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Original research article

Efficacy and safety of propolis mouthwash in management of radiotherapy induced oral mucositis; A randomized, double blind clinical trial

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ABSTRACT

Aim and Background: Propolis has been used for the management of oral mucositis in a number of studies. Due to lack of sufficient evidence especially in radiotherapy induced oral mucositis, the present study was designed to evaluate the efficacy and safety of propolis mouthwash in oral mucositis and dysphagia in patients undergoing head and neck radiotherapy.

Materials and methods: This study was a prospective, randomised, double-blind, placebo-controlled trial. The patients randomly divided into two groups receiving either the propolis or the placebo mouthwash. Patients were advised to rinse their mouth with 15 mL three times daily for four weeks. Severity of mucositis and dysphagia were evaluated by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and Common Terminology Criteria for Adverse Events (CTCAE), respectively.

Results: Thirty patients completed the study. Each group consisted of 15 patients. Although, there is not any significant difference between two groups in the first week of radiotherapy, a significant difference was seen in the second, the third and the fourth week ($p = 0.03$, 0.02, 0.02, respectively). Dysphagia reported as a mild score in the propolis group only in the fourth week which is significant compared with the placebo group ($p = 0.01$). There is not any serious adverse effect related to propolis or placebo during the study.

Conclusion: It seems that propolis mouthwash is an effective and safe medication for alleviation of oral mucositis and dysphagia in patients under head and neck radiotherapy.

1. Background

Oral Mucositis (OM) is an erythematous and painful ulcerative lesion in the oral cavity of patients with cancer who are treated with radiotherapy, chemotherapy or both.[1] It is also one of the most debilitating and troublesome acute side effects that profoundly affects the quality of life. OM is associated with symptoms such as pain, infections, dysphagia and food intake impairment, which increases morbidity and mortality and contributes to rising health care costs.[2] Radiotherapy induces OM at daily dose of 2 Gy with standard fractionation from the first week and reaches the peak in the third week.[3] OM occurs in 10% of patients receiving adjuvant chemotherapy, 40% of patients with induction chemotherapy and 80% of patients who are undergoing stem cell transplantation. All of patients receiving head and neck radiotherapy also suffer from this complication.[4] Erythematous and ulcerative lesions following OM lead to severe pain and compromise nutrition and oral hygiene as well as increase the risk for local and systemic infection.[5] The OM induced pain can be severe, which requires hospitalization and use of parenteral opioid analgesics and, as a result, causes the interruption of the planned cancer therapy.[6] The Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) regularly assess available literature relating to pathogenesis, mechanisms, and novel therapeutic approaches regarding OM. In the last version, they have that the exact pathogenesis of OM has not been determined yet. Mucosal

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restricted, inflammatory based, host innate immune response, microbial mediated and neuro-immune signalling have been considered as the mechanism of OM induced by radiotherapy.[7]

Growth factors,[8] anti-inflammatory agents. such as allopurinol[9] and selenium,[10] antimicrobial agents. such as chlorhexidine.[11] and natural products like royal jelly[12] have been tried in previous studies for the management of OM. Yet, there is still no definite and standard way to treat or prevent this condition. Propolis also known as "bee glue" is a multi-component hard resin found in bee hives from certain bee species which has been employed extensively since ancient times. Antioxidant and antimicrobial activity have been reported frequently by Propolis in the literature.[13] There are several studies in animal model regarding a good effect of Propolis in alleviation of radiotherapy-induced OM.[14,15] Recently a systematic review, as a clinical practice guideline, has been published regarding the effect of natural products such as propolis in management of OM. It has referred to the lack of knowledge about Propolis either topical or systemic in alleviation of OM.[16]

2. Aim

We conducted a double-blind placebo-controlled trial to assess the effect of Propolis mouthwash in the prevention of radiotherapy-induced OM.

3. Materials and method

This is a double-blind, placebo-controlled trial conducted in two centers of radiotherapy in Tehran, Iran. The study was approved by the ethical committee of the Shahid Beheshti University of Medical Sciences with number IRSBMU.PHNM.1394.309. Also the trial was registered in the Iranian Registry of Clinical Trials under the code IRCT2016010225726N2. To be eligible for the study, patients with cancer in oral cavity, nasopharynx, tongue, hypopharynx, parotid, larynx, sub-mandibular and paranasal sinus that had undergone radiotherapy alone or in combination with chemotherapy were selected for the study. Mucositis usually becomes clinically evident during the second or third week of radiotherapy, so we have decided to evaluate the results during four weeks after starting the radiotherapy, to dose 36–40 Gy.

Radiotherapy was administered using cobalt 60 at a dose of 2 Gy per day, five times a week. Duration of radiotherapy was seven to eight weeks for all patients, to total dose of 70 Gy. Patients who needed chemotherapy in addition to radiotherapy were treated with a constant regimen weekly cisplatin (40 mg/ m2 body surface). In fact, no patients received induction chemotherapy in this trial.

Exclusion criteria were (a) history of hypersensitivity reactions to honey and propolis; (b) pre-diagnosed or therapy for oral diseases; (c) chronic kidney disease (stage 4,5); (d) chronic liver disease (stage 2,3); (e) receiving anticoagulants such as warfarin; (f) patient with candidiasis; (g) history of active collagen vascular disease; (h) white blood cell count of less than 3000/mm.[3]

The study was explained to the patients and informed consent forms were received. A questionnaire was designed in which the first part contained demographic data of patients including name, sex, age, diagnosis, location of tumour, history of drinking alcohol, smoking habits, oral hygiene, and plan of treatment (radiotherapy alone or radiotherapy plus chemotherapy). The second part was designed for the registration of grade of OM and dysphagia before and during the 4 weeks of radiotherapy. Other preventing modalities were applied to the patients who participated in the study based on hospital protocol, such as advice to avoid alcohol, smoking, and to maintain a good oral hygiene during the course of radiotherapy.

By using an online statistical computing web program (http://www.graphpad.com/quickcalcs/randomize1.cfm), eligible patients were registered and randomized in a 1:1 ratio to receive one of the two treatments, propolis solution (case group) or placebo solution (control group). Patients in the case group from the first day of radiotherapy were administered 20 mL propolis oral solution (0.8 mg/mL, Soren Tektoos, Mashhad) three times a day. The control group received 20 mL placebo solution (sterile water with allowable neutral additives, Soren Tektoos, Mashhad) every 8 h. Each time, all the patients were instructed to brush their teeth and then gargle and rinse their mouth with 20 mL of placebo or propolis for 1 min and swallow the solution for 4 weeks simultaneously with the radiotherapy protocol from the first session of radiotherapy. As we want to evaluate the effect of propolis in dyspepsia, participants were asked to swallow mouthwash after gargling in order to cause a direct contact of the solution with the pharynx and upper oesophagus tissue. In addition, patients who complained about pain or other signs attributed to severe OM were excluded from the study and received a more aggressive therapy, such as opioid analgesics for OM. Each patient was evaluated weekly for one month by the same clinical radiotherapist.

OM and dysphagia were assessed at baseline and every week for one month by using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) criteria and Common Terminology Criteria for Adverse Events (CTCAE), respectively. NCI-CTC scale of oral mucositis is classified as 0: none, 1: erythema of the mucosa, 2: patchy pseudomembranous reaction with patches generally $\leq$ 1.5 cm in diameter and non-contiguous, 3: confluent pseudomembranous reaction with contiguous patches generally >1.5 cm in diameter, 4: necrosis or deep ulceration and may include bleeding not induced by minor trauma or abrasion.[10]

Dysphagia was determined by the CTCAE criteria. In this criterion, dysphagia scored from 0 to 4 by the clinician based on symptoms, diet, and tube dependence. In Grade 0, patient is asymptomatic, in Grade 1 patient is symptomatic but able to eat regular diet, in grade 2, patient is symptomatic and altered eating or swallowing. In grade 3, severely altered eating or swallowing appears and tube feeding or Total Parenteral Nutrition (TPN) or hospitalization is indicated. Finally, in grade 4, life-threatening consequences occur and urgent intervention is indicated.[17] If any serious adverse events occurred during the intervention, regarding propolis or placebo usage, the intervention was withheld and patient was excluded from the study.

Data were analysed by using SPSS software. P value less than 0.05 was considered significant. Comparisons between propolis and placebo groups were performed using independent samples t test, Mann–Whitney test, and Pearson's Chi-squared test as appropriate. The sample size for each group was calculated according to a previous study in which an average of OM severity 3.15 and 3.90 were reported for propolis and placebo groups, respectively. Based on the standard deviation equal to 0.7 after four weeks of radiotherapy,[18] the sample size of at least 28 patients (14 in each group) was estimated (using a power of %80 and at a significant level of %5).

4. Results

Participant's flow is summarized in Fig. 1. Thirty patients were enrolled and completed the study. Demographic data, baseline oral hygiene and treatment plan of two groups are shown in Table 1. There were no differences between the 2 groups in terms of age ($p = 0.6$), gender ($p = 0.26$), alcohol habit ($p = 0.48$), smoking habit ($p = 0.59$), opioid addiction ($p = 0.99$), oral hygiene ($p = 0.21$), tumour location ($p = 0.54$), and treatment plan ($p = 1$).

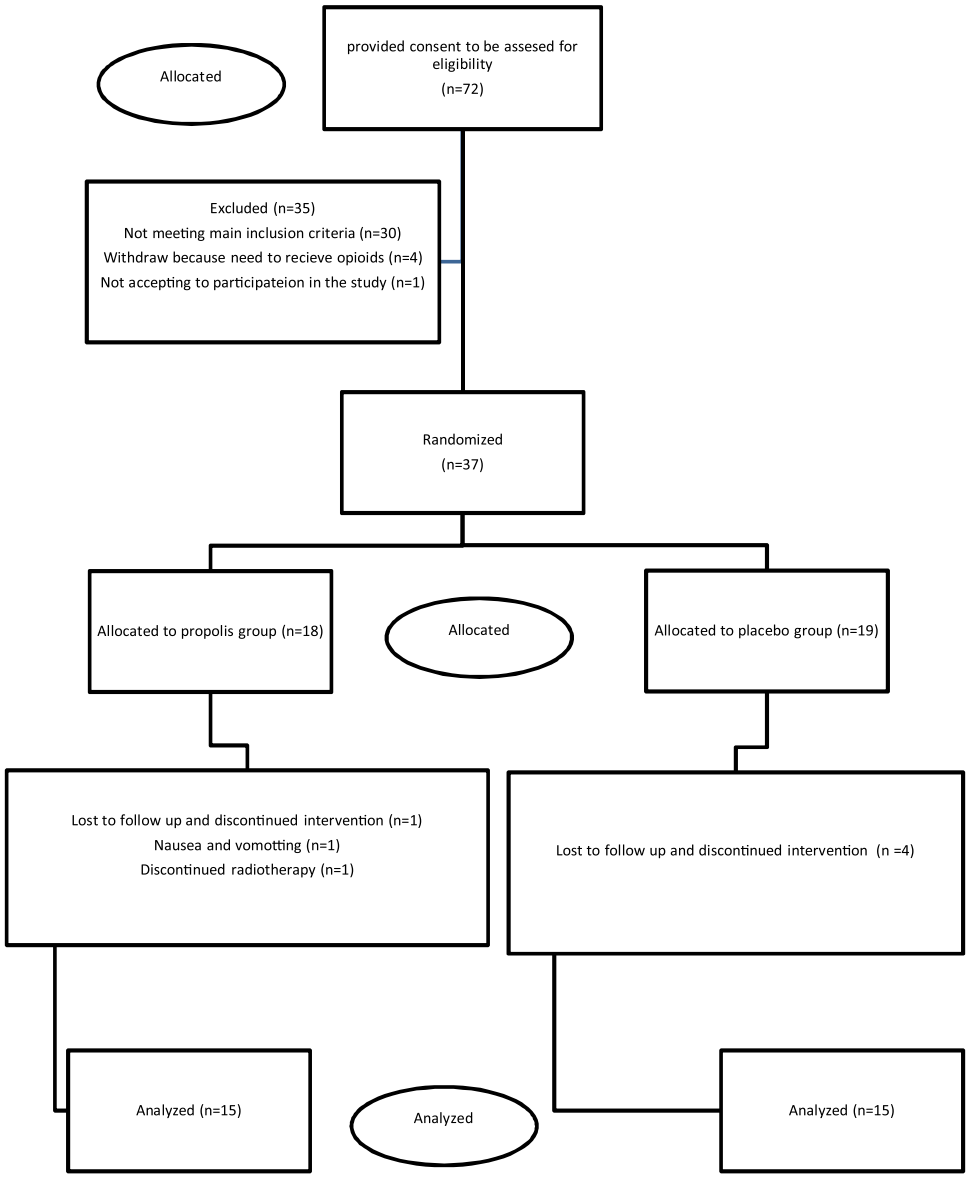

Fig. 1. Flowchart of the study.

Distribution of the severities of OM was determined separately in the first, second, third and fourth weeks of radiotherapy on the basis of NCI-CTC score (Fig. 2). Data analysis of NCI-CTC criteria showed that there was no significant difference between the groups in severity of OM in the first week ($p = 0.07$); however, there was a significant difference between the two groups in severity of OM in the second ($p = 0.03$). The frequency of grade 3 of OM in the third and fourth week was 0% in the propolis group, whereas grade 3 of OM in the third and fourth weeks were 33.33% and 13.33%, respectively, in the placebo group. Statistical analysis showed that the difference of OM between the two groups was significant in the third ($p = 0.02$) and fourth ($p = 0.02$) weeks of treatment, too.

Severity of dyspaghia in the two groups is shown in Table 2. Analysis showed that there was no significant difference between the two groups in the first, second and third weeks of treatment ($p = 0.06, 0.24, 0.13$, respectively) regarding the CTCAE score. However, in the fourth week of radiotherapy, a dominant difference in dysphagia severity was observed where 53.33% of patients in the placebo group and 6.66% patients in the propolis group had grade 3 dysphagia. Also 86.66% and 46.66% of patients in placebo and propolis had grade 2 dysphagia in the fourth week of radiotherapy. Statistical analysis showed that there was a significant difference between the two groups in dysphagia severity in that week ($p = 0.01$).

5. Discussion

The mechanism of OM is complex but the control of oxidative stress has been tried to prevent and manage OM in several studies.[19] Previous studies have reported the antimicrobial, anti-inflammatory, and wound healing effects of propolis. Its antioxidant properties, having the potential for treatment and prevention of oxidative stress mediated diseases.[20] Kuo et al. evaluated the efficacy and safety of propolis in cancer therapy induced OM in a meta-analysis. They reported that the incidence of severe OM was significantly lower in the propolis group than in the control group (OR = 0.35, $p = 0.003$).[21] In that meta-analysis, four studies out of five involved patients treated with chemotherapy alone, and only one study involved patients treated with radiotherapy. In general, there are only two published studies regarding the effect of propolis

Table 1
Demographic data of patients.

		Propolis (n = 15)	Placebo (n = 15)	P
Mean age (year)		54.2 ± 15.8	57.1 ± 14.4	0.6
Sex	Female	8	4	0.26
	Male	7	11	
Smoking habit	Never	10	10	0.59
	Present smoker	4	3	
	Stop smoking	0	2	
	Past smoker	1	0	
Alcohol habit	Never	13	15	0.48
	Present drinker	2	0	
Tumour location	Tongue	6	4	
	Larynx	5	3	0.54
	Nasopharynx	1	3	
	Parotid	0	1	
	Submandibular	1	0	
	Hypopharynx	0	2	
	Paranasal sinus	2	2	
Addiction	No	2	1	0.99
	Yes	13	14	
Treatment plan	Radiotherapy alone	10	9	1
	Radiotherapy + chemotherapy	5	6	
Oral Hygiene	Normal	6	3	0.21
	Abnormal	9	12	
Radiotherapy dose after four weeks	Range (Gy)	36–40	36–40	1
	Median(Gy)	38	38	1

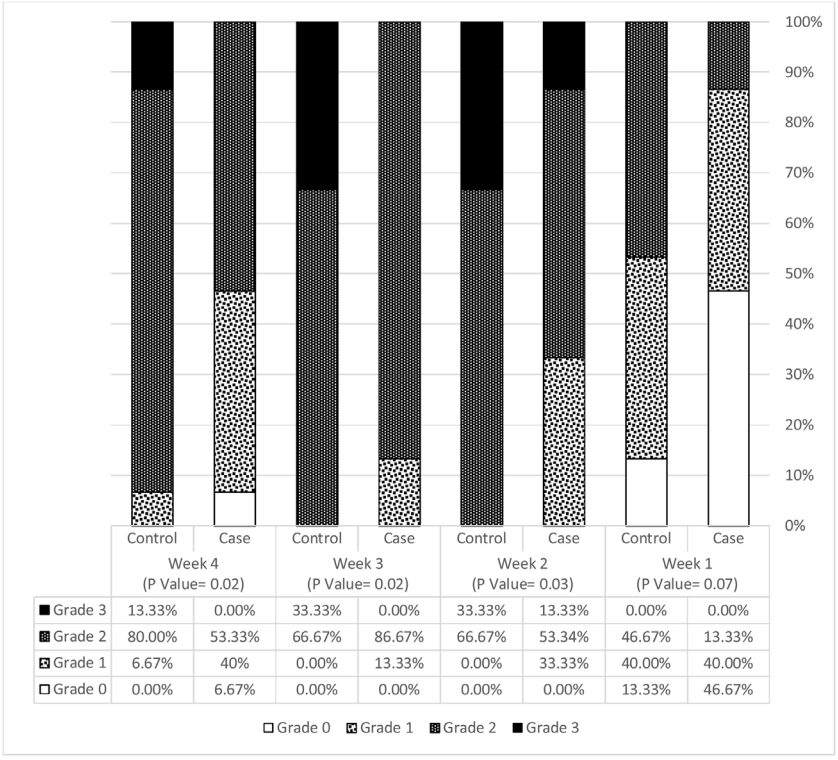

Fig. 2. Severity of oral mucositis in two groups during the study.

on radiotherapy-induced OM. One of them was done by Javadzadeh et al. published in 2015. In their study, 20 patients were selected randomly to swish and swallow 15 mL of propolis mouthwash or placebo 3 times a day, and NIC-CTC scale used for assessment of OM grading.[18] In another study, Akhavan-Karbassi et al. administered propolis or sterile water mouthwash in a double blind clinical trial. OM in patients was assessed at baseline and after three and seven days of treatment. They have reported that propolis mouth-

Table 2
Severity of Dysphagia in two groups.

	Case (%)				Control (%)				P Value
Grade	0	1	2	3	0	1	2	3	
First week	46.67%	53.33%	0.00%	0.00%	13.33%	73.34%	13.33	0.00%	0.06
Second week	0.00%	66.67%	33.33%	0.00%	0.00%	40.00%	46.67%	13.33%	0.24
Third week	0.00%	66.67%	33.33%	0.00%	0.00%	33.33%	53.34%	13.33%	0.13
Fourth week	6.66%	86.67%	6.66%	0.00%	0.00%	46.67%	53.33%	0.00%	0.01

wash may be helpful to alleviate OM in patients with head and neck cancer receiving radiotherapy plus chemotherapy. One limitation of their study was the time of patient's evaluation. Long term efficacy and safety of propolis were not seen in their trial because they performed the study only for seven days. They stated that a well designed research was needed to confirm their findings.[22]

Therefore, the lack of evidence regarding the effect of propolis in radiotherapy-induced OM leads to the present study. Age, gender, oral hygiene, smoking and radiation dose have been reported as risk factors of radiotherapy induced OM.[23] In our study, two groups were similar regarding mean age, distribution of sex, basal oral hygiene, smoking habits and radiation dose. So, these parameters could not be important as confounding factors for our results. Like in Javadzdeh et al. study, the beneficial effect of propolis in alleviation of OM was seen in our study. In both studies, NCI-CTC has been used for the assessment of OM but we determined dysphagia severity in the patients, too. Previous studies have not evaluated the effect of propolis on dysphagia in patients under treatment with either chemotherapy or radiotherapy. Our results showed that propolis had a protective effect versus placebo against radiotherapy-induced dysphagia in the fourth week by using the standard criteria for assessment of dysphagia (CTCAE). Also, our results showed that propolis was effective in alleviation of OM sooner than dysphagia. In this trial there was no drop out because of adverse drug reactions related to propolis or placebo. It seems that propolis solution is safe and it can be tolerated well. In summary, this study found that oral care by propolis mouthwash for patients undergoing head and neck radiotherapy was an effective and safe intervention to improve oral health. The exact mechanism of propolis have not been determined yet. In a reciprocal way, given the kinetics of mucosal regimen-related injury, studies that determine how mucosal injury is elicited by radiation may provide fundamental knowledge about the mechanism of propolis. As mucositis is the most frequent during the second and third weeks of radiotherapy, we evaluated patients only for four weeks and this is a limitation of our study. In the future it is recommended that patients are assessed during the whole course of radiotherapy.

Conflict of interest

Declared.

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