RESEARCH ARTICLE

Randomized Double-Blind Placebo-Controlled Trial of Propolis for Oral Mucositis in Patients Receiving Chemotherapy for Head and Neck Cancer

Mohammad Hasan Akhavan-Karbassi[1], Mohammad Forat Yazdi[2], Hakimeh Ahadian[1], Maryam Jalili Sadr-Abad[1]*

Abstract

Background: Propolis based preparations have a wide range of applications in various specialties of dentistry. The aim of this clinical trial was to test the efficacy of propolis as a mouthwash in the reduction of chemotherapy induced oral mucositis (OM) in a single center. Materials and Methods: In this randomised, controlled study patients undergoing chemotherapy were included consecutively and randomised to an experimental group receiving propolis mouthwash (n = 20) and a control group receiving diluted water (n=20). Oral mucositis, erythema and eating and drink ability were assessed at baseline and after 3 and 7 days using the World Health Organization (WHO) scale and the oral mucositis assessment scale (OMAS) . Results: There were significant differences in OM, wound and erythema in propolis group compared to placebo, but no significant difference in eating and drink ability. However, it was interesting that 65% of the patients in the propolis group were completely healed at day 7 of the trial. No significant adverse events were reported by the patients. Conclusions: This study found that oral care with propolis as mouthwash for patients undergoing chemotherapy is an effective intervention to improve oral health. Our findings shouldlencourage health practitioners to apply propolis mouth rinse for the oral care of patients under chemotherapy.

Keywords: Oral mucositis - propolis - mouth wash - chemotherapy - head and neck cancer

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Introduction

Oral mucositis is a common side effect of cancer therapies, particularly radiation therapy for head and neck cancer and various forms of chemotherapy (Redding 2005). Oral mucositis is an inflammation of the mucosa that is characterized by colour alteration, atrophy, ulceration, edema, and alteration of the local perfusion (Naidu et al., 2004). It seems despite the morbidity and the impacts of oral mucositis to patients' quality of life during the treatment and control of oncohematological diseases, there is no effective evidence of prophylactic agents, or agents for its treatment (Sarvizadeh et al., 2015; Wong 2014). Diverse oral care solutions have been applied for managing chemotherapy-induced OM in patients under chemotherapy. However, conflicting effects on these solutions were reported (Choi et al., 2012).

According to preliminary human studies and a controlled trial found Propolis containing mouthwash effective in healing oral wounds (Dodwad et al., 2011). Propolis contains protein, amino acids, vitamins, minerals, and flavonoids. For this reason; some people are use propolis as a natural nutritional supplement, although it would take large amounts of propolis to supply meaningful amounts of these nutrients (Steinberg et al., 1996; Dodwad et al., 2011). In test tube studies, propolis has shown considerable activity against bacteria and yeast associated with dental cavities, gingivitis, and periodontal disease, but one human study showed that propolis was no better than a placebo in inhibiting dental plaque formation (Palombo et al., 2011; Dodwad et al., 2011). As a natural anti-inflammatory product, propolis is shown to inhibit synthesis of prostaglandins, activate the thymus gland, aid the immune system by promoting phagocytic activity, stimulate cellular immunity, and augment healing effects on epithelial tissues. Additionally, propolis contains elements, such as iron and zinc that are important for the synthesis of collagen (S VK et al., 2014; Hegde et al., 2013).

To our knowledge, the effect of Propolis on OM in patients under chemotherapy has not yet been studied. The aim of the present study therefore was to assay effect

*[1]Department of Oral and Maxillofacial Diseases Diagnosis, [2]Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran *For correspondence: hn_1364@yahoo.com*

of Propolis on OM in patients with head and neck under chemotherapy. This was done by comparing the OM, wound, erythema and eating and drink ability at baseline and two intervals, and the mouthwash was compared with a placebo control.

Materials and Methods

The study was conducted in the Radiation oncology department of Shahid Sadoughi hospital, Yazd, Iran in association with Imam Hasan regional cancer center and department of Oral Medicine, Dental school, Yazd, Iran during 2014.

Histopathologically confirmed cases of head and neck tumors under chemotherapy with different cytotoxic regimen as well methotrexate at standard doses, selected for radiotherapy and those who were willing to give informed consent and ready to report for post treatingment review, were included in the study. Study subjects were selected into the study based on the criteria set and 40 patients (≥18 years of age) satisfied the criteria. The patients were briefed about the study and the probability of selection in to the interventional and the control groups were described. History and personal data were recorded in a questionnaire.

The patients are allotted either to the intervention group or to the control group with the help of a random number table. A two digit random number was selected with the help of a random number table on every entry to the study. An odd number would select the patient to the intervention group and an even number enrolls the patient to the control group. Patients in the study group were administered Propolis mouth rinse (30% extract, Soren Tektoos, Mashhad). Group II was the control group who were given placebo mouth rinse (Sterile water with allowable additives, Soren Tektoos, Mashhad). Designated blinded nurse administered 5 ml of the rinses and the patients swished the solution in their mouth for 60 seconds, gargled, and expectorated. Dosing with oral rinse will be every 8 hours for a three times daily to a seven consecutive days. All subjects were requested to visit the oral dentistry department of the cancer center on the third and 7th day of treatingment. At these visits, the subjects were underwent an oral examination conducted by a qualified observer for rating mucositis severity scales.

This placebo study primary goal was to determine the efficacy and safety of propolis mouth rinse when used to reduce the incidence of OM associated with mucotoxic cancer therapy. Secondary goals were to determine the treatingment effect of propolis on oral cavity erythema according (0: no erythema, 1: mild erythema, 2: moderate erythema, 3: severe erythema), wound formation (0: no wound, 1: less than 1cm, 2: 1-5 cm, 3: more than 5cm) and the normalcy of eating and drink ability (0: easy eating and drink, 1: liquid eating and drink ability only, 2: unable to eating and drink).

Ethical clearance was obtained before starting the study. All subjects were instructed with standard oral care and hygiene procedures. Subjects were instructed not to perform any oral care procedures (including tooth brushing and saline or other rinses) for 1 h after study drug administration.

Results

A total of 40 patients were enrolled. Baseline demographic characteristics of the participants are shown in Table 1. According to the WHO Mucositis Assessment Scale, 25% of patients had grade 3 mucositis in the Propolis and Placebo groups. As shown in table 1, 75% of patients had normal eating and drinking ability in placebo group and 30% in the Propolis group.

As shown in Table 2, evaluation of mucositis revealed that in the placebo and propolis groups mucositis significantly decreased at 7 days of experiment, while

Table 1. Distribution of Erythema, Wounding, Eating and Drinking Ability and Oral Mucositis in Randomized Patients at Baseline

Variable	Placebo (n=20)	Propolis (n=20)
Mucositis Grade		
0	-	-
1	5 (25.0)	8(40.0)
2	10(50.0)	7(35.0)
3	5 (25.0)	5 (25.0)
4	-	-
Wound		
0	5 (25.0)	5 (25.0)
<1cm	5 (25.0)	9(45.0)
1-5cm	5 (25.0)	6(30.0)
>5cm	5 (25.0)	-
Erythema		
0	-	-
1	10(50.0)	4(20.0)
2	10(50.0)	6(30.0)
3	-	10(50.0)
Eating and drink ability		
0	15(75.0)	6(30.0)
1	5 (25.0)	9(45.0)
2	-	5 (25.0)

[a]0: None, 1: Soreness/erythema, 2: Erythema, ulcers but able to eating solids, 3: Ulcers but requires liquid eating and drink ability, 4: Oral alimentation not possible. [b]0: no wound, 1: less than 1cm, 2: 1-5 cm, 3: more than 5 cm. [c]0: no erythema, 1: mild erythema, 2: moderate erythema, 3: severe erythema. d0: easy eating and drink, 1: liquid eating and drink ability only, 2: unable to eating and drink.

Table 2. Scores of Erythema, Wounding, Eating and Drinking Ability and Oral Mucositis between Placebo and Propolis Groups at Days 3 and 7

Variables	3rd day			7th day		
	Placebo(n=20)	Propolis(n=20)	P	Placebo(n=20)	Propolis(n=20)	P
Erythema	1.5 (0.76)	0	0.76	1.5	0	0
Wounding	1.5(0.001)	-0.006	0.001	1	0	0.006
Eating and drinking ability	0.00(0.853)	-0.318	0.853	0	0	0.21
Mucositis	2.00(0.041)	0	0.41	1.5	0	0

Table 3. Scores of Erythema, Wounding, Eating and Drinking Ability and Oral Mucositis at Baseline and at Days 3 and 7[t] in the Placebo and Propolis Groups

Variables	Placebo (n=20)				Propolis(n=20)			
	Baseline	3 days	7 days	p-value	Baseline	3 days	7 days	p-value
Erythema	1.5	1.5	1.5	0.72	2.5	1.5	0	0
Wounding	1.5	1.5	1.5	0	1	0	0	0
Eating and drinking ability	0	0	0	0.92	1	0	0	0
Mucositis	2	2	1.5	0.007	3	1	0	0

Table 4. Distribution of Erythema, Wounding, Eating and Drinking Ability and Oral Mucositis between 3th and 7th Days in the Placebo and Propolis Groups

Variables	Placebo (n=20)		Propolis (n=20)	
	3th day	7th day	3th day	7th day
Mucositis Grade				
0	-	-	-	13(65.0)
1	5 (25.0)	10(50.0)	14(70.0)	5 (25.0)
2	10(50.0)	5 (25.0)	2(10.0)	-
3	5 (25.0)	5 (25.0)	2(10.0)	2(10.0)
4	-	-	2(10.0)	-
P-value	0.025		0	
Wounding				
0	5 (25.0)	10(50.0)	16 (80.0)	18(90.0)
<1cm	5 (25.0)	10(50.0)	2(10.0)	2(10.0)
1-5cm	5 (25.0)	-	-	-
>5cm	5 (25.0)	-	2(10.0)	-
P-value	0.02		0.04	
Erythema				
0	-	-	-	13(65.0)
1	10(50.0)	10(50.0)	10(50.0)	5 (25.0)
2	10(50.0)	10(50.0)	8(40.0)	2(10.0)
3	-	-	2(10.0)	
P-value	0		0.002	
Eating and drinking ability				
0	15(75.0)	15(75.0)	16 (80.0)	18(90.0)
1	5 (25.0)	5 (25.0)	2(10.0)	2(10.0)
2	-	-	2(10.0)	-
P-value	1		0.046	

at third day it was shown only Propolis. Assessment of eating and drink ability of patients not showed a significant improvement in both groups ability. There were significant differences in oral mucositis, wound and erythema in propolis group compared to placebo, but no significant difference in eating and drink ability was observed between the propolis and placebo groups.

In Table 3, scores of erythema, wound eating and drink ability and mucositis at three points in the placebo and propolis groups are shown. Results shown that all variables (erythema, wound, eating and drink ability and mucositis) significantly improved during study in propolis group, while in placebo group wound and OM scores significantly decreased.

In Table 4, distribution of erythema, wound, eating and drink ability and mucositis between 3th and 7th days within the placebo and propolis groups are shown. It was interesting that 65% of the patients in Propolis group were completely healed at day 7 of the trial. No significant adverse events were reported by the patients.

Discussion

It is estimated that there is 40% incidence of mucositis in patients treated with standard chemotherapy and this will not only increase with the number of treatment cycles but also several problems, including pain, nutritional problems as a result of inability to eating, and increased risk of infection due to open sores in the mucosa. It has a significant effect on the patients quality of life and can be dose- limiting (Castaldo et al., 2002; Naidu et al., 2004).

Propolis is a natural resinous substance that honeybees collect from various tree sources and use as a glue to build, repair, and protect hives (Castaldo et al., 2002). In general, this substance is composed of 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% various other substances, including organic debris (Hwu et al., 2014). The primary function of propolis in the hive is to act as a biocide, being active against invasive bacteria, fungi, and even invading larvae (Jafarzadeh Kashi et al., 2011). Propolis and its constituent flavonoids exhibit an antitumor effect both *in vivo* and *in vitro*.

In this study, the severity of OM was significantly reduced in the Propolis and placebo groups. However, it was interesting that 65% of the patients in Propolis group were completely healed at day 7 of the trial. In the present study, the normal saline used in placebo group showed a significant effect on the chemotherapy induced OM. However, the severity of OM was decreased in the control group during the experiment.

In third day of experiment, we have seen significant differences in the incidence rates of oral wound and mucositis between the propolis group and the placebo group. In the 7th day there were significant differences in the incidence rates of oral wound, mucositis and oral cavity erythema between the propolis group and the placebo group. No previous studies are available on using Propolis mouth wash to treating OM due to cancer chemotherapy. However, findings of the present study were consistent with a study by Javadzadeh Bolouri et al. For first time, they reported about the effects of propolis on treatment of radiotherapy induced mucositis in head and neck cancer patients. They have found encouraging results for the prevention and treatment of radiation induced mucositis by propolis mouth rinse (Javadzadeh Bolouri et al., 2015). In this study, we have found that propolis based mouth rinse is safe and effective in treatment for radiotherapy induced mucositis.

Hwu et al., in a meta-analysis including 8 studies published between 1969 and 2012 with 194 participants have reported that, although propolis had an effect on reducing dental plaque, this effect was not statistically significant. The results were not statistically significant for oral infection or stomatitis. However, it seems the number of studies available for inclusion in this meta-analysis was small, which reduced the generalizability of

conclusions. The review highlights the need for additional well-designed trials to draw conclusions that are more robust (Hwu et al., 2014).

In this study did not investigate the mechanisms of action of Propolis on oral mucositis, but some observations are in order that may have a bearing on the outcome. The findings of this study revealed that neither in the experimental group nor in the control group, there was no significant decrease in eating and drink ability in the patients. However, some of previous studies have reported that significant results (Naidu et al., 2004). This discrepancy might be explained by the different chemotherapy regimens.

Propolis mouth rinse is thought to aid in the formation of granulation tissue and to promote healing. The result of this study suggest a significant decreased incidence and scale of oral wound (>5cm) in the intervention group. As formerly mentioned, propolis has been considered a pleiotropic substance with a variety of anti-inflammatory, antioxidative and wound-healing effects, which are mediated by different compounds such as caffeic acid, quercetin, naringenin, and caffeic acid phenethyl ester (CAPE) (Jacob et al., 2015; Mirzoeva et al., 1996). It has found these compounds contribute to the suppression of prostaglandins and leukotrienes synthesis by macrophages and have inhibitory effects on myeloperoxidase activity, NADPH-oxidase, ornithine decarboxylase and tyrosine-protein-kinase as well as inhibiting the production of pro-inflammatory cytokines.

In addition, the crossover analysis of the data showed significant results in favor of propolis mouthwash, supporting that there were not biases in the study and its results (Tables 1-4). However, this study findings were shown that both propolis and distilled water as oral rinses helped in controlling oral mucositis, wounds and erythema, however propolis was more efficient and had better patients compliance.

Strengths of this study include the randomized, double-blind, placebo controlled design which minimized the risk of bias in outcome measurements. Limitations of the study include the small sample size and lack of comparison propolis efficacy with other materials. While this study demonstrates the absence of a large effect of the interventions, a smaller effect, albeit less clinically significant, cannot be ruled out.

In summary, this study found that oral care by Propolis as mouthwash for patients undergoing chemotherapy was an effective intervention to improve oral health. Our findings will encourage health practitioners to apply propolis mouth rinse for the oral care of patients under chemotherapy. In addition, the lack of effect of propolis mouthwash in patient's eating and drink ability normality undergoing chemotherapy may be explained by the different chemotherapy regimens.

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