

The Gulf Journal of Oncology

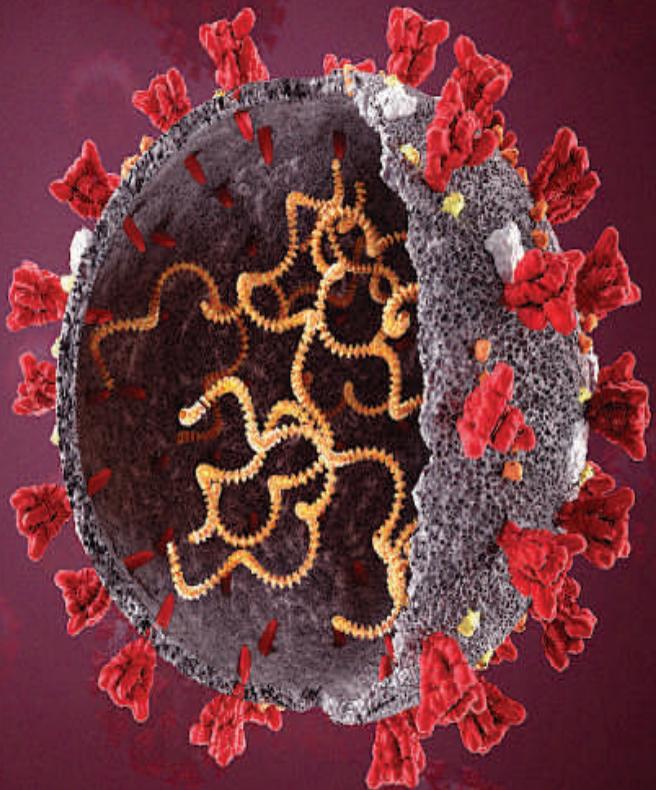


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Comparative Study of the Effect of Licorice Muco–adhesive Film on Radiotherapy Induced Oral Mucositis, A Randomized Controlled Clinical Trial

Fahimeh Pakravan,¹ Niloofer Heydari Salehabad,² Fatemeh Karimi,² Mehdi Nasr Isfahani³

¹Department of Oral Medicine, Dental Implants Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran

²Dental Students Research Committee, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran

³Department of Emergency Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Oral mucositis is a common complication induced by radiation in head and neck cancer patients. OM can cause pain, dysphagia, dehydration and impaired quality of life. The main objective of this study was to assess the effectiveness of licorice mucoadhesive film on symptoms of head and neck radiotherapy–induced mucositis.

Methods: sixty head and neck cancer patients who have been scheduled to undergo radiotherapy were randomly assigned to receive radiotherapy plus licorice mucoadhesive film (30) or radiotherapy plus placebo mucoadhesive film. In this double blinded randomized clinical trial, oral mucositis was estimated by world health organization scales, a quantitative scale, and symptoms were evaluated by visual analog scale.

Results: The results showed a meaningful difference in pain score between two groups in third and fourth weeks (P–value <0.05). Also, there was a significant difference in scale of mucositis between the two groups in weeks 3 and 4 (P–value <0.05). However, there were no meaningful differences with regard to pain and scale of mucositis in weeks 0, 1, 2. (P–value>0.05)

Conclusion: This study showed that licorice mucoadhesive film can be effective in decreasing pain and level of radiation–induced mucositis and it could be administered as an alternative agent in OM management.

Key words: Oral mucositis, Radiotherapy, Licorice, Mucoadhesive film, Placebo.

Introduction

Head and neck cancers are one of the most common cancers in the world and include a variety of cancers involving oral cavity, salivary glands, paranasal sinuses, pharynx, larynx, nasal cavity and lymph nodes of the neck. Head and neck cancers represent 6% of all diagnosed cancers.^{1, 2,3} Common treatments for head and neck cancer include surgery, radiotherapy and chemotherapy. Radiotherapy causes different complications such as periodontal infections and salivary dysfunction but the main complication is oral mucositis (mucosal inflammation).^{4,5} Mucositis has been reported in 100% of head and neck cancer patients being irradiated.⁶ The impaired barrier often permits the development of super–imposed bacterial and fungal infections and places Patients at significant risk of bacteremia and

sepsis resulting in increased days of fever, antibiotic use and hospitalization. This painful condition may require the use of strong analgesics.^{7,8,9} Oral mucositis starts in early phases of treatment and becomes more severe as the treatment continues. It may discourage patients from resuming the treatment and leads to decrease in prognosis.^{5, 10, 11}

Corresponding Author: Dr. Mehdi Nasr Isfahani, Department of Emergency Medicine, Al–Zahra University Hospital, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Email Address: m_nasr54@med.mui.ac.ir
Phone: 81746–73441 & 8194856781

Mucositis can cause difficulties in deglutition, swallowing and talking and also complications such as dehydration, diarrhea, micronutrient deficiencies and weight loss, it can result in diminished quality of life.^{8,9,12,13} Mucositis management is crucial since interrupting radiotherapy can interfere with its cancer destroying ability and increase tumor cells.¹⁴

Many methods have been assessed to prevent, treat or manage mucositis in patients with head and neck cancer including mouthwash, cryotherapy, mucosal coating agents, subcutaneous or topical macrophage stimulating factor, anti-inflammatory agents, drugs such as antibiotics and analgesics, growth factors and cytokines.^{15,16}

Oral mucositis treatment is challenging and although many researche has been conducted. No definitive treatment is acquired. All of the current treatments have their own disadvantages.

Licorice is an herbal remedy which has a great potential in treating orofacial diseases and lesions. Recently, a lot of research have reported that the active compounds from licorice have antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, anti-ulcerative, anti-carcinogenic and several other effects.¹⁷ Therefore, licorice has benefits in treating candidiasis, periodontitis, oral cancer and aphthous ulcer.¹⁸

Therefore, this study was planned to evaluate the effectiveness of licorice mucoadhesive film versus placebo mucoadhesive film in treating oral mucositis in patients undergoing radiotherapy.

Materials and methods

This double blinded RCT was carried out at the dentistry faculty of Isfahan University of Medical Sciences.

This study was designed to compare the safety and efficacy of licorice mucoadhesive films with the placebo mucoadhesive films in treating oral mucositis in HNC patients undergoing radiotherapy.

The research group consisted of 60 patients suffered from OM caused by head and neck radiotherapy who were willing to participate in the study.

The patients, diagnosed with scale 2 and 3 mucositis based on WHO organization, received standard oral care plus licorice (30) and placebo (30) four times a day applied on the upper lip mucosal surface. Safety and efficacy assessments were conducted by physical examination, laboratory determinations, vital signs, WHO scores, the ability to eat and drink, dehydration, body weight changes, lifestyle qualification, local control and survival.

Each participant was initially screened by the research nurse before entry into the trial. The inclusion criteria were:

over 18 years of age, non-pregnant women or women of child-bearing age using contraceptive drugs, the ability to hold on in the trial, with documented histologic diagnosis of head and neck cancer, and grade 2 and 3 oral mucositis (as defined by WHO scale). The severity of OM is commonly estimated by clinicians using the WHO Oral Toxicity Scale¹⁹, which is based on both objective and subjective criteria (Box1).

Grade 0	None
Grade 1	Soreness ± erythema
Grade 2	Erythema, ulcers. Patient can swallow solid diet.
Grade 3	Ulcers, extensive erythema. Patient cannot swallow solid diet.
Grade 4	Mucositis to the extent that alimentation is not possible

Box1: WHO mucositis scales

The study exclusion criteria were: pregnant women, concurrent chemotherapy, a history of heavy alcohol or drug abuse considered to be important by the researcher, concomitant therapy with an investigational drug, or cancer chemotherapeutics or immunosuppressive medications. Sensitivity or intolerance to the drug ingredients, lactose or similar formulations, inability to provide informed consent, actively bleeding gastric ulcer, severe esophageal reflux, recent major surgery, trauma or burns in the last 4 weeks, and clinically significant hepatic, neurologic, endocrine or other systemic diseases that made implementation of the protocol or results difficult, were also considered as exclusion criteria, as well as a medication compliance of less than 70% and an obedience of less than 70%.

Each participant who had the eligibility criteria to receive RT by a two-dimensional cobalt based technique was irradiated with 5600–6000 cGy in 28–30 fractions (200 cGy per fraction a day). The patients were randomized to one of the two groups after they were diagnosed with grade 2 or grade 3 mucositis of WHO assessment scales. This study maintained for about 4 weeks or until complete remission.

Patients in both groups received the standard oral care as usual rinsing of the mouth with boiled cool water, tooth brushing and flossing, scaling and plaque removal during the treatment. One group also received licorice applied 4 times a day while the other group received placebo. In this trial placebo is composed of a formulation exactly identical to the study product but has no licorice in it. To avoid misinterpretation, patients were not allowed to consume any pain killer or analgesic. Two clinicians independently

examined patients clinically following obtaining the participant’s subjective assessment. The intervention was cut off in case of complete response but continued for the next week if improvement occurred without complete recovery. Upon the occurrence of side effects or patient’s unwillingness the study would discontinue.

Result:

In present research; patients with mucositis in licorice group, were 19 (63.3%) men and 11 (36.7%) women and in control group; there were 17 (56.7%) men and 13 (43.3%) women, and also average age in treatment group with licorice mucoadhesive film was 57.33± 10.05 years old and in control group the average age was 56.46 ± 9.36 years old, therefore, there was no statistically significant difference in age and sex between the two groups; in other words; these two groups were similar in age and sex (p–value > 0.05). average pain score in patients during 4 consecutive weeks by using analysis of variance had significant change with repeated observations (p–value < 0.05). The process of pain reduction in control group, in comparison with case group was insignificant. Also; comparison by pain scores between two groups with “independent sample T test” showed that in weeks 0, 1 and 2 there were no significant difference between case and control group (p–value > 0.05) but in weeks 3 and 4, average pain score difference between two groups were statistically significant (p–value < 0.05). So that the pain score in control group was much more than the pain score of case group (table1 and pic1).

Moreover, the average scale of mucositis in case group, in 4 consecutive weeks, using Fridman test showed considerable difference (p–value < 0.01); in other words, during the treatment, therapeutic method of using licorice mucoadhesive film can have a significant effect on scale of mucositis. However, the average scale of mucositis in control group didn’t have any significant difference during the trial (p–value = 0.116). also 2 by 2 comparison for scale of patient’s mucositis between two groups by using Man Whithney test showed that in weeks 0, 1 and 2, there was no significant difference between case and control groups (p–value > 0.05); but in weeks 3 and 4, the difference in average mucositis scale between the two groups was statistically significant (p–value < 0.05) in a way that mucositis scale in control group were more than case group (table3 and pic2).

Discussion

One of the most common and dose–limiting side effects of radiotherapy among HNC patients is mucositis.²⁰ In recent years mucositis has increased between these patients.²¹

Factors		Control (n=30)	Licorice (n=30)	P–Value
Age		56.46±9.36	57.33±10.05	0.731
Sex	Male	17(56.7%)	19(63.3%)	0.792
	Female	13(43.3%)	11(36.7%)	
Smoking	Yes	11(36.7%)	15(50%)	0.435
	No	19(63.3%)	15(50%)	
Denture	Yes	21(70%)	18(60%)	0.589
	No	9(30%)	12(40%)	

Table1:.Baseline characteristics of the study participants

	Control (n=30)	Licorice (n=30)	P–Value
Pain score at week0	5.34±0.78	5.33±1.18	0.967
Pain score at week1	5.16±0.68	4.80±2.23	0.399
Pain score at week2	4.96±0.67	4.70±1.66	0.677
Pain score at week3	4.84±0.92	2.60±1.84	0.000
Pain score at week4	4.69±0.77	2.08±1.90	0.000
P–Value	0.014	<0.001	

Table 2: Comparison of the mean pain score in study groups

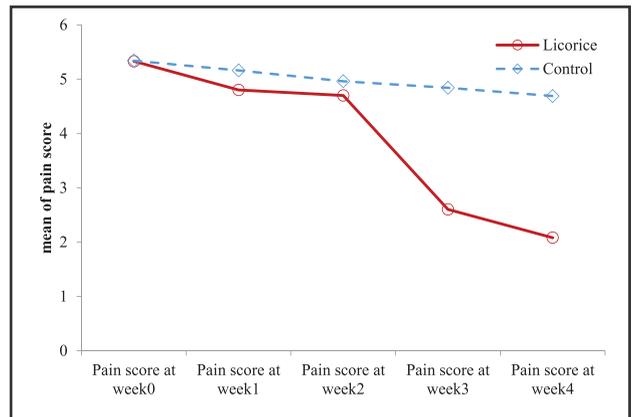


Figure 1: Line chart of the mean based on the groups

Oral mucositis causes several difficulties such as appetite and weight loss, mouth sores, pain, fatigue, problematic swallowing, dehydration, aspiration, and an overall decrease in life quality.^{1,2,13} Therefore, it is a necessity to limit the severity of oral mucositis to reduce patient’s discomfort.¹⁴

So far, many studies have been conducted to prevent and treat OM in head and neck cancer patients who receive radiotherapy, using different materials such as honey, Aloe Vera, and antibiotics.^{22,23} The authors of this research have compared the effectiveness of licorice mucoadhesive film with placebo in radiotherapy induced mucositis.

	Control (n=30)	Licorice (n=30)	P-Value
Grade mucositis at week0	2.36±0.80	2.36±0.49	0.999
Grade mucositis at week1	2.23±0.81	1.93±0.83	0.163
Grade mucositis at week2	2.20±0.76	1.90±0.71	0.120
Grade mucositis at week3	1.96±0.92	1.30±0.79	0.004
Grade mucositis at week4	1.86±0.93	0.93±0.78	0.000
P-Value	0.116	<0.001	

Table 3: Comparison of the mean pain score in study groups

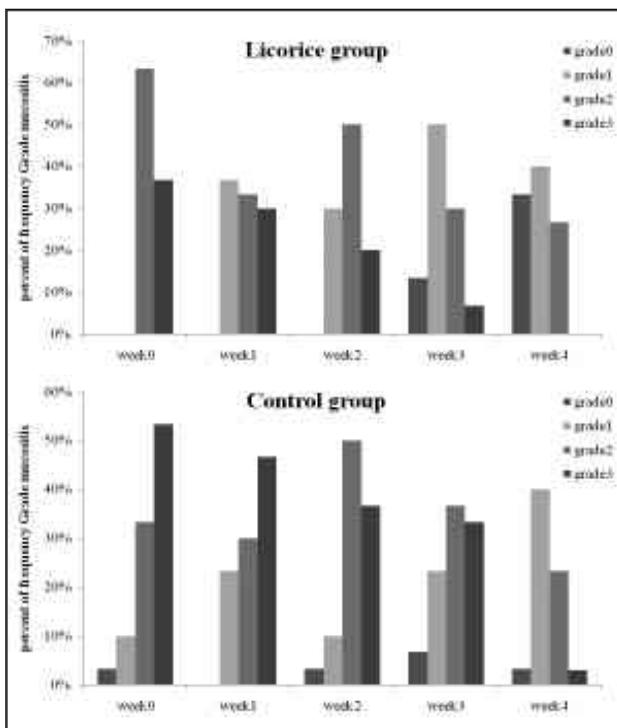


Figure 2: Bar chart of the percent of frequency Grade mucositis based on the groups

Mucoadhesive films have been developed to apply medications for oral health problems. Mucoadhesive drug delivery system provides us a longer drug residence time at the site of absorption, such as 30 minutes or more. The other advantages of using this drug delivery system include targeting and localization of the dosage form at a specific site, and creating close contact between drug and intended mucosa.^{24,25} The adhesive feature of this system causes a high concentration of drug at the mucositis area.²⁶ Also passing the hepatic first pass metabolism, enhanced drug bioavailability, and reduced dose which will limited the possible side effects are the benefits of mucoadhesive drug delivery system.²⁷

According to this research's result, applying licorice mucoadhesive films in the test group caused a significant decrease in pain score and scale of mucositis compared with the control group with placebo mucoadhesive films. The difference was statistically meaningful in weeks 3 and 4.

D.Martin Micheal et al. assessed the effect of oral patch containing licorice extract on aphthous ulcers in a controlled trial. They recorded lesions dimension by digital photography. The results showed that at day 8 after treatment. The ulcer size among Licorice patch treatment group was significantly lower.²⁸

Prateek Jain Et al. compared licorice mouthwash and chlorhexidine in testament of plaque induced gingivitis. They found that Licorice mouthwash was comparable to chlorhexidine in reducing bleeding on probing and licorice mouthwash can be used as an alternative to chlorhexidine and also can be used for longer duration without any side effects and discoloration.²⁹

Mahmudpourmotesshakker T et al. compared the effect of licorice and doxycycline on chronic periodontitis in an interventional clinical trial study. They measured Plaque Index (PI), Pocket Depth (PD), Clinical Attachment Loss (CAL) and Bleeding on Probing (BOP) in 45 patients with chronic periodontitis and concluded that licorice decreases clinical periodontal indices almost same as doxycycline in chronic periodontitis.³⁰

These studies results were consistent with our results regarding anti-inflammatory features of licorice therefore licorice is useful in treating oral inflammatory lesions such as aphthous, gingivitis and mucositis.

Biswal et al.³¹ and B. Khanal et al. have utilized 20 ml of topical honey at oral mucosa three times a day during radiotherapy treatment. Patients were evaluated for the development of radiation mucositis using the Radiation Therapy Oncology Group (RTOG) grading system the results showed that the severity of OM reduced significantly.¹⁴

Melike Demir Dogan et al. used the national cancer institute common terminology criteria for adverse events, the university of Washington quality of life assessment questionnaire and the oral assessment guide (OAG). This study indicated that experimental group with black mulberry molasses usage had lower incidence and severity of oral mucositis than the control group. However there were no difference in quality of life scores between experimental and control groups. In this study, the control group didn't receive any placebo.²⁸⁻³⁰

The last two studies were similar to our study in using herbal material for treating oral mucositis and the results were consistent with ours.

Debabrata das et al. conducted a study regarding protective effect of yashtimadhu against side effects of radiation /chemotherapy treatment. In this study total 75 patients divided into 4 groups the first group received yashtimadhu powder, honey and oral intake of yashtimadhu ghrita. The second group received yashtimadhu powder local application and honey. The third one received honey local application and the fourth only received conventional modern medication. They concluded that the intensity of mucositis was reduced to a great extent by yashtimadhu ghrita. Their grading system was recommended by radiation therapy oncology group (RTOG) / European organization for research and treatment of cancer (EORTC) radiation morbidity coring scheme.²⁸ This study didn't confirmed blinding for assessment of mucositis in contrary our trial was a double blinded experiment. But their result, *Yashtimadhu (Glycyrrhiza glabra)* can be used effectively in prevention and treatment of oral mucositis post radiation and chemotherapy in patients of cancer, especially of the head and neck region, is very close to ours.

Akhavan karbasi MH et al. performed a double blinded randomized clinical trial on 40 patients under chemotherapy treatment dividing them into two groups: an experimental group with Propolis mouthwash and a control group with placebo mouthwash. They used WHO mucositis assessment scale. The results showed that Propolis mouthwash was more effective in mucositis than placebo.²⁹ This research and the trial we have done, both evaluate mucositis by WHO assessment and result confirm the need to do more experiments on herbal material as they show beneficial effects.

Amirhossein Ahmadi conducted a review about the potential preventive effect of Aloe Vera mouthwash on RT induced oral mucositis. This trial considered Aloe Vera as a potent agent for prevention of mucositis and candidiasis.³⁰ This study tests Aloe vera's anti–fungal effects in addition to its anti–inflammatory effects. While we concentrated on the anti–inflammatory effects of licorice.

Sencer SF et al. conducted double blinded randomized trial comparing traumeel with placebo in patients aged between 3 to 25 years. Efficacy of the treatment was assessed using the modified Walsh scale for mucositis, there was no statistical difference in mucositis (AUC) between the groups.³⁰ The evaluation assessments we used in our research is different from this research. They didn't find traumeel effective while in our research, there was statistical differences between the two groups and licorice had some expected effects.

Limitations:

There are some limitations in this study. First, the results were based on a small sample size that weakens

our evidences. Second, this trial occurred in a specific oncology institute. Therefore, the results are applicable to this conclusive patient population. Also, our sampling method which was convenience sampling could have led us to bias. Our study didn't review the effect of licorice mucoadhesive film on microbial colonization related to OM. Laryngeal cancer Patients with dysphagia enrolled in the study could have made the results vitiated by imitating scales 2 and 3 of WHO mucositis assessment.

Conclusions:

This study depicted that licorice mucoadhesive film is effective in pain relieving and decreasing level of radiation–induced mucositis. The authors conclude that it could be administered as an alternative agent in OM management. Can licorice muco–adhesive film substitute current standard of care agents in OM management, is yet to be determined by future multi–centered researches with larger sample size.

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Conflict of Interest:

Authors declare no conflict of interest.

Ethical approval:

This study is ethically approved by the Vice Chancellery for research at Isfahan University of Medical Sciences (Ethical approval number is IR.MUI.RESEARCH.REC.1398.548).

Informed consent was obtained from all individual participants included in the study.

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