Short-Term Effects of 1% Topical Phenytoin Suspension on the Donor Site Pain and Wound Size after Free Gingival Grafts

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Abstract

Objective: Post-surgical wound and pain are among major complications following periodontal surgery. The present study evaluated the healing properties and analgesic effect of Phenytoin on the donor site of free gingival grafts.

Methods: This interventional randomized controlled clinical trial was conducted on 10 patients who received free gingival grafts. Understudy subjects were selected among patients presenting to a private office and dental clinic of Hamedan Dental School and randomly divided into two groups. The wound size was measured with digital caliper. Phenytoin suspension and the placebo were applied on the palatal donor site wound in cases and controls, respectively. The wound size was measured at days 14 and 28 post-operation and compared with baseline value. Also, severity of pain was measured using visual analog scale (VAS). Statistical analysis was performed using paired t-test and Wilcoxon signed rank test.

Results: The case group showed significantly faster healing at days 14 (α=0.1, p=0.078) and 28 (α=0.05, p=0.049). Pain Score was significantly lower in patients treated with phenytoin (p=0.18).

Conclusion: Phenytoin can effectively accelerate the process of healing at the donor site and reduce pain following periodontal surgeries.

Key words: Free gingival graft, Phenytoin, Healing, Donor site

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Introduction:

Gingival recession occurs as the result of incorrect tooth brushing, malposed teeth, inflammation, self-inflicted injury and some iatrogenic factors. Some surgical procedures are indicated for treatment of this condition. Use of autogenous graft is among the most common techniques in this respect. Keratinized palatal tissue is used as the donor site for these surgeries (1). This process results in a new incision wound that needs to be healed as quickly as possible to decrease related pain and swelling and improve patient’s quality of life. Analgesics and mouth washes are used to reduce post-surgical pain but a solution to facilitate and expedite the process of wound healing is yet to be found. Wound care and process of healing are especially important to prevent complications like infection and formation of short scar tissue that compromises esthetics. Thus, achieving a solution to accelerate wound healing is still an important goal in medicine. Phenytoin (Hydantoin) is a medication that was first introduced in 1938 by Putnam and Merritt for treatment of all forms of epilepsies except for petit mal epilepsy (1, 2). The analgesic, antibacterial, anti-inflammatory and healing properties of this drug were first studied by a dentist in 1958. Findings of Shapiro 30 years later made the surgeons’ dream come true and caused a turning point in the world of medicine (3).

Pain is among the most common symptoms in dentistry and fear of pain always plays a significant role in daily life of people. Many patients avoid visiting a dentist because of their fear of pain (4, 5). All physicians and dentists use various medications like analgesics and antibiotics to reduce and eliminate pain. In 1958, Shapiro noticed that gingival surgeries
are associated with less pain and faster wound healing in patients who take phenytoin for reasons other than epilepsy (3). Following this discovery, he found that phenytoin can significantly accelerate the healing process of skin wounds, second degree burns and periodontal disease.

Some other studies focused on lichen planus and epidermolysis bullosa and found that skin lesions healed as the result of topical and systemic administration of phenytoin. These studies confirmed the positive effect of phenytoin on reducing the number of blisters and acceleration of wound healing. Phenytoin’s mechanism of action is probably through regulating cellular immunity and decreasing the immigration of white blood cells to the lesion site (3).

In India, some studies were performed on the effect of phenytoin on peritoneal abscess and reported reduction in pain and inflammation and accelerated healing of abscesses in all patients (3). Numerous studies have also evaluated the effect of this cheap and abundant drug on healing of oral lesions and aphthous ulcers (6).

Considering all the above, we are constantly searching for a solution to accelerate surgical wound healing because the materials that are presently used for wound dressing only have supportive effect and there is no medication or chemical agent to enhance and facilitate the process of wound healing and reduce post-surgical complications at the same time.

**Methods:**

This study was confirmed by the Ethics Committee of the University. In this interventional pilot study 10 patients (6 females and 4 males) with a mean age of 33 years were selected among patients presenting to the Periodontics Department of Hamedan Dental University and a private office during 24 months. The inclusion criteria were as follows:

1- Indication of gingival graft surgery at both sides of the oral cavity
2- No systemic underlying disease
3- No pregnancy or nursing
4- No history of medication intake during the past three months
5- No history of alcohol consumption, cigarette smoking or substance abuse
6- Patient must have/gain optimal oral health before the surgery (Plaque index below 20%)
7- Patient should be willing and capable of presenting for frequent visits

Before each surgery, oral health instructions were given and phase I of treatment was performed. Patients signed a written informed consent and entered the study. The side of surgery and the intervention group were randomly determined by flipping a coin. Before the initiation of surgery, the patients were asked to rinse chlorhexidine mouth wash 0.2% for one minute. According to Karring protocol (7) the required tissue was removed from the palate (1). The palatal wound size was measured using a digital caliper (MITUTOYO, ABSOLUTE Crop, Tokyo, Japan) by a third party who was familiar with working with caliper and was unaware of the objectives of the study and type of treatment. In order to increase accuracy, measuring was repeated three times and the mean of three values was recorded.
In order to prepare the phenytoin suspension, the contents of two phenytoin capsules made by Alhavi Pharmaceutical Company were mixed with 20 mm distilled water. The surgeon applied the suspension on the palatal donor site using cotton swabs with rubbing motion and mild pressure. In the control group, the cotton swabs were soaked in physiologic saline solution and applied on the site.

At the end, the area was covered with periodontal dressing (Periodontal dressing, Regular, Coe Pack, MI, USA)(Figures 1-8).

In this study each patient was his/her own control. Thus, it has high reliability. On day 14 post-operation, the patients were asked about the severity of pain during the 14-day post-op period and were requested to fill out the Visual Analog Scale form and the pain assessment questionnaire for intra group comparison. Also,
the dressing and the sutures were removed on day 14. Wound size was measured at days 14 and 28 post-operation. The area of the wound was calculated and subtracted from the initial wound area immediately after the operation and the rate of wound healing was determined as such. Wound area % = wound area at day x / wound area at day one × 100
Healing percentage= 100-percentage of wound area
All surgeries were performed by two expert surgeons. Measurements were all done by one operator. Data were analyzed using SPSS software, paired t, test, independent t-test, Pearson’s correlation coefficient or similar non-parametric tests.

Results:

In the present study, 10 patients who had surgical indication for free gingival grafts at both sides of oral cavity were studied during 24 months in the two groups of intervention (phenytoin application) and control (placebo). Wilcoxon signed rank test was used to find statistically significant differences between the two groups in terms of the frequency of pain based on VAS. This test showed that the pain score was significantly lower in patients who used this medication during the first 14 days post-operatively. The mean difference in pain score between the two groups was 6.7 scores which was statistically significant (α=0.05, P=0.18)(Tables 1,2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Number</th>
<th>Mean± SD</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in wound area at days 0 and 14</td>
<td>With medication</td>
<td>10</td>
<td>16.223±24.569</td>
<td>t=1.989</td>
</tr>
<tr>
<td></td>
<td>Without medication</td>
<td>10</td>
<td>42.767±40.457</td>
<td>P=0.078</td>
</tr>
<tr>
<td>Difference in wound area at days 0 and 14</td>
<td>With medication</td>
<td>10</td>
<td>15.409±22.949</td>
<td>t=-2.268</td>
</tr>
<tr>
<td></td>
<td>Without medication</td>
<td>10</td>
<td>46.062±34.750</td>
<td>P=0.049</td>
</tr>
</tbody>
</table>

Table 2- Comparison of the frequency of pain in the two groups of cases and controls based on VAS

<table>
<thead>
<tr>
<th>Total number</th>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>With medication</td>
<td>10</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7.15</td>
<td></td>
</tr>
<tr>
<td>Without medication</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>13.85</td>
</tr>
</tbody>
</table>

Table 3- Comparison of the two groups based on the score of pain and number of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total number</th>
<th>No pain</th>
<th>Tender when touched</th>
<th>Moderate pain, no problem in daily activities</th>
<th>Severe pain, problem in daily activities</th>
<th>Mean rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>With medication</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>7.50</td>
</tr>
<tr>
<td>Without medication</td>
<td>10</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>13.50</td>
</tr>
</tbody>
</table>
Wilcoxon signed rank test was used for evaluation of level of pain reported by the patient (through marking the closest choice in the questionnaire) in the two groups which showed that patients who used Phenytoin in the first 14 days had a significantly lower pain score \((P=0.041)\). The difference in the mean score between the two groups was 6 which was statistically significant \((\alpha=0.05)\)(Table 3).

**Discussion:**

Phenytoin was first administered for the control of epileptic attacks and its side effects like gingival hyperplasia in epileptic patients have been well documented \((7, 8)\). Gingival side effects of phenytoin encouraged the researchers to evaluate the mechanism of action of this medication on wound healing. According to the theories suggested by researchers, phenytoin enhances the proliferation of fibroblasts and increases collagen production in tissues resulting in fast recovery and rapid wound healing \((7)\). Phenytoin has analgesic properties as well. Based on the conducted studies, the analgesic effects of phenytoin are due to the inhibitory mechanism of muscles in the wound borders \((9)\). According to Karring et al, protocol \((10)\) the most suitable donor site in the palate is in between the canine and mesial aspect of the palatal root of the first molar (because this area has the greatest thickness of the required tissue). Thus, in the present study the graft was taken from this area. This study showed the difference in wound area at days 14 and 28 compared to day zero (operation day) and showed that the healing of palatal wound at day 14 compared to day zero in the intervention group was significantly faster than in the control group. The difference in this respect with 90% CI was statistically significant \((P=0.078)\). Our study results were in accord with those of Yadav and Kolbert. They believe that phenytoin can accelerate wound healing. Facilitated healing due to phenytoin has also been attributed to the enhanced proliferation of fibroblasts. Shapiro et al, \((9)\) demonstrated that application of phenytoin gel has favorable healing effect due to the rapid organization of blood clots and quick formation of connective tissue elements. Furthermore, other studies have shown that phenytoin stimulates fibroblasts and facilitates collagen deposition \((8)\). The present study results indicated that at day 28, wound healing in the intervention group was significantly faster than in the control group and the difference in this respect with 95% CI was statistically significant \((P=0.049)\). Our findings were in agreement with those of Layegh et al, \((3)\) who showed that phenytoin reduces wound size and pain of patients. Abirshami et al, \((2002)\) in their study on the effect of 1% phenytoin gel application on improving periodontal parameters in chronic periodontitis patients reported similar results indicating that the difference between the mean values of case and control groups at week 8 was greater than other times. The reason may be the longer course of healing of periodontal parameters in comparison to surgical wounds. Comparison of the level of pain between the two groups based on VAS revealed that the intervention group had a significantly lower VAS pain score \((P=0.018)\) and marked the “less pain” choice in the questionnaire \((P=0.041)\) in the first 14 days. Half the patients in the intervention group did not report any pain experience and the other half mentioned experiencing a mild pain. However, in the control group, 20% of subjects experienced moderate pain which did not interfere with their daily activities. Another 20% reported experiencing a severe pain. These findings were in accord with those of Kasaj et al, and Vaitkeviciene et al, \((10)\). Winckelmann et al, \((11)\) in 2008 attributed the analgesic properties of phenytoin to promoting the inhibitory mechanism and fighting the stimulatory mechanism of muscles.
Conclusion:
The present study results showed that phenytoin can effectively accelerate palatal wound healing and reduce post-op pain following periodontal surgeries.

Suggestion:
Similar studies are required to be performed on larger sample sizes, other models of wound healing, and different formulations, prescription methods and concentrations of phenytoin in various age groups. Along with clinical evaluation, histopathological analysis of the process of healing may be helpful as well. Also, the medication can be used in the form of mouthwash several times a day or in combination with periodontal dressing in future studies to further illuminate the statistical differences between the intervention and the placebo groups.

Acknowledgement
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References:

