

Efficacy of Phenytoin Mucoadhesive Tablet versus Mouthwash on Chemotherapy-Induced Oral Mucositis: A Randomized Clinical Trial

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Abstract

Background: Oral mucositis is one of the painful, debilitating and common complications in the patients under chemotherapy for which no certain and effective treatment has not been considered. The aim of this pilot study was to evaluate the efficacy of phenytoin mucoadhesive tablets on treating oral mucositis compared with phenytoin mouthwash.

Methods: In this clinical trial, after preparation and in vitro characterization of phenytoin mucoadhesive tablets, 27 patients were enrolled from oncology department of Nemazee Hospital, Shiraz, Iran. 21 patients with oral mucositis, who had the inclusion criteria due to chemotherapy, were divided into two groups of A (11 patients received phenytoin mouthwash 0.5%) and B (10 patients received phenytoin mucoadhesive tablet). Severity of oral mucositis (WHO grading), oral pain Visual Analogue Scale and the extension of lesions (number of involved sites) were assessed on three intervals (at the beginning and one or two weeks after beginning of the study).

Results: In the first visit, there was no significant statistical difference between the two groups regarding mean age, mucositis severity and visual analogue scale. However, on first and second weeks after beginning of the study, mucositis severity, extension of lesion and visual analogue scale in both groups were significantly lower than onset of the treatment; however, no significant difference between the two groups was observed.

Conclusions: Phenytoin mouthwash and mucoadhesive tablets used for oral mucositis care in patients after chemotherapy showed significant improvement in the lesions. Patients were more satisfied with mouthwash and all the patients in this group were free of lesion after two weeks.

Keywords: Mucositis, Phenytoin, Mucoadhesive, Mouthwash

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Introduction

In addition to surgery, chemotherapy and radiotherapy are alternative treatments for cancer patients. Chemotherapy may cause complications such as oral mucositis.¹ Oral mucositis is one of the painful, debilitating and common complications in the patients who undergo chemotherapy for which no certain and effective treatment has been considered.² In several studies, oral mucositis has been observed in 40% of patients who experienced chemotherapy and almost 100% in patients received radiotherapy for which mouth is in the range of treatment.¹ Mucositis is caused by direct toxic effect on oral epithelium.^{2, 3} Increasing free radicals and inflammation in early stages will cause mucositis.⁴ Viral, bacterial or fungal infections might be added to oral ulcers which lead to dysphagia, ageusia and increases the risk of oral or even systemic infections; thus, treatment seems rational for this period.²

In order to improve symptoms such as pain and dysphagia, different treatments like diphenhydramine solution, lidocaine, milk of magnesia, Maalox, kaopectate, gentle mouthwash (salt and water) or promethazine are suggested.⁴⁻⁶

The effect of different topical medications on mucositis treatment has been investigated in different studies. Abbasi et al. studied the effect of allopurinol mouthwash on mucositis and mentioned its positive effects on mucositis prevention and treatment.⁴ Kazemian et al. also studied the effect of benzydamine mouthwash on mucositis prevention and reported significant effects.⁷ Some studies have investigated the effect of some herbal extracts such as peppermint essence or honey on treating this disease and have reported positive results.^{8, 9}

Phenytoin as an antiepileptic drug, accelerates wound healing due to stimulation of fibroblasts production, facilitates the deposition of collagen and has antibacterial effect. Topical phenytoin also had been reported to accelerate healing process in skin and mucosa wounds.^{10,11} Given that phenytoin topical complications are rare and their systemic absorption is insignificant, its

topical application in treatment of different diseases was considered by some researchers.^{5,12,13}

Other studies have indicated that this medication was also effective in healing acute and chronic inflammatory lesions such as leprosy, pressure ulcers, diabetic wounds and traumatic wounds.^{5, 14} Another study in 2012 has investigated the effect of phenytoin mouthwash on aphthous ulcers and reported positive effects.¹⁵ In a pilot study, Baharvandi et al. has indicated significant effect of phenytoin mouthwash on chemotherapy-induced mucositis.⁵ In another study, phenytoin syrup was used for patients with oral mucositis and positive effects on healing of ulcers was reported.¹⁶ Moreover, Bahri Najafi et al. suggested an appropriate formula for producing phenytoin Bucco adhesive film for oral wounds.¹⁷ Given the results of mentioned studies regarding desired effects of phenytoin, and lack of studies on investigating and comparison of different forms of topical phenytoin effect on oral mucositis lesions, we decided to perform a study based on comparison of phenytoin mouthwash effects and its muco adhesive tablet on chemotherapy-induced mucositis.

Materials and Methods

Preparation of phenytoin formulations

In order to prepare phenytoin mouthwash, appropriate amount of sodium phenytoin was dissolved in 1 L of distilled water which contain 0.1% Tween 80 and Disodium hydrogen phosphate (2.38 g/L), with adjusted pH on 7.0 ± 0.02 by using phosphoric acid. The final concentration of phenytoin mouthwash was 0.333 mg/mL.

Muco adhesive buccal tablets were prepared by direct compression method. The ingredients (10 mg sodium phenytoin and the remaining ingredient was HPMC: Chitosan; NaCMC, 25:25:50 w/w %) were weighed accurately and mixed by trituration in a mortar by pestle for 15 minutes. Afterwards, all of the ingredients were passed through sieve no.100. Finally the mixture was compressed to tablet by using Korsch single punch compression machine (Erweka, Germany). The properties of muco adhesive tablet such as

Table 1. Physicochemical characteristics of the phenytoin mucoadhesive tablets

	Weight variation (g)	Hardness (Kg/cm ²)	Thickness (mm)	%Friability	Drug content	Surface pH
Phenytoin mucoadhesive tablet	0.197 ±0.02	2.4 ±0.54	1.39 ±0.17	0.48 ±0.21	98.64±0.30	6.88 ±0.26

weight variation, hardness, thickness, friability, surface pH, swelling index and content uniformity were evaluated for tablets in vitro (Table1).

The design of clinical trial study

This clinical trial (interventional study) was designed as a prospective, comparative and block randomized study. The study population was consisted of patients underwent chemotherapy process, due to various types of malignancies, from April to August 2014. Patients were enrolled from the oncology department of Nemazee Hospital, Shiraz, Iran. This study was registered in the Iranian Registry of Clinical Trials (IRCT20130521013406N5).

All patients included in the study had oral mucositis due to chemotherapy. They were divided into two groups of A (who received phenytoin

mouthwash) and B (who received phenytoin mucoadhesive) based on block randomization. Inclusion criteria for patients included receiving chemotherapy without concurrent radiotherapy, mucositis grade 2 or 3 (WHO criteria),¹⁸ and signing the consent form. The exclusion criteria were as follows: patients with mucositis of grade 1 or 4, signs of hypersensitivity (such as sensitivity to phenytoin), lack of patient cooperation to complete the treatment process, systemic diseases with oral mucositis (such as connective tissue diseases and Sjogren syndrome) or diseases interfering with healing process of tissues (such as diabetes), and smoking and alcohol consumption.

Data was gathered by observation and interview. Patients were examined for oral mucositis and were assessed using the WHO

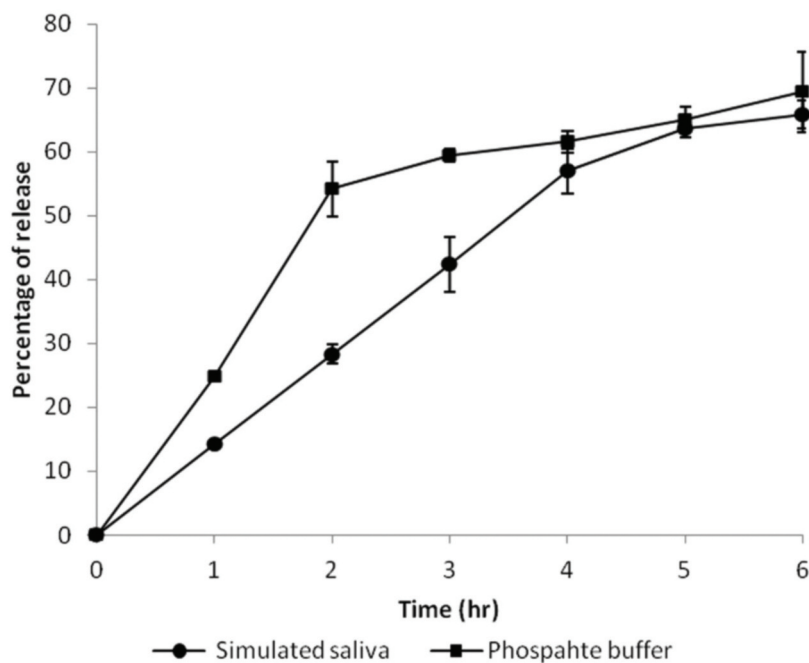


Figure 1. In vitro release of phenytoin from buccal tablets in phosphate buffer (pH=6.8) and simulated saliva (pH=6.8).

Table 2. Patients' mucositis grade at different intervals

Grade	After 1 week		After 2 weeks	
	mouthwash	tablet	mouthwash	tablet
0	7	6	11	8
1	4	0	0	1
2	0	3	0	1
3	0	1	0	0
<i>P</i> -value (within group)	0.003	0.007	0.002	0.004
<i>P</i> -value (between groups)	0.69		0.32	

grading on a scale of 0-4. Severity of oral pain was evaluated by using a Visual Analogue Scale (VAS) scoring 0-10 (0 no pain at all, 10 the worst pain possible). The extension of lesions was also recorded by the number of involved sites. These examinations were performed at three intervals: prior to the start of the study, one and two weeks after treatment.

After examination, the phenytoin mouthwash and mucoadhesive tablets which were prepared by the department of pharmaceutics, at the Faculty of Pharmacy of Shiraz University of Medical Sciences, was delivered to the patients. The verbal and written instructions for correct use of these

two medications were given to the patients. Patients in group A were instructed to rinse (gargle) 10 mL of the solution for one minute, three times a day (to distribute evenly to all parts of the oral tissues), and then spit it out (to minimize the systemic absorption). They were told to avoid eating during the first hour after treatment. The solution was prepared every day freshly. For patients in group B, two tablets should have been attached inside the cheek until being dissolved. Both treatments were continued until the complete healing of oral lesions or for a maximum of two weeks.

In this study all the ethical criteria of the

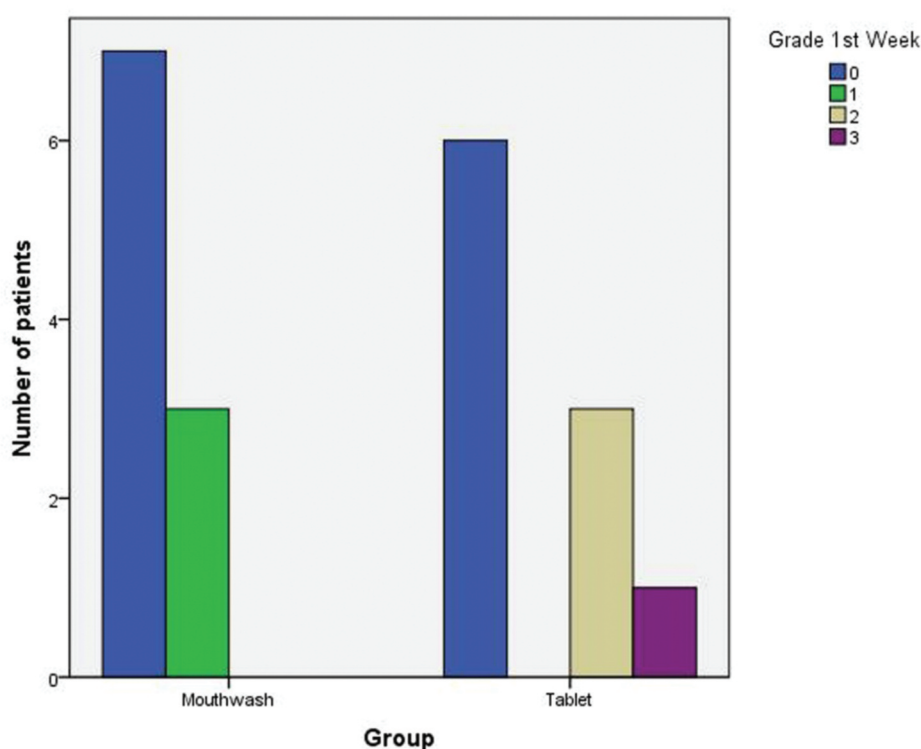
**Figure 2.** Oral mucositis severity in terms of WHO grades in both groups after one week.

Table 3. Extension of mucositis at different intervals

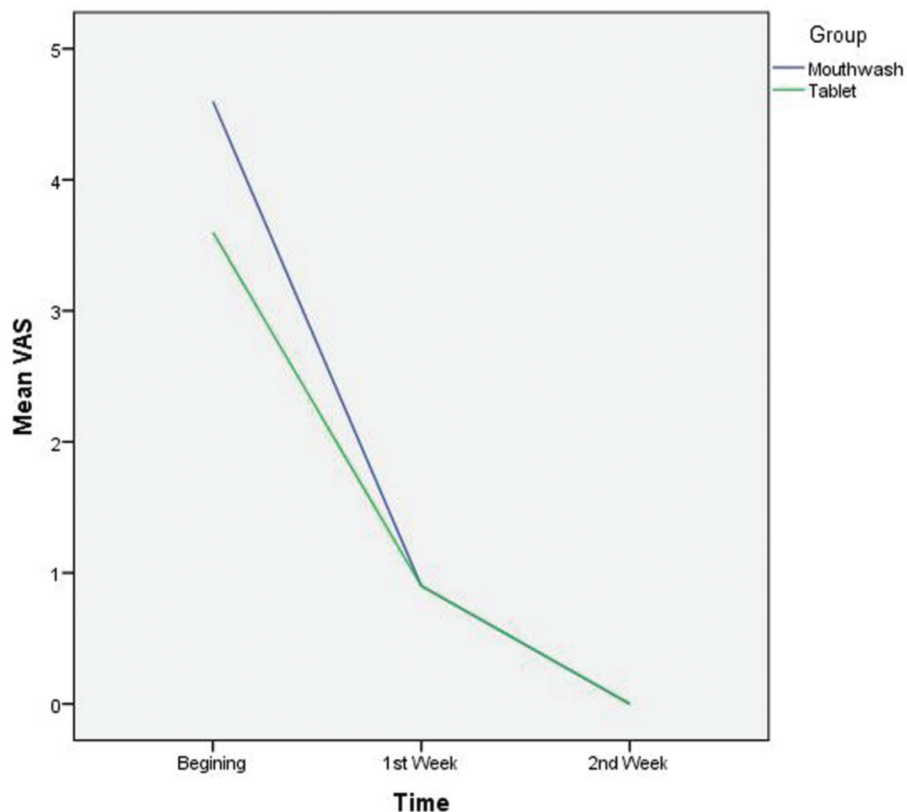
Extension of lesion	After 1 week		After 2 weeks	
	mouthwash	tablet	mouthwash	Tablet
0	8	6	11	8
1	2	1	0	0
2	1	1	0	1
3	0	1	0	0
4	0	0	0	0
5	0	1	0	1
<i>P</i> -value (Within group)	0.004	0.016	0.004	0.011
<i>P</i> -value (Between groups)	0.45		0.14	

Research Ethics Committee of Shiraz University of Medical Sciences were met, and the informed consent form was signed by all the patients. All data were analyzed by SPSS 17.0 software. The data were described by mean Standard Deviation (SD) and relative frequency. The comparison of qualitative and quantitative variables, severity of mucositis and the severity of related pain between groups were done by using Fishers exact test and Mann-Whitney, respectively. Repeated measure ANOVA was employed to determine the effect of

time on variables responses. Type-1 error (α) was considered to be equal to 0.05 and $P < \alpha$ was considered statistically significant.

Results

During the study period, 27 patients were enrolled in the study that 21 were evaluable for final analysis. Six patients were excluded from the study, two patients refused to participate early after the start of chemotherapy and four were lost due to poor cooperation and missing the clinical

**Figure 3.** Mean VAS of patients in different intervals between two groups.

appointments for oral examination (Figure 1). The sample of this study consisted of 11 men and 10 women, with ages ranging from 20 to 63 years (mean age = 42 ± 15.28 years). The patients' mean age in the groups of mouthwash and mucoadhesive tablet were 42.2 ± 16.505 and 41.8 ± 14.853 years old, respectively and their difference was not statistically significant ($P > 0.23$). Patients with majority of 90% had blood malignancy (acute leukemia was the most common, 65%) and the others had lung SCC and brain tumor. Eleven patients were placed in the study group A (phenytoin mouthwash) and 10 in group B (mucoadhesive tablet of phenytoin). On the first visit, there were no difference between the VAS, mucositis grade and extension of lesions of the two groups. ($P = 0.37$, 0.06 and 0.46 , respectively).

Mucositis Evaluation

After one week, mucositis severity (according to the WHO scaling) in groups A and B decreased significantly ($P = 0.003$ and 0.007 , respectively); however, no significant difference was observed in the severity of mucositis between the two study groups ($P > 0.69$) (Figure 2). In second week, there was also no significant difference between the two groups ($P > 0.32$); nevertheless, patients in group A had no lesions, while two patients in group B had mucositis with grade 1 and 2 (Table 2). The extension of lesions were significantly lower after one week in the both groups; however, no difference was found between group A and B in this situation ($P = 0.45$). After two weeks, all oral lesions of patients in group A were cured; however, in group B two patients had still two sites of involvement (Table 3). The median survival duration of the lesions was 6 days in group A and 7.4 in group B.

Pain Evaluation

Oral pain, assessed on the 0–10 VAS in both groups A and B after one week, was decreased significantly ($P = 0.009$ and 0.011 , respectively); however, it was similar between two study groups ($P = 0.65$). In second week, patients in group A did not report any pain (VAS=0); however, after two

weeks only one patient reported pain (VAS=5).

Lower mean number of pain with the score of 0 were observed in group B during the treatment; whereas, group A had no significant mean pain reduction compared to group B after one and two weeks ($P = 0.65$ and 1.00 , respectively). During the first week, only one patient of group B reported severe pain (VAS=7), while maximum of VAS in the patients of group A was 4 (Figure 3).

Discussion

During this study, the efficacy of two different dosage forms of phenytoin including its mouthwash and mucoadhesive tablet were assessed regarding healing the oral lesions and reducing the pain of lesions in the patients who underwent chemotherapy.

At the beginning of the study, patients in both groups had the same mean age, mucositis severity and VAS. However, after one and two weeks, mucositis severity and VAS in both groups was significantly lower than onset of the treatment. Although severity of mucositis was decreased in both groups, no significant differences were observed between the two groups. Therefore, both of phenytoin forms were effective in the treatment of mucositis. In this study, mucositis was evaluated by three criteria including WHO grading, extension of lesions and duration of healing. All of them showed alleviating of lesions in two groups. However, a previous study suggested that mucositis duration was a more valuable measurement comparing to the grading of mucositis and pain severity.⁵ In fact, most of the lesions were healed in the treatment groups after two weeks; however, there was a trace of few lesions in group B. So, the presented results showed that the use of topical phenytoin in both forms was effective on healing of mucositis lesions, similar to previous studies by Hamian and Baharvand that evaluated phenytoin mouthwash (0.5 and 1%, respectively).^{5,19} Most of the patients in both groups were free of pain after one week (70% in group A and 80% in group B). Although group B showed better results on pain reduction, no significant difference was observed between

the two groups. This result was in accordance with a previous study which was done by Hamian et al.¹⁹ and in contrast with Baharvand et al.⁵ that failed to show any significant pain reduction after using 0.5% phenytoin mouthwash.⁵ For pain measurement, VAS is one of the most valid and helpful criteria. This scale is subjective and related to the patient and may be different between individuals. Another reason for this difference may be due to time and frequency of VAS assessment. Regarding the fact that VAS is introduced only for pain measurement at a single session; nevertheless, in Baharvand study it was assessed every day by patients.⁵ Small sample size could also affect the result of the study.

It seems that the maximum effect of both types of treatments on pain reduction and healing process was established after one week (mean duration of the lesions lasted for 6 days in the group A and 7.4 for group B). As patient with several episodes of mucositis (after chemotherapy) or long duration of involvement (after radiotherapy) needs a medicine that significantly reduces this duration and its complications, this treatment can be considered advantageous. In this study, the healing effect of phenytoin mucoadhesive tablet formulation was investigated. Applying this form of medicine because of its slow releasing system without any cleansing by saliva, can induce higher concentrations in the oral mucosa.²⁰⁻²² Only few experiments evaluated the effect of this form of phenytoin;^{17,23} however, the results obviously showed that topical phenytoin formulations had significant healing effect especially in patients with oral ulcers. Patient compliance with usage of medicine had an important effect on the results and it should always be considered. In this study, more satisfactory results were obtained with phenytoin mouthwash, comparing to mucoadhesive tablet, while both of the formulations showed maximum healing effect after one week. This result was in agreement with a previous study on phenytoin mouthwash and topical cream.¹⁹ From psychological point of view, patients may prefer medication in liquid form for oral mucositis, so they have more

compliance with mouthwash formulation. Sensing an external object in the mouth, in form of tablet may reduce patient compliance. Moreover, it should be noted that using mouthwash, which provides rapid physiological relief of symptoms, is associated with a total exposure of phenytoin concentration to the lesion, while in tablet formulation the drug needs to be released from the formulation to the delivery site and it takes six hours to release the total concentration of the drug. Thus, it may take longer to show its physiological effects comparing with mouthwash.²⁴ Moreover, in this study, patients who received the mucoadhesive buccal tablet of phenytoin, had prolonged salivation, which may be another reason of their poor compliance with tablet. In addition, our result showed that after two weeks, all patients were free of lesion except two in group B who had used tablet. Also the median duration of the healing in the group A was lower than group B. This could be related to the mechanical effect of rinsing (more intense in this group) and probably contact of mouthwash with all part of oral mucosa. However, this suggestion needs further evaluation in order to make any concrete conclusions.

According to the result of a study by Buffa et al.,²⁵ for delaying each day of treatment, a reduction of almost 1% in survival for the patient is estimated. Therefore, it appears essential to consider this problem and to bring effective pain-reducing interventions as a part of nursing care.

In this study, based on the results of previous studies^{5,26} that showed the irrelevant systemic absorption of topical phenytoin, the serum level of phenytoin was not measured.

Since the sample size of this study was one of the limitations, for future studies, it is suggested to conduct randomized controlled clinical trials on larger group of patients with longer follow-up visits and also to consider more variables such as quality of life.

Conclusion

In conclusion, using both forms of phenytoin in this study (mouthwash and mucoadhesive

tablet) reduced the severity of chemotherapy-induced mucositis and pain; however, it seems that mouthwash is more suitable than its mucoadhesive tablet form.

Conflict of Interest

None declared.

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