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Effect of topical phenytoin on chemotherapy-induced oral mucositis

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ABSTRACT

Oral mucositis is one of the most common complaints of patients who had chemotherapy. Different of mouthwashes have been used to alleviate the symptoms but none of these agents help in wound healing. This study evaluates the effectiveness of phenytoin mouthwash on these ulcers. In this cross sectional study oral mucosa of 40 patients undergoing chemotherapy due to blood malignancy, was examined. All patient with oral mucositis grade 2 and 3(NCI scale) during 2 weeks after chemotherapy were assessed for severity and duration of lesions at three intervals (0, 3, 14 days) by using serial photographs and clinical observation. Oral pain severity was recorded daily by a visual analogue scale (VAS). Patient rinsed 10 ml of PHT syrup in their mouth for one minute, three or four times a day and then expectorated. To describe the qualitative data, simple frequency, means, standard deviations was used. The study population consisted of 17 female (42.5%). and 23 male (57.5%) with mean age of 29 years old .The most common affected area was buccal mucosa. During two weeks after treatment, oral ulcers disappeared totally and pain relief was seen in all subjects gradually. There is no any side effect after using of topical phenytoin in this period. Phenytoin mouthwash accelerated healing of oral ulcers due to mucositis and decreased pain.

Introduction

Oral mucositis is one of the most common complaints of patients who had chemotherapy, which manifests as erythema, edema, atrophy or ulceration (1) .The prevalence of oral mucositis after chemotherapy estimated about 15- 40% but, it may increase to 75-100% after bone marrow transplantation (1, 2). Severe Oral mucositis affect quality of life and compromise the daily functioning of patients such as swallowing, eating, drinking, and talking. It may also leads to septicemia and elongation of hospitalization period, so increases the cost of care (3). These complications may cause missing or reducing doses that affect the prognosis of disease and then increase morbidity and mortality (2, 3). Some strategies for the management of mucositis have been reported that consist of debridement of lesions, control of bleeding and pain management (1, 4). Different of mouthwashes such as alopurinol, chlorhexidine, diphenhydramine, benzydamine have been used to alleviate the symptoms (1, 5). Unfortunately none of these agents help in wound healing. One of the agents that have been accelerated wound healing is phenytoin. Phenyton (PHT) was first used clinically in control of convulsive disorders in 1938 and it has been used for wound healing since 1950 (7). The common side effect of oral phenytoin is gingival hyperplasia which led Shapiro to carry out first clinical study to evaluate the effect of this medication on gingival wounds (12). This drug has been shown to be effective on healing of ulcers with various etiologies such as leprosy, burns, traumatic ulcers, periodontal wounds, diabetic ulcers, aphthous stomatitis or lichen planus (8,9,10,11). PHT appears to stimulate fibroblast proliferation, collagen production, activity of growth factors and reduce collagens activity ,edema and bacterial load (8, 12). It also contributes to the topical pain relief by decreasing the inflammatory response and stabilizing neural fiber membranes (4, 8). Other studies have been reported that in vitro, topical PHT had no effect on human fibroblasts or keratinocytes (14).so the mechanism of this action remains a subject for debate (15) and the efficacy of topical PHT in treatment of ulcers is still controversial. In review of literature there are limited studies to investigate this efficacy on healing of oral lesions. Since topical use of PHT is safe, easy and not so expensive (8), this study conducted to determine this imaging effect on oral mucositis.

Material and Methods:

In this cross sectional study oral mucosa of 40 patients who attended oncology department of Namazi hospital, Shiraz, Iran was examined. This group was undergoing chemotherapy due to blood malignancy. Patients were recruited from December 2008 to May 2009. Sampling method was performed on an easy- to-access basis. Data were collected by observation and interview. Inclusion criteria were oral ulcers (oral mucositis grade 2 and 3, according to NCI) (16) during 2 weeks after chemotherapy and having informed consent form. Every patient who had other systemic disease that cause ulcers or interfere with wound healing was heavy smoker, was excluded from study. Patients were examined for severity and duration of oral mucositis at three intervals by using serial photographs and clinical observation with dental mirror and proper light .This examination began at the first day of treatment, 3 days and finally 2 weeks after consumption of phenytoin. Oral pain severity was recorded on a piece of paper daily by a visual analogue scale (VAS). Patient rinsed 10 ml of PHT syrup in

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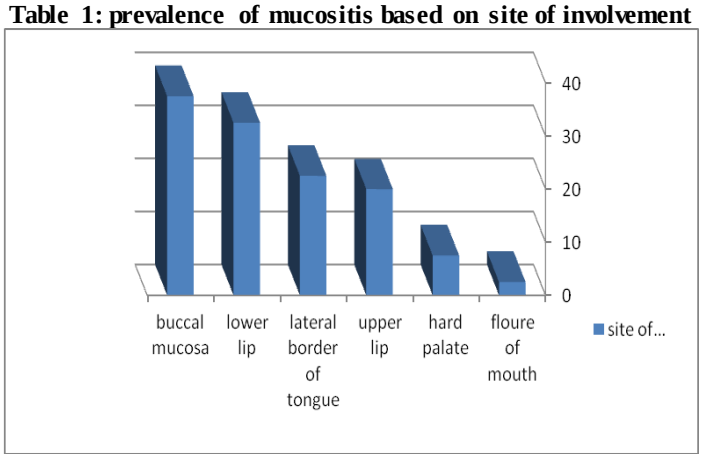
their mouth for one minute, three or four times a day and then expectorated. This administration was continued until the complete healing of oral ulcers or for two weeks. All data was analyzed by SPSS software (Version 11). To describe the qualitative data, simple frequency, means, standard deviations, ranges, and variation domains was used.

Results:

The study population consisted of 17 female (42.5%). and 23 male (57.5%) with mean age of 29 years old (15-72).In clinical examination oral ulcers in male were more than female. The most common affected area was buccal mucosa followed by lower lip, lateral border of the tongue, palate and floor of the mouth (table1). Size of ulcers varied from 2-15 mm and VAS means was 5-8 .In this study we found that three days after starting phenytoin consumption, mucositis severity was decreased and ulcers were improved in a large number of patients. During two weeks after treatment, oral ulcers disappeared totally and pain relief was seen in all subjects and drop of pain was gradually. There is no any side effect after using of topical phenytoin in this period.

Table 1: prevalence of mucositis based on site of involvement



Discussion:

There are some controversial results about effect of topical PHT on wound healing especially in the experimental models. Various etiologies such as increase fibroblast proliferation, collagen production and activity of growth factors and reduce collagen activity (8, 12); have been reported to determine this effect, but the exact mechanism is not clear. Antibacterial activity of PHT and local pain relief also has been reported in some studies, but little attention pays to its role on healing of oral lesion. Therefore we evaluated effect of topical PHT on oral mucositis.

Our data suggest that topical PHT has positive effect on healing of these ulcers after 2 weeks in all patients. this result is in agreement with several research that have been shown this effect on burns (12), diabetic ulcer(9) , aphthous stomatitis(10) and oral mucositis(4).In contrast other studies have been reported no significant effect for this medication, that may be due to study design, type of lesion and sample size. To the best of my knowledge, only one study evaluated this medicine on oral mucositis. Then there was no enough study to compare this effect.

According to our results, phenytoin reduced pain gradually that in agree with most of studies.

In conclusion, regard to results of this study due to positive effect of topical PHT on ulcer healing, pain reduction and rare side effect; we proposed PHT mouthwash (syrup) for treatment of mucositis after chemotherapy.

Even with all positive result, the use of topical PHT for healing of ulcers by FDA is not approved at present. Although, the double blinding studies with control group and randomized process(RCT) with longer follow up period and more sample size is suggested. Evaluation of systemic absorption (serum level of PHT) also is warranted.

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