



Antimicrobial Activity of Natural Honey: Topical Application of Pure Natural Honey in Prevention of Chemotherapy Induced Oral Mucositis

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ABSTRACT

Background: Oral mucositis is a frequent problem after high-dose chemotherapy which could impair patient's quality of life, higher rates of infections, and delay in subsequent chemotherapy.

Objectives: The present study was performed to assess the effect of topical application of pure natural honey in prevention of chemotherapy induced mucositis in patients with cancer.

Patients and Methods: In this randomized clinical trial 48 patients with acute leukemia requiring chemotherapy were assigned to three equal groups. During induction or reinduction period of chemotherapy, first group received honey plus normal saline; the second one received just normal saline and third, (in control group) did not receive any prophylaxis. Patients were evaluated weekly for progression of mucositis according to the WHO mucositis scale. Data were analyzed with the Pearson Chi-Square and Fisher Exact test, by fifteen edition of SPSS software.

Results: In group of 'honey plus normal saline' no patients developed mucositis, while in normal saline group 4 patients and in control group 12 patients developed mucositis. The rate of mucositis was significantly lower in both intervention groups compared to control ($P < 0.001$).

Conclusions: This study demonstrates that using either honey or normal saline can reduce the rate and severity of chemotherapy induced mucositis.

Keywords: Honey; Mucositis; Chemotherapy

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We tried to assess the effect of topical application of pure natural honey in prevention of chemotherapy induced mucositis in patients with cancer.

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1. Background

Oral mucositis is inflammation of the mucosal surfaces and manifests as erythema, inflammation, ulceration, and hemorrhage in the mouth and throat. Despite that, mucositis is not a life threatening condition but may increase sepsis rate and bleeding together with poor outcome, more hospital cost, antibiotic and analgesic over usage. Chemotherapy-induced mucositis frequently occurs in the course of treatment of patients with cancer who received immunosuppressive agents. Painful ulcers often necessitate administration of sedative or anti-inflammatory agents (1, 2). Duration of hospitalization is significantly longer during chemotherapy cycles with mucositis. Infection rate is significantly higher during cycles with mucositis than during cycles without mucositis. Also, the risk of infection increases with increasing the severity of mucositis (3, 4). Patients undergoing radiation therapy show mucosal changes by the end of third week. Chemotherapy-induced mucositis typically begins 4 to 5 days following the infusion and peaks 5 days later. The lesions are usually limited to non keratinised surfaces, like lateral and ventral surfaces of tongue, buccal mucosa, and soft palate (5). Management of oral mucositis is based on pain control, nutritional support, decontamination, and management of oral bleeding. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) mucositis guidelines recommend patient-controlled analgesia with morphine for patients undergoing hematopoietic cell transplantation. These guidelines also recommend using a standardized oral care protocol including brushing with a soft tooth-brush, flossing and using non-medicated rinses; e.g. saline, sodium bicarbonate rinses (6). In the sight of these guidelines other researchers try to show effect of other agents (such as honey) to treat mucositis. The oral microbial flora often has been a suspect in the pathogenesis of mucositis (7). Honey has been shown to affect such infectious agent in various reports (8-13). Thus, some benefits of honey on mucositis could be explained with these theoretical effects. Honey also has high-antioxidant properties (14). It has been mentioned directly in the Koran that honey has curative properties (15, 16). Abu Ali al-Hussain Ibn Abdallah Ibn Sina (Avicenna), the philosopher and the greatest Iranian man in medicine recommended many prescriptions using honey and bees wax thousands years ago. About the miraculous effects of honey he says that: «Honey is effective to improve infectious sores and help them to cure. Honey is the best medicine for the infections of gum, if honey is heated and concentrated and rubbed frequently on fresh sores, it can get them better ». Motallebnejad et al. investigated the effect of honey in patients with head and neck cancer received radiation. Patients received pure natural honey 14 minutes before radiotherapy, then 15 minutes

and 6 hours after radiotherapy. Mucositis severity was scored by the OMAS scores. Significant differences were noted during the sixth week of therapy, and Mean weight loss was significantly higher in the control group (17). In another study by Rashad et al. patients smeared 20 ml of pure natural honey on the inside of their mouths 15 minutes before, 15 minutes after, and 6 hours after radiation. Patients were randomized to treatment or control group, and results were statistically significant (18).

2. Objectives

Because most previous studies on the effect of honey in the prevention of mucositis have been performed in patients undergoing radiotherapy, in this study; we investigated the effects of topical application of pure natural honey in prevention of chemotherapy induced mucositis in patients with cancer.

3. Patients and Methods

This prospective randomized clinical trial was performed on 48 pediatric patients, age range from 7 to 16 years who had acute leukemia in Besat teaching hospital from 2007 to 2008. Patients with Acute Lymphoblastic Leukemia (ALL) were in the induction or reinduction phase, and patients with Acute Myeloid Leukemia (AML) were in induction period. Treatment protocol that was used for ALL and AML were REZ-BFM 2002 and 3+7 protocol respectively. Any patient with acute leukemia requiring chemotherapy who was able to brushing and mouth washing were included. Patients who had liver disease, renal failure, diabetes mellitus, and history of previous hyperglycemia were excluded from the study. Patients who received neck radiotherapy were not enrolled in this study. Participants were randomly assigned to three equal groups with 16 cases: honey plus normal saline group, only normal saline, and control group. Randomization was performed by someone other than the examiner physician with block randomization method. The study was approved by the research committee of the Hamadan University of Medical Sciences and informed parental or own consent was obtained prior to testing. Demographic characteristics of patients were entered in a form. Two forms were given to each patient; the first, for patient's compliance and adherence to his or her protocol and the other one as instruction for general hygiene, normal saline usage or honey application. For these reason sheets were prepared to any patient who enrolled in the survey for universal education and exactly alike practice in all patients. instruction forms were: A) general recommendations for all patient about periodontal and mouth hygiene during chemotherapy, consumption of high protein foods, soft foods, and frequent consumption of liquids and brushing with soft tooth-brush for 90 seconds in explained uniform manner after awaking and

before sleeping the same as morning brushing; B) protocol guidance for normal saline group, how to use mouth washing during chemotherapy. This protocol was included morning, after meal and before sleep notification. After awaking, each patient was advised to brushing with soft tooth-brush for 90 seconds in explained uniform manner. In the next step, 60 ml of normal saline should be gargled for 30 seconds and finally, he or she cleaned his or her month and tongue with tooth-brush soaked in normal saline. Half hour after each meal 60 ml of normal saline should be gargled for 30 seconds. Before sleeping same as morning brushing for 90 seconds, normal saline gargling and month/tongue cleaning with tooth-brush soaked in normal saline should be performed. Brushes prepared and delivered to all patients before starting the program; C) protocol guidance for honey group ;in addition to the measures recommended in the saline group in this group 60 ml of honey should be gargled for 30 seconds after the mouth washing with normal saline in the morning and at night. Patients advised to avoid drinking or eating anything up to 30 minute after honey use.

Uniform Iranian soft tooth-brush was given to all patients in three groups. Normal saline solutions were provided from an Iranian drug manufacturer in 500 mL packs, and delivered to target groups. Pure natural honey (acidic with a pH of about 3.55) applied in our study

provided from the Zagros Mountains in the best quality. Quality Control and chemical analysis performed and approved in the advisory institute of Food control and investigation in Esfahan. Safety profile and purity of honey controlled by application of one product and analysis performed for PH, viscosity and density. Sugar content detect by HPLC method. After production and before using honey, it was kept in a cool and dark place to save its quality. Honey and saline were given to each of target groups by a medical student who was doing her thesis. Each protocol lasted for two cycles of chemotherapy, and each protocol achieved in the first three weeks of treatment. Patients were discouraged to use any other mouth washing during the treatment protocol. Adherence to protocol was addressed by parent's supervision, daily home checklists about tooth brushing, mouth washing after meal, Honey and normal saline usage, and serial regular visits in clinic by observer. Adherence to protocol was assumed to be in 80% of ideal point. Each patient examined three times during his or her protocol and the grading/severity was determined according to the WHO Mucositis scale (Table 1) (19). The study was single-blinded and patients were aware of used method but all patients were examined by the same physician who was unaware of the used methods in each patient. The Pearson Chi-Square and Fisher Exact test were performed to find statistically significant differences.

Table 1. WHO Mucositis Scale

Grade	Description
0 (none)	none
1 (mild)	oral soreness, erythema
2 (moderate)	oral erythema, ulcers, solid diet tolerated
3 (severe)	oral ulcers, liquid diet only
4 (life-threatening)	oral alimentation impossible

4. Results

From February 2007 for a period of 12 Months forty eight pediatric patients between 7-16 years old were included in this study, and their adherence to protocol was more than 80% of ideal point according to daily home checklists. Mean age in honey group was about 10 years (10.34), about 12 years (12.80) in normal saline group, and about 15 years (15.22) in control group; no statistically differences were found between 3 groups of patients. Sex and Primary diagnosis also were not statistically different between 3 groups of patients. Other Demographic characteristics of cases are shown in Table 2. In group of 'honey plus normal saline' no patients developed mucositis, while in normal saline group four patients, and in control group 12 patients developed mucositis. The rate of mucositis was significantly lower in both intervention

groups (Honey plus normal saline-normal saline alone) compared to the control group. 95% CI (P Intervention -P Control): 0.33 to 0.91 (Table 3). But the differences between two intervention groups (Honey plus normal saline-normal saline alone) were not statistically meaningful (P = 0.13). From 16 cases in which mucositis was developed, 14 cases occurred in the first week of treatment and primary diagnosis had not any effect on results. Also in this study there was no significant difference in the severity of mucositis in group with just normal saline compared to control group (0.569) (Table 4). In the intervention groups there was not any side effect of honey or saline.

5. Discussion

Regarding mucositis pathophysiology, and in the fact of irreversible histological change in oral mucosa which

Table 2. Demographic Characteristics of Patients

Patient's Characteristics	Honey Plus N.S. ^a	Normal Saline	Control Group	P value
Age, y, Mean ± SD	10.34 ± 5.80	12.8 ± 11.40	15.22 ± 12.40	0.41 ^b
Weight, Kg, Mean ± SD	33.38 ± 20.50	30.1 ± 18.70	37.53 ± 19.20	0.63 ^b
Sex, F/M	12/4	11/5	8/8	0.99 ^c
ALL ^a /AML ^a	15/1	13/3	13/3	0.99 ^c

^a Abbreviations: N.S., normal saline; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia

^b ANOVA Test

^c Chi-square Test

Table 3. Frequency of Mucositis Between Study Groups ^a

Arms	Mucositis	Without Mucositis	Total
Honey and Normal Saline, No. (%)	0 (0)	16 (100)	16 (100)
Normal Saline, No. (%)	4 (25)	12 (75)	16 (100)
Control, No. (%)	12 (75)	4 (25)	16 (100)

^a Analyzed by Pearson Chi-Square ($X^2 = 21$, $df = 2$; $P < 0.001$)

Table 4. Severity of Mucositis Between Study Groups

Study Group	Severity of Mucositis			Total	P value
	Grade 1	Grade 2	Grade 3		
Normal Saline, No. (%)	3 (75.0)	1 (25.0)	0 (0.0)	4 (100)	0.569 ^a
Control, No. (%)	5 (41.7)	6 (50.0)	1 (8.3)	12	

^a The 2nd and 3rd columns (Grade 2 and 3) have been combined and the Fisher Exact test has been used.

exposes to repeated irritation, it is reasonable to expect that control measures might be more effective than treatment in this setting. For these reasons Tooth-brushing and the frequent use of normal saline are generally recommended for individuals undergoing radiation therapy or chemotherapy. Because of high prevalence of mucositis during induction chemotherapy, we designed our study in patients with cancer undergoing induction chemotherapy to compare normal saline and honey in prevention of mucositis. Our results revealed statistically significant differences between control group and those who receive normal saline alone or normal saline plus honey for prevention of oral mucositis. About normal saline these data are compatible with previous reports that showed effectiveness of normal saline in prevention of oral mucositis in patients with cancer (20). Rashad's study demonstrated that topical application of honey on the oral mucosa 15 minutes

before, 15 minutes after, and 6 hours after radiation would cause a significant reduction in radiation induced mucositis. Although there are few reports on the preventive effects of honey in mucositis, most of them have investigated patients who have received radiation therapy for head and neck cancer (1, 18-25). This study added new information about other high risk patients who undergo induction chemotherapy for leukemia. However no difference was found in our two treatment protocols ('honey plus normal saline group', and 'normal saline group') with paired comparison analysis, this result may be due to the low number of participants, and presumably statistically significant differences would be found with larger number of cases. In the report of Motalebnejad et al. the mucositis severity (by the OMAS scores) showed statistically significant better outcome in honey group compared to normal saline group (17). Some studies demonstrates that using either honey or normal saline can reduce the rate and severity of oral mucositis in patient with cancer and advocated as a more expedient way for the management of these patients. In our study there was no significant difference in the severity of mucositis in group with just normal saline compared to control group which may be due to the low number of participants, and accuracy for severity measurement, so presumably statistically significant differences would be found with larger number of cases and more accurate severity measurement scales.

In conclusion, our results demonstrated that topical application of honey would cause a significant reduction in chemotherapy induced mucositis. Based on our results and because honey is a healthy food with no side effects we suggest topical honey administration for prevention of mucositis. Some other questions still exist which should be answered with further investigation such as whether honey has a direct local protection on radiation, or whether honey has any systemic protection on cytotoxic drugs.

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Authors' Contribution

Iraj Sedighi and Shima molae designed the study; hossein khoeinipoorfar and Shima molae made substantial contributions to the acquisition of data; ali amanati and shahla nouri performed data interpretation, and drafted the manuscript.

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There is not any financial disclosure.

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