Journal of Radiotherapy in Practice

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The efficacy of pomegranate flower on the radiation-induced oral mucositis in the head and neck malignancy: a phase II clinical trial

Ahmad Mosalaei[1], Maliheh Dayani[1], Mansour Ansari[1], Hamid Nasrolahi[1], Mohammad Mohammadianpanah[1], Shapour Omidvari[1], Susan Andalibi[1] and Ehsan Mohammad Hosseini[2]

[1]Department of Radiation Oncology, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran and [2]Department of Neurosurgery, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Original Article

Cite this article: Mosalaei A, Dayani M, Ansari M, Nasrolahi H, Mohammadianpanah M, Omidvari S, Andalibi S, and Mohammad Hosseini E. (2025) The efficacy of pomegranate flower on the radiation-induced oral mucositis in the head and neck malignancy: a phase II clinical trial. *Journal of Radiotherapy in Practice*. **24**(e7), 1–5. doi: 10.1017/S1460396925000032

Received: 30 August 2024
Revised: 8 December 2024
Accepted: 8 January 2025

Keywords:
Head and neck cancer; oral cavity; oral mucositis; pomegranate flower; Radiotherapy

Corresponding author:
Ehsan Mohammad Hosseini;
Email: Ehsan_m_h76@yahoo.com

Abstract

Introduction: Oral mucositis (OM) emerged in the late 1980s to describe the adverse effects of radiation therapy (RT) on the oral mucosa. OM is the most common and clinically significant acute adverse effect of radiotherapy for head and neck cancer. Symptoms of OM vary from pain and discomfort to an inability to tolerate food or fluids, and it may affect the quality of life, breaks in treatment, hospitalisation, and therefore cancer treatment and outcome. This study aimed to evaluate the pomegranate flower's efficacy in preventing and treating radiation-induced mucositis due to antioxidant, anti-inflammatory and anti-cancer effects.

Methods and materials: This phase II clinical trial was conducted on 50 patients (case and control) with head and neck malignancy. Patients in the case groups were instructed to rinse their mouths with 5 mg Pomegranate powder with 15 cc of sterile water three times a day. The patients in the control group rinsed their mouths with normal saline mouthwash, which is the most relatively accepted preventive and supportive care in this setting. The onset and degree of radiation-induced mucositis were graded during treatment, with 'WHO mucositis grading' and the 'quality of life questionnaire' (QLQ-OES18).

Result: Forty-eight patients were analysed. There was a significant difference between the two groups on onset and severity of mucositis in the two groups. There were longer intervals for the incidence of different grades of mucositis in the case group, in comparison with the control groups (P value < 0·05). Also, Complaints of dysphagia in the case groups were lower than in the control.

Conclusion: Pomegranate flower seems to be effective at the time of onset, and the severity of oral mucositis during head and neck radiation. It could be a simple, potent, and inexpensive agent, which is easily available.

Introduction

Oral mucositis (OM) is one of the most common adverse effects in radiotherapy of head and neck cancer (HNC). Mucositis may compromise nutritional status, and affect cancer treatment and patient's quality of life. Severe OM may lead to hospital admission compromise the outcome of cancer therapy and increase the cost of care.[1–3] The incidence and severity of mucositis will vary from patient to patient.[4,5] All patients who receive radiation therapy (RT) for HNC develop some degree of OM. OM occurs in about 80% of patients and severe OM has been reported in up to 60% of patients with standard RT, 100% of those with hyperfractionation or accelerated hyperfractionation[6] and more than 90% of patients receiving chemoradiation therapy.[4] The incidence of OM has been reported to vary. Some risk factors include advanced age, gender, smoking and alcohol consumption, altered oral intake, preexisting periodontal disease, low body mass index, poor functional status, low leukocyte count, advanced disease and stage, a prior history of severe mucositis, type of malignancy and various comorbid conditions. The radio-induced mucositis process begins at the start of radiotherapy treatment. In patients who received a standard dose of 200cGy daily for 6–7 weeks, OM presents as erythema of the oral mucosa in the first 2–3 weeks then peaks during the 4–5 weeks of treatment and continues for 2–4 weeks post radiotherapy,[2,7] depending on the severity of the lesions and the addition of chemotherapy or target therapy. Management of OM in HNC RT patients remains symptomatic. Oral hygiene and avoiding hot and spicy food, alcohol and smoking are crucial in preventing and reducing the severity of OM. Mouthwashes with normal saline, soda bicarbonate, benzylamine (non-steroidal analgesic and anti-inflammatory),[8] doxepin,[9] palifermin[10,11] and certain proprietary coating agents, treatment of coexisting infection (topical and systemic), opioids if OM progress from a week up to strong(morphine or fentanyl)[12] are effective in the prevention and treatment

of RT- induced OM.[13] Pomegranate is used for the treatment of various diseases, such as ulcers, hepatic damage and snakebite.[14] Pomegranate is rich in many fatty acids that exert various biological activities such as antioxidant, anti-inflammatory, anti-cancer, anti-atherosclerotic and antibacterial properties.[15,16] Therefore, pomegranate has been examined for its possible antioxidants and radioprotective effects against OM in the radiotherapy of HNC.

Although many studies about cancer treatment-related mucositis have been done, the optimal treatment strategies for oral complications and related sequels are unknown. Many approaches exist to prevent and treat oral mucositis; most of these are not generally accepted and are mainly empirical.[17] Other antioxidants that have been tried for efficacy with oral mucositis include vitamin C, zinc, and glutathione.[18,19] The lack of extensive, well-designed randomised clinical studies adds to the confusion.

Materials and Methods

This phase II clinical trial was conducted on 50 patients in Shiraz University of Medical Sciences. The study was approved by the Clinical Research Ethics Committee of Shiraz University of Medical Sciences by the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Additionally, written informed consent was obtained from all the patients before the trial.

At least 24 patients in each arm were required to ensure 80% power at the 5% significance level for detecting a 40% improvement in the clinical complete response rate from 30% to 70%.

Fifty patients with a new histopathological diagnosis of any site of head and neck Squamous Cell Carcinoma (SCC) without a history of surgery for their cancer were enrolled in this study. They were randomised according to the random digits from www.random.org into two groups. Each group consisted of 25 patients. Eligible patients for this study were those who planned to receive radiation to 1/3 or more than the oral cavity mucosal surface, had no previous history of radiation to this site, or receiving systemic chemotherapy. Radiotherapy was done with Electa LINAC, and the 6 MV photon ant treatment planning system was Prowess. The radiotherapy dose was at least 6000 cGy, 200 cGy/fraction, 5 days a week. Treatment was usually given through two parallel opposed fields for the primary tumour site and lower neck. The use of other oral care medicine was prohibited during the trial. For those who received concurrent chemotherapy, the agents were cisplatin or cetuximab. Cisplatin was administered at 40mg/m^2 weekly and for cetuximab, it was 250mg/m^2. The exclusion criteria were a previous history of radiation or chemotherapy, allergy to the Pomegranate's products and receiving chemotherapy other than cisplatin or cetuximab and patient refusal. Patients were allowed to exit from the study whenever they wanted.

Mandatory pretreatment evaluation included a complete history and physical examination and biopsy-proven diagnosis of malignancy. Metastatic evaluations included a neck and chest CT scan. They were also evaluated for oral hygiene, the state of gingiva and teeth by a dentist. They were treated if they had dental foci infections or other problems before treatment. Patients in the case groups were instructed to rinse their mouths with 5 mg Pomegranate powder with 15 cc of sterile water three times a day.

The patients in the control group rinsed their mouths with the normal saline mouthwash. They were visited weekly during radiation up to receiving 60 Gray. Both groups of patients were advised to swallow the mouthwashes.

Table 1. Patient information in control and case groups

Variable	Treatment group		P value
	Study Group	Control Group	
Patients number			
Sex	24	24	1
Male	21	20	
Female	3	4	
Age(mean ± SD)	52.87±14	55.54±10	0·73
Stage			
Early	20	18	0·48
Advanced	4	6	
Smoking			
Yes	15	14	0·768
No	9	10	
Concurrent Chemotherapy			
Cisplatin	16	16	1·000
Cetuximab	6	5	
No	2	3	

SD, standard deviation.

Also, all patients were visited weekly by a radiation oncologist who was unaware of the case or control group and was asked to complete the quality of life questionnaire (QLQ-OES18) at the end of treatment. These self-reporting questionnaires consist of 18 questions assessing dysphagia, deglutition, abdominal/gastrointestinal symptoms, eating difficulties and painare related to the side effects of chemotherapy/radiotherapy.[20] This questionnaire is translated into Persian and is a valid and reliable one for Iranian patients.[21] We used it because of items related to oropharyngeal dysfunction.

Results

In our study, a total of 50 patients participated. One patient discontinued the use of Golnar after the second week of treatment. Also, one patient in the control group was excluded because of cessation of treatment. There was no major difference in gender, age and smoking in the two groups. Also, no difference was detected in the type of chemotherapy, different types of malignancy and TNM (T: Tumor; N: lymph Node; M: metastasis) staging. The individuals' ages ranged from 26 to 75 years old, with a mean of 54 years old and a median of 57 years old. The mean age in the case group was 53 (±14) years old and in the control group, it was 55·5 (± 10) years. Homogeneity in the two groups was evaluated with the Mann–Whitney test; no statistical difference was detected (p value = 0·73) Table 1.

The homogeneity of the gender of the two groups was evaluated, and no difference was between the two groups. (p value = 1). The male gender was more prevalent (85%) in both groups. Among the patients, 60·5% were smokers (62·5% in the case groups and 58·5% in the control group) without any statically significant differences. (p value > 0·99). In our study, 67% and 23% received cisplatin, cetuximab as chemo-radiotherapy. Ten per cent received radiotherapy alone. No significant difference was found in the two groups using Fisher's exact test. (p value > 0·99).

https://doi.org/10.1017/S1460396925000032 Published online by Cambridge University Press

Table 2. Comparison of symptoms reported by questionnaire, between two groups

Variable	Treatment group		P value
	Study Group	Control Group	
Dysphagia (mean±SE)	42.13±2.8	50.61±2.8	0.000
Eating (mean±SE)	45.19±3.7	47.39±3.74	0.68
Reflux (mean±SE)	49.76±4.082	50.231±4.082	0.52
Pain (mean±SE)	52.87±14	55.54±10	0.518

According to the manual of our questionnaire, three questions related to the symptoms of dysphagia were evaluated together. The mean score of the case group was 42·13(2·8) and 50·61(2.8) in the control group (p value = 0·000). It means the complaint of dysphagia in the case groups was lower than the control group during treatment. Three questions were related to eating problems. There were no differences between both groups (p value = 0·68). Pain score had changed over time with increasing severity (p Value = 0·001), but there was no remarkable difference between the two studied groups (p value = 0·518) The mean changes in the reflux scoring in the two groups were the same without time effect (p value = 0·124). Within the time, the changing process happened (p value < 0·001) but with the same pattern in the two groups (p value = 0·322) and without a significant difference (p Value = 0·52) (Table 2).

Discussion

The primary endpoint of our study was the patient-reported measurement for oral symptoms (OES18 questionnaire). There was no difference between the two groups by age, gender, smoking, type of chemotherapy and also the stage of the disease.

The mean score of dysphagia in the case group was 42·13 2.8 and 50·61 2·8 (mean SE) in the control group with a significant difference (p value: 0·00). It means that complaint of dysphagia in the case groups was lower than the control group during treatment. Also, there was no difference in pain, reflux and eating problems, according to the questionnaire between the two groups. The mean time to the onset of oral mucositis and incidence of different grades according to the World Health Organization criteria (objective evaluation) in the case group was significantly later in comparison with the control group.

It seems that zinc sulfate administration is beneficial in decreasing the severity of radiation-induced mucositis and oral discomfort during head and neck radiation therapy. However, there is a study that showed no significant benefit in relieving oral mucositis and pharyngitis with satisfactory side effects.[22,23] These conflicting results should be confirmed by additional evaluation in randomised studies with a larger number of patients.

Amifostine is a thiol radio-protectant pro-drug that has been approved by the US Food and Drug Administration for salivary gland protection during radiation. It acted as a free-radical scavenger and resulted in decreased pro-inflammatory cytokine levels[24] The protection of normal cells results in improved vascularity. A systematic review showed that amifostine-related studies for the prevention and treatment of oral mucositis have found deficient evidence to support its use in any cancer treatment setting for this purpose. Moreover, additional well-designed research is needed to explain the role of amifostine as an intervention for oral mucositis.[25]

Chlorhexidine diminishes mucosal colonisation by micro-organisms. However, this effect has never been interpreted into clinical benefits for patients who are receiving either high-dose radiotherapy or chemotherapy or conventional.[26] In a randomised trial in patients with head-and-neck tumours receiving radio-therapy, chlorhexidine was discovered to be less effective than a placebo rinse and also more toxic.[27]

Several studies have been done, and its relative effects on oral pain, duration and severity of mucositis are detected. A meta-analysis of using GM-CSF in radiation-induced mucositis has shown some benefits.[28,29] On the other hand, there are some studies that showed no effect of it on mucositis.[30–32]

Several studies suggested that pomegranate extract might be useful in the control of adherence of different bacteria in the oral cavity and reductions in oral plaque.[33,34] Gingivitis is an inflammation of the gums in reaction to bacterial plaque sticking to tooth surfaces. It needs treatment because of the subsequent adverse effects such as periodontal disease and tooth loss.

Sastravaha and his colleagues showed that the use of pomegranate peel extract chips for subgingival use resulted in decreased plaque. Moreover, significant decreases in pocket depth and bacterial attachment compared to placebo were observed. Also, a marker of inflammation (IL-1beta) was lower at and six months compared to baseline.[35] Few studies have shown the invitro susceptibility of H-pylori to a pomegranate methanol extract.[36]

Flowers of pomegranate, known as Golnar in Iranian traditional medicine, are used in diarrhoea, dysentery, hyperacidity, cardiotonic, dental disorders, anaemia, piles and cough.[37] It contains a variety of secondary metabolites such as polyphenols and flavonoids with strong antioxidant and anti-inflammatory activity.[38,39] Pomegranate flower extract was beneficial for wound healing in diabetic rats when compared with the control.[40,41] The powdered flower buds are used in bronchitis. Many studies have been done on the different parts of pomegranate, but no adverse effect has been reported.[42,43]

The pomegranate flower (Golnar) showed a significant reduction in the wound area and decreased inflammatory cells and antioxidant activity.[40,44,45] Studies showed that pomegranate rinse reduced activities of cell injury by this plaque. Moreover, it increased the activity of ceruloplasmin, which protects against oral oxidative stress. The authors of this trial suggest the possibility of the use of Pomegranate extracts in oral health products such as toothpaste and mouthwash.[46,47]

Abdollahzadeh and his colleagues showed that pomegranate extract had antibacterial activity against S.mutans and Porphyrymonas gingivalis but not against actinomyces viscous.[48] Several studies suggested that pomegranate extract might be useful in the control of adherence of different bacteria in the oral cavity and reductions in oral plaque.[33,34]

In Iranian traditional medicine, pomegranate flower has been used for oral problems, such as an aphthous lesion, gingivitis and as anti-inflammatory and also antibacterial agent. Many studies have been done on different parts of pomegranate, but no adverse effect has been reported.[43,48] There was no study on the efficacy of Golnar on mucositis in the literature. The philosophy of using pomegranate flowers (Golnar) in radiation-induced oral mucositis was derived from the basic research evidenced by Golnar's anti-inflammatory activity and also folkloric-based data.

According to our findings, it appears that Golnar has a preventive effect on mucositis and also on its progression. However, this study had some limitations (no blinding, no placebo

https://doi.org/10.1017/S1460396925000032 Published online by Cambridge University Press

and small groups). We studied it on patients with radiation to 1/3 or more of the oral cavity apart from the type of cancer. Although no difference was found between the two groups in our study, it would be considered that its benefit may be specific for certain cancer types and treatment and field of radiation and patient characteristics.

In conclusion, Golnar seems to be effective for the time of onset, and the severity of oral mucositis during head and neck radiation. It could be a simple, potent and inexpensive agent, which is easily available. However, there is a need for future well-designed and randomised trials with sufficient numbers of participants to validate this effect.

Since mucositis is multifactorial, the best measures should be taken to achieve maximum control by influencing different pathways. So it seems that a combination of modalities is the trend of care in the future and combined preventive therapy strategies are needed to ensure more successful results.

Acknowledgements. None.

Financial support. None.

Competing interests. None.

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