

Investigation of the effect of *Calendula officinalis* extract on preventing radiotherapy-induced oral mucositis

Babae N¹, Moslemi D², Khalilpour M³, Vejdani F⁴, Bijani A⁵, Moghadamnia A⁶, Ameri A⁷

1. General dentist, Assistant professor of oral diseases, Babol University of Medical Sciences, Babol, Iran
2. Radiation Oncologist, Babol University of Medical Sciences, Babol, Iran
3. General dentist, Babol University of Medical Sciences, Babol, Iran
4. General dentist, Babol University of Medical Sciences, Babol, Iran
5. General practitioner, Non-Communicable Pediatric Disease Research Center, Babol University of Medical Sciences, Babol, Iran
6. Professor of pharmacology, Department of Pharmacology, Babol University of Medical Sciences, Babol, Iran
7. Associate professor of radiation oncology, Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author: Moslemi D

Email Address: moslemi_d@yahoo.com

Abstract

Introduction: The objective of this study was to investigate the effect of *Calendula officinalis* mouthwash on preventing radiotherapy-induced oral mucositis

Materials and methods: Patients with head and neck cancers referred to our center for radiotherapy were divided into two groups, one receiving drug and the other group receiving placebo. Patients in the drug group received 2% *Calendula* extract. Oral Mucositis Assessment Scale was used to evaluate oral mucositis intensity at the end of each week. The scale of mucositis at the end of each week was compared between groups.

Results: *Calendula* extract significantly decreased the intensity of oral mucositis as compared to placebo at the end of the 2nd ($p=0.019$), 3rd ($p<0.0001$) and 6th week ($p=0.031$).

Conclusion: *Calendula* extract could be effectively used to decrease the intensity of radiotherapy-induced oral mucositis.

Key words: Radiotherapy, mucositis, *Calendula officinalis*.

Introduction

Oral Mucositis (OM) is a painful, treatment limiting, debilitating and resource-draining toxicity which results from radiotherapy and chemotherapy used for the treatment of cancer⁽¹⁾. OM that results from cancer therapy is defined as inflammation of the oral mucosa, typically manifesting as atrophy, swelling, erythema and ulceration in a stepwise manner⁽²⁾. OM affects almost all patients during the course of radiotherapy for the cancer of the mouth, oropharynx and nasopharynx, and also in two thirds of the cancers of larynx and hypolarynx⁽³⁾. OM is described as a five-phase process including initiation, primary damage response, signal amplification, ulceration and healing⁽⁴⁾. Radiotherapy-induced OM is a contagious condition since the patients are treated with incremental

doses of radiation over a 4 to 7 week period (2 Gy to 70 Gy per day). When using 30 Gy of radiation, ulceration, covered by a pseudomembrane, develops. Ulcerations resolve after 3 to 4 weeks following the completion of the radiotherapy course⁽⁵⁾. Historically, OM risk has been correlated with patient and treatment characteristics⁽⁶⁾. Treatment-related variables include the total dose of radiation, field size, fractionation, and the type of ionizing beam⁽³⁾. Age, body mass, and gender are believed to be possible patient-associated risk factors⁽⁶⁾.

To date, no approved intervention has been found for the prevention or treatment of radiotherapy-induced OM. Several strategies are being actively investigated, which are based on

the mechanistic interruption of one or more of the pathobiological pathways causing the condition ⁽⁷⁾. The plant *Calendula officinalis*, commonly known as Marigold, is used in the West and Asia for its anti-inflammatory properties ⁽⁸⁾. According to some reports, the extract of the plant possesses many pharmacological properties including antioxidant, anti-inflammatory, antibacterial, antifungal, and antiviral ⁽⁹⁾. Pommier et al. showed that *Calendula officinalis* can prevent acute dermatitis during breast cancer in a phase III trial ⁽¹⁰⁾. It has been shown that this plant has cytotoxic effects on tumor cell lines in vitro and anti-cancer properties in vivo ⁽¹¹⁾. There is a positive correlation between the severity of mucositis in the head and neck cancer patients and the level of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF)- α , Interleukin (IL)-1, and IL-6 ⁽¹²⁾. Reactive Oxygen Species (ROS), which are generated in the initiation phase of mucositis, later initiate a series of interacting biological events in the primary damage response phase that ultimately contributes to progression to the ulceration phase. Mucositis induced ulcers are deep and prone to be colonized by oral bacteria. The bacteria residing on the ulcer surface have an active role in the mucositis process. In granulocytopenic patients, there is a risk of bacteremia or sepsis when bacteria invade the submucosal vessels ⁽⁵⁾. According to the known properties for *Calendula officinalis* such as anti-inflammatory, anti-bacterial, antioxidant activities and the pathobiology of OM, we found it interesting to evaluate its effect on radiation-induced OM.

Materials and methods

Patient Selection

This study was conducted as a prospective

placebo-controlled clinical trial. The protocol was approved by Ethics Committee of Babol University of Medical Sciences, Babol, Iran and was registered in the Iranian Registry of Clinical Trials. In this study, forty patients (20 males and 20 females) with a diagnosis of head and neck cancer from Shahid Rajaie Radiotherapy Center (Babolsar, Northern Iran) were recruited. Patients above 45 years of age with a planned prescription dose of at least 40 Gy to the entire oral cavity were included after stratification based on sex. Patients with allergy to mouthwash ingredients, pregnant women, patients with preexisting oral disease for reasons other than cancer, patients receiving interfering drugs (anti-inflammatory, antibacterial) and patients with any uncontrolled systemic disease were excluded. Informed consents were taken from the patients.

Study design

The patients who met the inclusion criteria were entered in one of the two groups (drug or placebo) sequentially. In the end, there were an equal number of male and female patients in each group. An accumulative dose of radiotherapy between fifty and sixty Gy with a dose per fraction of two Gy, five fractions per week were prescribed based on the radiotherapy plan. From the beginning of the radiotherapy course, patients were given 5 ml of either placebo or 2 % *Calendula* mouthwash, three times per day, to be held for at least one minute in the oral cavity. All patients in both groups were asked to wash their mouths with normal saline at least 5 times per day and after each meal. Brushing the teeth was advised two times per day using non irritating toothpaste. All patients were recommended to use soft and nonirritating foods. They were also prohibited from using any

Table1: Mean OMAS scores in Calendula and placebo groups

Calendula/ Placebo	OMAS Scores (Mean +/- SE)					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Calendula	1.35 +/- 0.082	5.50 +/- 0.172	8.40 +/- 0.199	13.50 +/- 0.365	11.15 +/- 0.430	11.40 +/- 0.303
Placebo	1.65 +/- 0.108	6.80 +/- 0.194	11.05 +/- 0.258	15.30 +/- 0.393	12.70 +/- 0.390	13.35 +/- 0.302
P value	0.165	0.019	0.000	0.230	0.165	0.031

drug without prescription. The examiner and the patients were blind to the tested mouthwashes. Calendula and placebo mouthwashes both had the same taste, shape and odor. The intensity of OM was measured in all individuals using the OMAS score, a semi quantitative tissue score that is a validated reliable scale with demonstrated intra and interobserver reproducibility⁽¹³⁾. In the evaluation of OM based on OMAS, the oral cavity was divided into 9 areas including lower and upper lips, right and left cheek, right and left ventral and lateral tongue, floor of the mouth, soft palate/ fauces, and finally the hard palate. Each area was examined for two items of erythema and ulcer/ pseudomembrane. Erythema was scored 0, 1 or 2 meaning no erythema, not severe erythema, and severe erythema respectively. Ulcer/ pseudomembrane was classified as 0, 1, 2 and three for no lesion, lesion less than 1cm², lesion 1-3 cm² and lesion larger than 3cm² respectively. Indexes were taken at the end of each week during the treatment period. The minimum and maximum scores for each patient were 0 and 45 respectively⁽¹⁴⁾. For each week of treatment during the therapy a separate OMAS index was calculated. The OMAS index of each week was compared between drug and placebo groups.

Statistical analysis

Data were analyzed using t-test, Mann-Whitney U test and ANOVA repeated measures. The P values less than 0.05 showed a statistically significant difference.

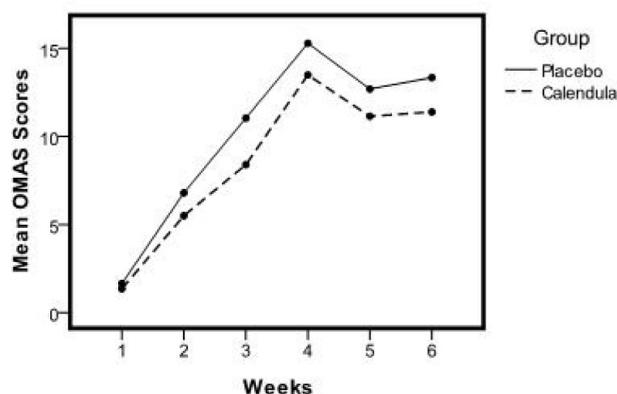
Mouthwash preparation

Dry and pulverized Calendula officinalis flowers were provided from local resources. The extract of Calendula was made by maceration in ethanol 70° for 72 hours. For preparing the vehicle of the mouthwash, we used the following ingredients: Carboxymethyl cellulose (CMC) (15 g), glycerin (25 g), methylparaben (105 g), propylparaben(0.2 g), ethanol 95°(10 ml) and distilled water (up to 1000 ml). The vehicle as the base of the mouthwash was prepared as follows: first, CMC was dissolved in about 250 ml distilled water; then, distilled water was added gradually to reach a total volume of 1000 ml. Afterwards, methylparaben and propylparaben were dissolved in glycerin at 70°C to 100°C and then, 100 ml of the primary extract (CMC+DW) was added to the compound. After this stage, 10 ml of ethanol 95° was added and finally, the remaining of the primary extract was added to this mixture. After the mouthwash base was prepared, we added 20g Calendula extract to the total volume of 1000 ml and mixed it until it became uniform to provide 2 % Calendula mouthwash (adding 20 gram to 1000 ml does not give a 2% solution, to prepare a 20 percent solution one should add 20 Calendula extract ml to 980 ml mouthwash base). The placebo mouthwash was the mouthwash base which was similar to the Calendula mouthwash in odor, shape, and taste.

Results

A total of 40 patients were evaluated (20 male and 20 female), with an age range of 46-72

Figure 1: Mean OMAS scores in Calendula and placebo groups.



years (mean age: 55.2 in the Calendula group and 52.8 in the placebo group). Two patients were excluded during the course of study due to using benzydamine mouthwash and at the end of study it was determined that these two patients had both received the placebo. None of the patients in the Calendula group received medication for OM severity and radiotherapy was not ceased for this reason. Significant difference was noted between the Calendula and placebo groups at the end of the 2nd ($p=0.019$), 3rd ($p<0.0001$), 6th ($p=0.031$) week and the mean OMAS scores were lower in the Calendula group (Table 1 and Figure 1).

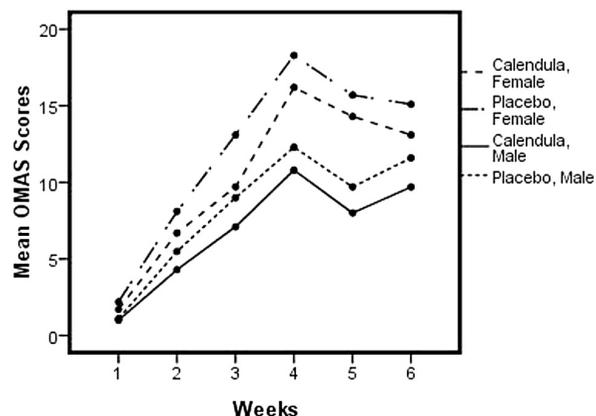
The mean rank of OMAS scores was also lower in week one, 4 and 5 but the difference was not statistically significant. According to the repeated measures test, index differences between Calendula and placebo were generally significant in all 6 weeks and the OM mean rank was less in Calendula group ($p=0.048$). Although the OM mean rank was higher in women as compared to men, Calendula had better results in both genders in comparison with placebo (Figure 2).

Discussion

OM is reported as the worst side effect of cancer therapy by patients⁽¹⁵⁻¹⁶⁾. Triottie et al. stated that the incidence of radiotherapy-induced OM in head and neck cancer patients was more than 80%⁽¹⁶⁾. All processes, in a stepwise pathobiologic process causing OM, begin within seconds after starting irradiation or chemotherapy administration. While destruction occurs within the sub-mucosa and both direct and indirect destruction of epithelial stem cells start almost immediately, there is a lag between

the damage at the molecular and the cellular level and its clinical manifestations. In administration of fractionated radiation, the precipitating events that lead to extensive mucositis occur in daily increments. When biological changes induced by radiotherapy accumulate, they can cause an extensive damage that culminates in the destruction of intact mucosa⁽⁵⁾; therefore, we administered the placebo and Calendula mouthwashes from the beginning of the radiation therapy and did not wait for clinical manifestations of OM to start. In this study, we matched two groups (placebo and Calendula) for the possible effect of the gender. Also because the age affects the intensity of OM we only studied patients older than 45 years of age^(36, 37). A large number of agents and strategies have been studied for preventing or treatment of OM such as growth factors, cytokines, antibiotics, anti-inflammatory agents, cryotherapy and mucosal protectors⁽¹⁷⁻¹⁸⁾ however, most interventions have been proven to be ineffective and current clinical management of OM is mainly palliative and focused on pain control⁽¹⁹⁾. To date, no study has investigated the effect of Calendula officinalis on radiation-induced OM. Many beneficial activities for this plant are mainly related to the various secondary metabolites content such as polyphenols, cartenoids, triterpenes and essential oils⁽²⁰⁾. The essential oils present in this herb possess many medicinal properties⁽²¹⁾ with several therapeutic properties such as, anti-inflammatory, anti-tumorogenic activities⁽²²⁾ and cicatrizing⁽²³⁾. In addition, the in vitro anti-microbial activities of its oils have been proven⁽²⁴⁾. The increase in gram negative bacteria that is seen during ulceration needs to

Figure 2: OMAS scores in Calendula and placebo groups based on patients' sex.



be reestablished by normal bacterial proportions for spontaneous ulcer resolution irrespective of bacterial numbers which may increase by more than 300% as compared to baseline⁽²⁵⁾. The plant is also believed to have anti-oxidant and wound healing properties⁽²⁶⁾. The initiation phase of radiotherapy or chemotherapy-induced injury is a critical first step in the development of mucositis, in which clonogenic cell death and the production of Reactive Oxygen Species (ROS) by injured cells are the two most noted components. "The initiation phase is a gatekeeper. Delaying or stopping it can prevent or minimize regimen-related injury"⁽²⁷⁾. Considering the fact that Calendula has antioxidant properties, it may act against ROS and prevent or delay the initiation phase. In one study which evaluated Laser Activated Calendula Extract (LACE), the LACE showed to be capable of in vitro inhibition of tumor cell proliferation when tested on a wide variety of human and murine tumor cell lines⁽⁷⁾. The inhibition range was from 70 to 100%. Interestingly, the same extract showed an opposite effect on peripheral blood lymphocytes and natural killer lymphocyte cell line in which the extract induced in vitro proliferation and activation of these cells⁽²²⁾. According to this study, LACE has immunomodulatory activities⁽²²⁾. It has been reported that ionizing radiation causes reduction of the helper T (Th) 1-like function but not the Th2-like function and so Th1 to Th2 clone ratios are shifted in favor of Th2 cells⁽²⁸⁾. This Th1/Th2 imbalance may result in the disruption of tissue homeostasis and lead to toxicity⁽⁷⁾. More precise evaluation of the effects of Calendula on immunomodulatory activities may be needed to see if this activity is beneficial in controlling OM or makes it worse. There is very few safety concerns related to Calendula. The internal use of Calendula products should be avoided in the early stages of pregnancy due to its ability to stimulate menstruation; also, allergic hypersensitivity may cause a problem in individuals sensitive to other members of the plant family Asteraceae⁽²⁹⁾. Among few clinical studies related to various uses of Calendula, a few stand out. In one study, Calendula extract toothpaste was effective in reducing plaque and bleeding indexes and authors concluded that anti-inflammatory, anti-bacterial and anti-oxidant properties of Calendula may be responsible for the above-mentioned effects on gingivitis⁽³⁰⁾. Loggia et al. found that

Calendula flowers extract ointment was effective in relieving the pain associated with cracked or tender nipples⁽³¹⁾. Duran et al. showed positive preliminary results for the use of Calendula ointment in the treatment of venous leg ulcers⁽³²⁾. Another study showed that a Calendula cream preparation was protective against irritant contact dermatitis caused by exposure to sodium laurel sulfate⁽³³⁾. Moreover, as mentioned earlier, Calendula is highly effective in the prevention of acute dermatitis in cancer patients receiving postoperative irradiation⁽¹⁰⁾. Although dermatitis and OM have different pathobiology, the above mentioned study was the closest one to our research among reviewed clinical trials. Generally, there are few studies concerning the effects of herbal extracts on OM. Data of one study which evaluated the effect of Chamomile mouthwash on the prevention of 5-FU-induced OM did not support its efficacy⁽³⁴⁾. In contrast, another study which evaluated the effect of Chamomile mouthwash showed its beneficial effects in reducing post chemotherapy induced OM⁽³⁵⁾ which may be explained by higher frequency of use (4 times vs. 3 times daily). Another major difference between these two studies was the application of cryotherapy with ice cubes for 30 minutes before chamomile mouthwash administration in the former study, which may have contributed to the resultant effect of Chamomile mouthwash.

The fact that Calendula mouthwash could not completely prevent OM can be explained by the complicated pathobiology of OM. It is also possible that higher doses of Calendula are required or it may need to be applied over a longer period of time. Furthermore, different protocols of herbal extraction should be considered while evaluating its effects. Regarding the comparison of OM in two genders, several studies have reported that women develop more severe stomatitis, and the side effects of radiotherapy such as OM are more severe in the female gender⁽³⁶⁾ which is in line with our findings.

Conclusion

Calendula officinalis might be effective on decreasing OM intensity, but cannot completely prevent it. Further research is required to determine its optimal dose and frequency of use in order to effectively prevent OM or decrease its intensity.

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