrahi and Vafaei studies.^[7,11]

In our study, phenytoin paste was able to reduce the inflammatory halo better than placebo up to 3 days after surgery, but its effect was not significantly better than placebo after 4 days. Previous studies demonstrated the anti-inflammatory effect of phenytoin.^[23-25] It seems that in acute wounds, the effects of topical phenytoin is more pronounced in a few days after onset of lesion when the natural healing process has not been reached its optimum effect yet.

Several studies have shown that VAS is a valuable method of pain measurement.^[26] Contrary to some previous studies, our results failed to show any significant analgesic effect of topical phenytoin when compared with placebo.^[6,8,18] In our study, the length of all incisions was short (1 cm), therefore, the pain quantity reported by both groups was of low intensity (VAS: 0–4) at different intervals. This might be the reason why phenytoin paste did not show outstanding effects on pain control.

During the study period, patients in phenytoin group reported no side effects. In the agreement to our finding, Hasamnis *et al.* pointed out that the topical application of phenytoin results in direct access of the drug to the target site, and avoids the risk of getting systemic side effects.^[4] However, according to Talas *et al.*, the most frequent side effect of phenytoin when administered systemically is gingival enlargement observed after approximately 1 month of drug use, begins

in interdental papillae, and usually in the anterior gingival regions.^[27] Other uncommon side effects of phenytoin include ataxia, ophtalmoparesis, megaloblastic anemia, hypertrichosis, exfoliative dermatitis, pruritis, toxic epidermal necrolysis, and immunoglobulin A deficiency.^[20]

In order to better clarification of the effects of phenytoin paste, it is suggested to design further studies to compare it with other formulations such as creams, powders, and mouthwashes. Meanwhile, additional studies in various types of oral lesions are recommended.

Conclusion

Mucoadhesive phenytoin paste has shown promising results in wound closure and reducing inflammation after oral incisional biopsies.

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