Original Article

Effect of 1% Phenytoin Muco-Adhesive Paste on Improvement of Periodontal Status in Patients with Chronic Periodontitis: A Randomized Blinded Controlled Clinical Study

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KEY WORDS
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ABSTRACT

Statement of the Problem: Phenytoin (PHT) has been known to promote wound healing in some medical conditions owing to its proliferative as well as anti-inflammatory effects. Yet, its application in oral lesions was less investigated.

Purpose: The aim of this study was to evaluate changes in periodontal indices following the topical use of phenytoin in chronic periodontitis.

Materials and Method: In this doubled-blind, randomized, split-mouth controlled clinical study, 20 patients with moderate to severe chronic periodontitis referred to Periodontology Department of Shahid Sadoughi Medical University of Yazd in 2014 were selected consecutively. After initial therapy (scaling and root planning and oral hygiene instructions), periodontal indices including bleeding on probing (BOP), periodontal pocket depth (PPD) and modified gingival index (MGI) were recorded. Gingival facial surface of two posterior sextants with at least two teeth with similar conditions, were selected randomly. Then one surface received PHT paste whereas the other side had placebo as control. Patients were received the mucoadhesive pastes under strict control by an examiner, twice a day for a week. Periodontal indices were measured 3 weeks after treatment. Data was analyzed with t-test and paired t-test by using SPSS 21 software.

Results: It was observed that periodontal pocket depth was significantly more decreased in phenytoin side in comparison with placebo one ($p< 0.05$). In addition, inflammatory indices including bleeding on probing and modified gingival index declined more in the phenytoin group ($p= 0.001$ and $p< 0.05$ respectively).

Conclusion: These encouraging results support the use of 1% phenytoin mucoadhesive paste as an adjunctive in periodontal treatment.

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Introduction

Periodontitis is a common, multi-factorial disease, primarily caused by microbial plaque. [1] In the presence of periodontal disease, bleeding on probing indicates bacterial plaque, which in turn, causes inflammation and ulceration in the epithelial lining wall of the pocket. [2] Based on epidemiological findings, chronic periodontitis is the most prevalent form of periodontal disease which, if left untreated, will cause irreversible bone loss. [3]

Periodontal pockets are chronic inflammatory lesions, which constantly undergo repair and destruction. Thorough healing cannot be completed due to the remained bacterial plaque and persistent inflammatory

response as well as subsequent degeneration. [4] The final outcome is brought about as a result of the interplay between destruction and construction. What tips the balance in favor of the latter includes infection eradication, inflammation relief and wound healing. [2]

A relatively new agent for accelerating wound healing, phenytoin (PHT) has already been used as an anticonvulsant drug since 1938. [5-6] A common side-effect, gingival hyperplasia, reported in as many as 50% of patients on long-term phenytoin therapy. [6-11] Deeply inspired, Shapiro initially assessed the potential effects of oral phenytoin on periodontal wound healing in 1958 with favorable outcomes. [5-7, 12-15] This also motivated other research investigating potential effects in burns, trauma, leprosy, [15-17] aphthous stomatitis, [7, 11, 18] diabetes, and lichen planus. [7, 11] PHT supposedly contributes to healing via modulating cellular immunity as well as hindering white blood cells (WBC) migration. [11, 19] It may also indirectly stimulate proliferation and migration of fibroblasts through the expression of growth factor genes, namely platelet-derived growth factor (PDGF) from macrophages and monocytes. [16] The drug is also claimed to trigger collagen fibers' maturation, promote collagen deposition and enhance angiogenesis. [6, 9, 20-21] Other desired effects regard edema reduction [22] by decreasing both exudate and transudate. [8, 16, 20] The antibacterial feature is still subject to controversy, yet the drug's potential effect in curtailing infection seems to be owing to enhanced blood flow as a result of the stimulus the pharmaceutical agent creates for angiogenesis. [7, 9] It is also claimed that PHT stabilizes neural fiber membranes, thus contributes in topical pain relief. [23]

There has also been research on the role of phenytoin in improving periodontal parameters [13, 16, 22] as well as healing process in the extraction socket. [19] The previous investigators almost all applied topical phenytoin but in different forms: mouthwash, [7] suspension, [24] gel [12] and mucoadhesive paste. [14, 23]

In this study, we primarily intended to investigate the effect of topical phenytoin use on periodontal indices.

Materials and Method

This was a double-blind, randomized, split-mouth controlled clinical study, conducted on 40 dental sites of twenty patients, five men and fifteen women, with a mean age of (36.2±12.2) years, diagnosed with moderate to severe chronic periodontitis. [25] Patients had all been referred to the Department of Periodontology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, from May to September 2014. This study was approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences. The IRCT (Iranian registry of clinical trials) code for this study was 201408171883 4N1.

Patients were included if they were nonsmokers, without any history of traumatic occlusion and systemic conditions namely diabetes and heart diseases. As for their drug history, they should not take antihypertensive, immune suppressants and anticonvulsants, which would have affected their periodontium. None were pregnant, nor had they taken antibiotics during last three months. They all had at least two contra-lateral teeth with similar conditions (number of roots, without furcation involvement and similar pocket depth) on posterior sextants, with no decay and restorations. All patients signed the informed consent form when an internist was consulted for medical assessment and possible drug interactions. Demographic data was provided via having patients filled a questionnaire whereas the rest was collected throughout oral examinations. Periodontal pocket depth (PPD), the distance from the gingival margin to the base of the probable crevice, was measured along six areas for each tooth (mesiobuccal, midbuccal, distobuccal, distolingual, midlingual and mesiolingual) using a William's periodontal probe. Bleeding on probing (BOP), sites which bled 30 to 60 seconds after probing in percentage terms, [26] as well as modified gingival index (MGI) were also recorded. [27] There were two periodontists both blind to the study. One clinician was assigned to carry out clinical measurements as described, both prior to applying the mucoadhesive paste, which was randomly (using toss of coin) chosen to be either PHT or placebo. This clinician also confirmed sufficient and acceptable oral hygiene before the measurements were calculated. All patients underwent thorough scaling, root-planning, and oral hygiene instructions such as bass brushing technique and flossing, conducted by a trained periodontology resident who was also blind to the study polishing were done of course if needed.

Following the first round of data collection, mucoadhesive pastes preserved in two different containers with different colors. Our pharmacist was aware of the containing. One containing PHT 1% and the other placebo (Figure 1) were applied to randomly selected sextants by a second periodontist who was blind to the study.

Figure 1: Containers in different colors

We also preferred to keep our patients incognizant to prevent any possible bias and/or incompliance, though they were given detailed instructions about their oral hygiene. Patients were then had their pastes applied on both sides. In each patient, gingival facial surfaces in two posterior sextants, with at least two teeth with similar conditions, were randomly selected as described before. One surface received a pea-sized amount of phenytoin paste (approximately 2 grams) as prepared, and the other side had placebo as control (Figure 2).

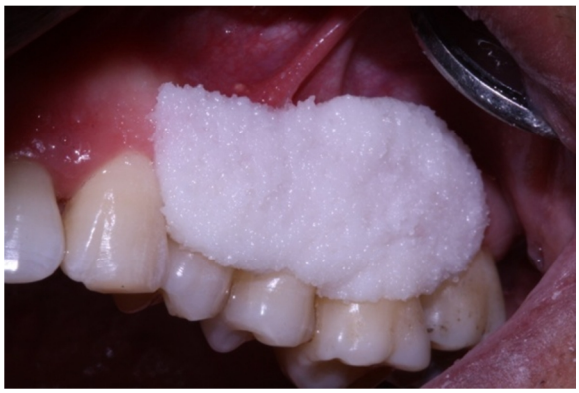

Figure 2: Application of mucoadhesive paste on facial surface of gingivae and cervical one third of teeth

The periodontist in charge of drug application used her index finger to rub this size of paste on the exposed gingival surface so as to cover cervical one third of the teeth. Patients were visited twice daily to receive applications for a week. Earlier, they had their teeth brushed and flossed most meticulously. They also had to abstain from eating and drinking one hour following applications. They were often kept busy in the waiting room so as to make sure they did as instructed.

Any patient who had failed to comply with paste application (7 patients) or refer for follow-up (10 cases) were excluded from the study, out of a total of 37-patients registry.

Preparation of phenytoin mucoadhesive paste

Since buccal phenytoin dosage is not commercially available, the common local skin dosage (1%) was mixed with a mucoadhesive paste formulation which is routinely used in Orabase. Phenytoin powder and carbopol 934 were purchased from Alhavi Pharmaceutical Corporation (Iran) and Lubrizol (USA) respectively. Methyl cellulose (Hydroxypropyl), nominal viscosity 2% in water: 2600-5600 cP and liquid paraffin was prepared from Sigma Aldrich, Germany.

One percent phenytoin mucoadhesive paste was prepared in Yazd School of Pharmacy, extemporaneously. To prepare this paste, one gram of phenytoin powder was mixed with 50 grams of mucoadhesive polymers including carbomer 934 and methyl cellulose (1:1 w/w). Subsequently, the mixed powders were gradually levigated with 50 grams of liquid paraffin using mortar and pestle to obtain a uniform consistency (Figure 3).

Figure 3: Preparation of mucoadhesive paste

The mixing was continued until the preparation of a homogenous paste without existence of separate particles. Thumb test was used for qualitative determination of peel adhesive strength of the paste.

The paste was then inserted into 100 mg containers (yellow and pink) (Figure 3). As for the placebo, the

composition and preparation method was almost the same except for the fact that it was PHT-free.

We used t-test and paired t-test for comparative analysis by using SPSS 21 software.

Results

There were statistically significant differences in indices (PPD, BOP and MGI) following three weeks after phenytoin application in test group. There could be seen a decline of 0.93±0.57 mm in PPD on the phenytoin-applied sites, as opposed to placebo-applied locus (0.56±0.49 mm). Paired t-test revealed a significant difference in this respect ($p< 0.05$) (Figure 4).

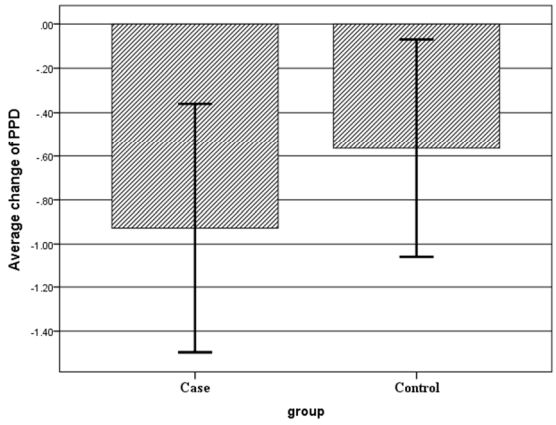

Figure 4: The average PPD changes in case and control groups (Error bars ±1 SD)

As can be seen in Table 1, BOP and MGI were also significantly declining in the phenytoin group. Thus as expected anti-inflammatory effects of PHT were highlighted based on changes in the latter inflammation indices (BOP, MGI). Also it should be noted that in this trial study, any adverse events or side effects were not reported by patients.

Discussion

It has been stated that PHT would accelerate healing rate in surgical wounds following the oral application of the drug. This encouraged the topical applications for skin breaches due to ulcers, burns, skin infections namely impetigo, infected dermatitis and boils, [15] with somewhat mixed results, especially in experimental models. [7] Former research on the role of phenytoin in periodontal lesions healing was disparate in terms of the drug form; such as gel, [12] mouthwash [7, 28] and suspensions. [24] We decided to use mucoadhesive paste 1% considering its longevity in the oral cavity and the relative immunity against potential interventional parameters namely saliva washout and tongue poking. This also enabled us to suffice to the application of the drug twice per day, which, in turn, made it possible to rule out incompliance as patients, from the walking and driving distances, managed to come and receive medication under our supervision.

To the best of our knowledge, mucoadhesive paste of phenytoin has not been assessed in human except in one study designed by Baharvand *et al.* They used this form of drug on oral biopsy ulcers. [23] The majority of earlier researches were animal studies or some of them have evaluated the effects of other forms of this drug such as cream or gel on human skin wounds. For example, Abrishami *et al.*, [12] though having applied phenytoin gel instead of paste, were shown consistent in their findings as their planned therapy led to the reduction of the pocket depth while promoting connective tissue strength.

Ghapanchi *et al.* [7] also used phenytoin mouthwash in cases of chemotherapy-related mucositis. A 2-week treatment including drug use three and/or four times per day yielded favorable results. Buccal mucosa was most influenced in this therapy. Baharvand *et al.* [23] applied the 1% mucoadhesive paste onto small biopsy-induced lesions, which had healed more quickly as a result. Patients were also reporting a lower incidence of pain. All the above findings were confirmatory of our findings about healing effect and reduce inflammation of topical use of phenytoin. Other studies reported accelerated healing in melanocytic mole removal scars [29] as well as stomatitis-related lesions. [7] Our reports are similar in that pocket lesions are indispensable to periodontitis. Najafi *et al.* [14] applied the same

Table 1: BOP and MGI changes in case and control groups

Variable	Group	Mean±SD	Mean differences	t	p-value
BOP	Phenytoin changes Placebo changes	-36.22±11.94 -19.25±12.48	-16.97±15.34	-4.95	0.001***
MGI	Phenytoin changes Placebo changes	-1.46±0.28 -1.06±0.29	-0.41±0.29	-6.36	0.001***

mucoadhesive paste on creeping attachment lesions with negative results. The drug was used on the surface of the de-epithelialized gingiva twice per day for two months, yielding no significant change in the height and width of the recession, without any plausible explanation.

Topical phenytoin was also shown to have alleviated pain, possibly owing to sodium channel blockage. [23] Kadkhodazadeh *et al.* [24] used PHT suspension 1% to soothe pain and induce healing in palatal graft donor sites. PHT was proven superior in these lesions for their being superficial and thus extensive exposure to the solution.

Our study was different, as periodontal pocket wall is less exposed to drug, requiring a longer span of time for healing (3-4 weeks) even under normal circumstances. We also managed to guarantee compliance, in order to diminish confounders. Meanwhile, it would promote pharmacological efficacy, yet more research is warranted to explore the mechanism of action as well as monitoring the healing process in detail.

In a microarray analysis investigating the role of phenytoin in wound healing, Swamy *et al.* [11] explored the global gene expression profile of phenytoin (20 Mg/Ml). The most striking finding of theirs was that PHT accelerated the autocrine as well as the paracrine activities pertaining to growth factors through up-regulating the related receptors. They implied that this may explain the mechanism of action of PHT *in vivo*. As mentioned earlier, periodontitis encompasses ulcerative lesions as inseparable components. [30] Thus, though not with a certain degree of certainty, the somewhat similar mechanism can be imagined to explain our positive findings.

Yet, it still remains unknown as to why PHT fails to stop creeping attachment in gingival graft cases. [14] With the drug inducing some growth factors such as transforming growth factor β (TGF-β) and PDGF, and also up-regulating various matrix remodeling genes and receptors at the messenger RNA (mRNA) level, [11] it sounds that further research is warranted regarding the possible differences between wound/ulcerative lesions and creeping attachment. Our study, however, was limited in certain respects. We were restricted in our choice of patients as we aimed to ensure that compliance was thoroughly fulfilled. We intended to apply the drug ourselves to rule out any possible negligence and/or misapplication.

We did not also investigate the possible mechanism of action as this was beyond the scope of our research. It seems that this has to be further investigated in future studies.

Conclusion

It is shown that the application of PHT mucoadhesive paste following conventional therapy for periodontitis contributes to improve clinical parameters. Given the low cost, relative safety and above all, user-friendly application, the drug seems to be a promising choice of adjunct therapy in cases of chronic periodontitis.

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Conflict of Interest

The authors of this manuscript certify no financial or other competing interest regarding this article.

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