European Journal of Oncology Nursing 19 (2015) 207–213

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

Effect of adding the herb *Achillea millefolium* on mouthwash on chemotherapy induced oral mucositis in cancer patients: A double-blind randomized controlled trial

Sedigheh Miranzadeh [a], Mohsen Adib-Hajbaghery [a, *], Leyla Soleymanpoor [a], Majid Ehsani [b]

[a] Department of Medical Surgical Nursing, Faculty of Nursing and Midwifery, Kashan University of Medical Sciences, Kashan, Iran
[b] Department of Internal Medicine, Shahid Beheshti Medical Center, Kashan University of Medical Sciences, Kashan, Iran

Keywords:
Achillea millefolium
Chemotherapy
Oral mucositis
Cancer
Mouthwashes

A B S T R A C T

Background: Oral mucositis (OM) is a debilitating side-effect of chemotherapy. It has different complications, including impairment of drinking, eating and even talking, sometimes so severe that physician stops the therapy.
Objective: Investigating the effect of *Achillea millefolium* distillate solution in the treatment of chemotherapy-induced OM.
Interventions/methods: In this randomized controlled trial, 56 cancer patients with chemotherapy-induced OM were randomly assigned into control and experimental groups in similar blocks based on the severity of OM. The experimental group gargled 15 mL of a mixture of routine solution and distilled *A. millefolium* 4 times a day for 14 days while the control group gargled 15 mL of routine solution. The severity of OM was assessed at three times before, 7 and 14 days after intervention. Data was analyzed using Wilcoxon, Kruskal–Wallis, Mann–Whitney U, Friedman, Chi-square and Fisher's exact tests.
Results: The mean severity score of OM was 2.39 ± 0.875 in both groups at start of the study that was changed to 1.07 ± 0.85 and 0.32 ± 0.54 in the intervention group in days 7 and 14 ($p < 0.001$). However, the severity of OM was increased to 2.75 ± 0.87 and 2.89 ± 0.956 in the control group respectively ($p < 0.001$).
Conclusions: A. millefolium distillate healed OM much more than the routine solution. Therefore, it is suggested to be used in patients with chemotherapy-induced OM.
The study was registered in the Iranian Registry of Clinical Trials, Number: IRCT2013092214729N1.

Introduction

Oral mucositis (OM) refers to mucosal damage secondary to cancer therapy occurring in the oral cavity. Mucositis can be caused by chemotherapy and/or radiation therapy (Lalla et al., 2014). It occurs in approximately 20%–40% of patients receiving conventional chemotherapy, 80% of patients receiving high dose chemotherapy as conditioning for hematopoietic stem cell transplantation, and nearly all patients receiving head and neck radiation therapy (Avritscher et al., 2004; Lalla et al., 2014; Vera-Llonch et al., 2007).

Pain induced by OM disturbs patients and makes it difficult to eat and drink, resulting in indigestion and dehydration (He, 2011; Pavesi et al., 2011; Potting et al., 2006). OM can also disturb speaking and communication with others, resulting in psychological and social stresses (Abedipour et al., 2006). In addition, OM is accompanied by a wide range of oral mucus alterations such as infection and bleeding, which could result in systemic infection (Abedipour et al., 2006; Potting et al., 2006). In severe cases, it can increase the length of hospitalization and even lead the physician to cease the chemotherapy (Pavesi et al., 2011; Potting et al., 2006).

A wide variety of agents have been tested to prevent OM or reduce its severity (Yarom et al., 2013; Lalla et al., 2014). The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published evidence based clinical practice

* Corresponding author. Tel.: +98 3615550021; fax: +98 3615556633.
E-mail address: adib1344@yahoo.com (M. Adib-Hajbaghery).

http://dx.doi.org/10.1016/j.ejon.2014.10.019
1462-3889/

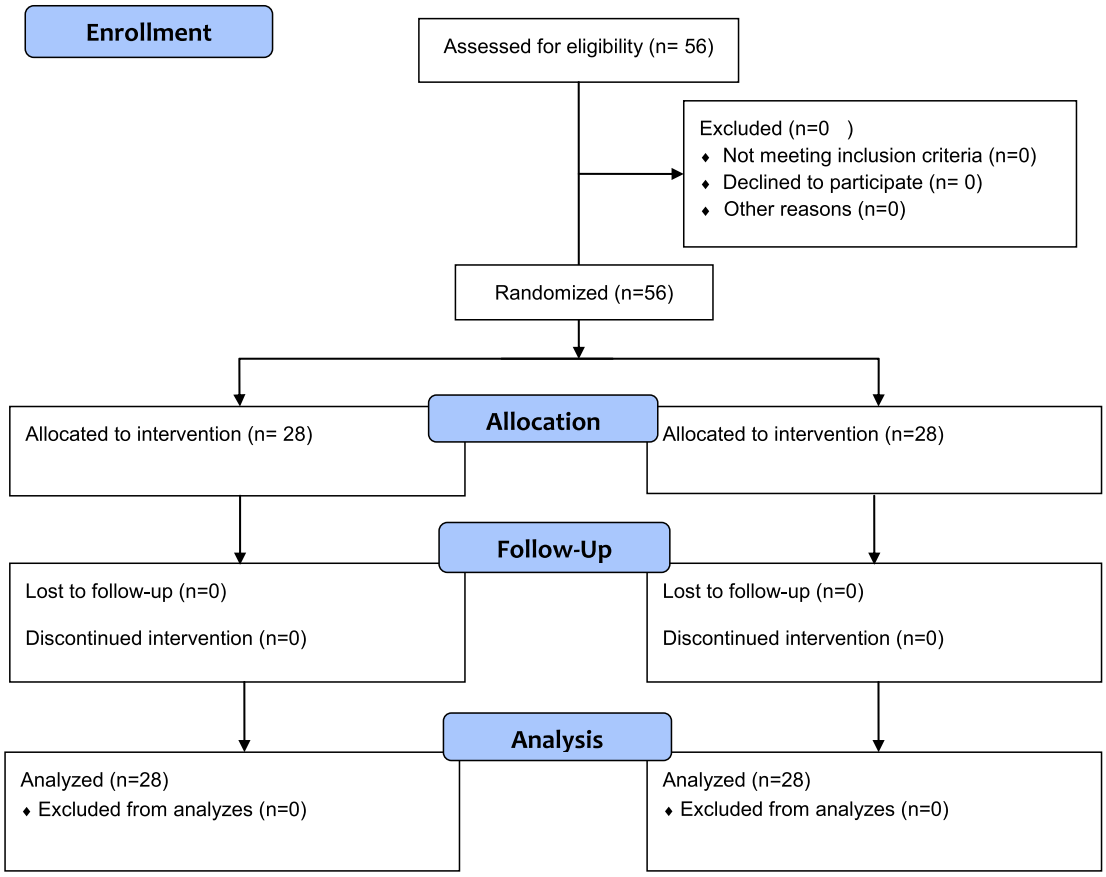

Fig. 1. Consort flow diagram.

guidelines for mucositis (Lalla et al., 2014), in order to facilitate evidence based patient care and improve outcomes. The current guidelines updated in 2013 examined the evidence for the following interventions: basic oral care, growth factors and cytokines, anti-inflammatory agents, antimicrobials, coating agents, anesthetics, analgesics, Laser and other light therapy, cryotherapy, natural and miscellaneous agents (Lalla et al., 2014). The most commonly used therapies often have no significant effect and sometimes cause additional side-effects (Arora et al., 2008).

Given the side-effects of chemical drugs, complementary therapies in the forms of herbal products are increasingly used all over the world (Adib-Hajbaghery and Hoseinian, 2014).

Most of ancient civilizations used different forms of herbal medicines. Among herbal plants, *Achillea millefolium* has attracted attentions due to its wide range of therapeutic effects. It is a well known herb from the asteraceae family, and has been extensively used in ancient medicine for treating different diseases in general and burns, injuries and infections in particular. One of the most important therapeutic effects of *A. millefolium* is its antibacterial effect on a wide range of pathogens (Aggarwal et al., 2011; Saeidnia et al., 2011; Tajik and Jalali, 2009). *A. millefolium* fresh flowers have been used to resolve respiratory problems (Düsman et al., 2013). It also was employed as anti-allergic (Aggarwal et al., 2011), anti-congestion, and expectorant (Nemeth and Bernath, 2008). Its flowers' distillates contain chamazulene, cineol, borneol (Orav et al., 2006), caffeic acid and salicylic acid with antibacterial, antispasmodic and anti-inflammatory effects (Aggarwal et al., 2011; Pires et al., 2009; Saeidnia et al., 2011; 2005). Some ingereduants of *A. millefolium* also exert beneficial effects on nervous, cardiovascular and digestive systems (Aggarwal et al., 2011). Despite historical background of this herb, reports about its application in treatment of wounds and injuries are rare (Tajik and Jalali, 2009). Aljancic et al. showed its significant inhibitory effect on candida albicans and bacillus subtilis in-vitro. They also reported that, the flavonoids existed in *A. millefolium* essence prevents the growth of aspergillus niger (Aljancic et al., 1999).

Sökmen et al. have also studied the antimicrobial effects of *A. millefolium* distillate on 12 bacterial species and 2 types of yeast. They have reported that though its aqueous extract had no antibacterial activity, the methanol one and the herb distillate had considerable antimicrobial activity (Sökmen et al., 2004). In another study, 32 separate ingredients have been extracted from *A. millefolium*, among which Comphor and Eucalyptol have significant inhibitory effects on candida albicens and clostridium perfringens. Also, Borneol and Piperitone in *A. millefolium* are two other compounds with considerable bacterial inhibitory activity (Sökmen et al., 2003).

During conversation with cancer patients, some revealed that to mitigate oral wounds, they gurgle *A. millefolium* distillate based on the recommendations received from some traditional groceries. Therefore, given the anti-inflammatory and antimicrobial effects of the plant, prevalence of chemotherapy-induced OM, and lack of studies on the effects of *A. millefolium* on chemotherapy induced oral muscositis, the present study was designed to investigate the effect of *A. millefolium* distillate-contained solution on the chemotherapy-induced OM.

Table 1
Demographic information of the cancer patients.[a]

Variable	Group		*P* value
	Experimental	Control	
Gender			>0.99[f]
Female	16 (57.1)	16 (57.1)	
Male	12 (42.9)	12 (42.9)	
Marital status			0.77[f]
Married	19 (67.9)	18 (64.3)	
Single, Widow, Divorced	9 (32.1)	10 (35.7)	
Education level			0.86[f]
Illiterate	14 (50)	12 (42.9)	
Literate	14 (50)	16 (57.1)	
Artificial teeth			>0.99[f]
Yes	17 (60.7)	17 (60.7)	
No	11 (39.3)	11 (39.3)	
Smoking habit			0.48[f]
Yes	4 (14.3)	6 (21.4)	
No	24 (85.7)	22 (78.6)	
Type of cancer			0.63[g]
Gastrointestinal	2 (25)	8 (28.6)	
Leukemia	9 (32.1)	7 (25)	
Lung	3 (10.7)	2 (7.1)	
Bone	2 (7.1)	2 (7.1)	
Kidney	1 (3.6)	5 (17.9)	
Breast	6 (21.4)	4 (14.3)	
Time of Cancer			0.76[g]
<12 months	21 (75)	20 (71.4)	
>12 months	7 (25)	8 (28.6)	
Chemotherapy regimens			0.84[g]
AMETAB[b]	5 (17.9)	4 (14.3)	
AMETAB + AK[c] + PD[d]	1 (3.6)	3 (10.7)	
AMETAB + AK + AA[e]	4 (14.3)	3 (10.7)	
AK + AA	5 (17.9)	8 (28.6)	
PD + AK + AA	4 (14.3)	4 (14.3)	
PD + AK	6 (21.4)	3 (10.7)	
AMETAB + AA	3 (10.7)	3 (10.7)	
Chemotherapy cycles			>0.99[g]
1–5 times	9 (32.1)	9 (32.1)	
5–10 times	15 (53.6)	13 (46.4)	
10–15 times	1 (3.6)	2 (7.1)	
15–20 times	3 (10.7)	4 (14.3)	
Receiving an Analgesic			>0.99[g]
Yes	5 (17.8)	5 (17.8)	
No	51 (82.2)	51 (82.2)	

[a] All data are presented as n (%).
[b] Antimetabolites.
[c] Alkylating agents.
[d] Plant derivatives.
[e] Antitumor antibiotics.
[f] Chi-square.
[g] Fishers exact test.

Methods

Study design and participants

This clinical trial study was conducted on cancer patients with chemotherapy-induced OM referring to Shahid Beheshti Hospital in Kashan, Iran, from September 2013 to January 2014.

Table 3
Comparison of mean severity of oral mucositis in the cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013 in three observations.[a]

Severity of oral mucositis	Group		*P* value[b]
	Control	Experimental	
Before intervention	2.39 ± 0.87	2.39 ± 0.87	>0.99
Day 7 after receiving mouthwash	2.75 ± 0.88	1.07 ± 0.85	0.001
Day 14 after receiving mouthwash	2.89 ± 0.95	0.32 ± 0.54	0.001
P value[c]	0.001	0.001	–

[a] All data presented as Mean ± SD.
[b] Mann–Whitney *U* test.
[c] Friedman test.

The patients were under chemotherapy and received an anti-inflammatory drug (Dexamethasone 8 mg) as well. Inclusion criteria were as follows: having clinical signs of chemotherapy-induced OM, being at age of 20 years old or over, complete consciousness, having no history of allergy, allergic rhinitis and asthma, no history of radiotherapy, and not receiving systemic antibiotic and antifungal drugs. Exclusion criteria were receiving radiotherapy during the study, fever, use of another mouthwash during the study, patient's decision to leave the study, irregular use of mouthwash in terms of time and amount, receiving systemic antibiotic or antifungal drugs at beginning or during the study.

Sample size was calculated using the results of a local study conducted by Shabanlouei et al. (2006), S1, S2, μ_1, and μ_2 were respectively equal to 3.62, 6.95, 14.75, and 3.18 (Shabanlouei et al., 2006). Accordingly, with a type I error of 0.05 and a power of 0.80, the sample size was determined to be seven patients for each group. However, for compensating probable attritions and achieving more reliable results, we recruited 28 patients for each group.

In the present study, 56 patients with inclusion criteria were entered the study consecutively and were randomly assigned into control and experimental groups (each 28 patients) in similar blocks based on OM severity. The randomization was performed using a computer software. The Consort flow diagram of the study is presented in Fig. 1.

The routine mouthwash was prepared by adding 1400 mg of Lidocaine, 224 mg of Dexamethasone, 35,000 mg of Sucralfate per liter to a Diphenhydramine solution. The Diphenhydramine solution was purchased from Alborz Daroo Company, Ghazvin, Iran. Control group received the routine mouthwash while patients in the experimental group received a mixture of the routing mouthwash and *A. millefolium* distillate (50/50). To keep the study blind from the patients and physician, both mouthwashes were prepared in bottles with similar shape, size and color and then all bottles were coded as “a” or “b.” The treating physician and the patients were not aware of codes. Also, the nurses who gave the bottle to the patients were not aware of codes. However, she documented the name of patients and the codes of the bottles and passed it to the researcher. In addition, the statistician who performed the data analysis was kept blinded to the allocation, as well.

Table 2
Comparison of grading the severity of oral mucositis in the cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013 in three observations.[a]

	Time					
	Before intervention		Day 7 of receiving mouthwash		Day 14 of receiving mouthwash	
Severity of oral mucositis	Experimental	Control	Experimental	Control	Experimental	Control
Grade zero	0 (0)	0 (0)	8 (28.6)	0 (0)	20 (71.4)	0 (0)
Grade 1	5 (17.9)	5 (17.9)	11 (39.3)	2 (7.1)	7 (25)	2 (7.1)
Grade 2	9 (32.1)	9 (32.1)	8 (28.6)	9 (32.1)	1 (3.6)	8 (28.6)
Grade 3	12 (42.9)	12 (42.9)	1 (3.6)	11 (39.3)	0 (0)	9 (32.1)
Grade 4	2 (7.1)	2 (7.1)	0 (0)	6 (21.4)	0 (0)	9 (32.1)

[a] All data are presented as n (%).

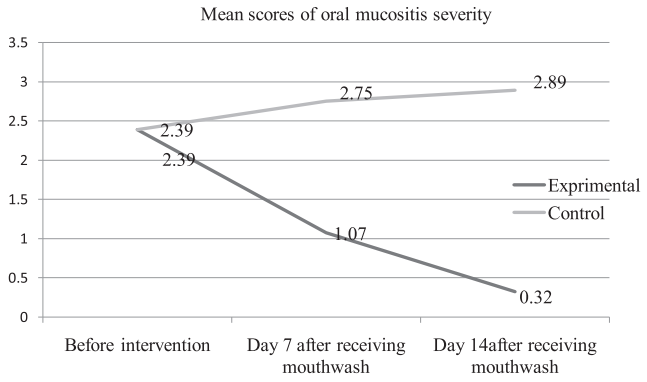

Fig. 2. Comparison of average severity of oral mucositis in the cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013 in three observations.

A. millefolium distillate was prepared from the yarrow herb growing in the plains of Ardahal, Kashan, Iran by Barij Esans Company, Kashan, Iran. In order to prepare 20 liters (L) of the distillate, 10 kg of yarrow plant flower with 50 L of water was boiled in a boiler connected to a condenser placed in cold water. The entire containers were from copper and the tubes from steel. The distillate used in this study had a concentration of 12 ppm.

The patients participated in the study were trained individually, how to perform mouth care, use of toothbrush and mouthwash. Patients' feedbacks were used to make sure they understood the provided information. All the patients were trained to wash their hands four times a day (after every meal: breakfast, lunch, dinner, and before going to bed), brush their teeth with a soft toothbrush and toothpaste and then use mouthwash. According to the instruction, for 14 days, they had to hold 15 mL of the solution for 3 min in their mouth, gargle the solution and then discard it. They were not allowed to wash their mouth or eat for an hour after mouth washing.

The instruments

The data were collected using a three-part instrument. The first part consisted of questions on demographics, type of cancer, chemotherapy information, and receiving an analgesic, smoking habit and using artificial teeth. The second part of the instrument was a checklist used to record the severity of OM at three times before, 7 and 14 days after the intervention. This checklist was based on the WHO criteria (2005) for assessment of OM severity as follows: grade zero: no wound; grade 1: pain and erythema; grade 2: erythema and wound, but the patient could swallow solid foods; grade 3: wound and extensive erythema, in this case the patient could not eat solid foods; grade 4: stomatitis has been spread to an extent that it could not be treated easily and eating is impossible. The severity of OM was scored according to its grade (i.e. ranging from zero to 4). The content validity and reliability of the Persian version of checklist were confirmed by Ashktorab et al. and its inter-observer reliability was 0.93 (Ashktorab et al., 2010). The third part of the instrument was another checklist for adherence monitoring. The checklist had 14 columns for each day one, and each column with four rows (four times a day). The patients or one of their companions were trained to mark the checklist. The researcher reviewed the checklists and also monitored the contains of the mouthwash bottles at seventh and fourteenth days and the adherence was equal between both groups.

Table 4
Comparison of average severity of oral mucositis in both groups in the cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013 in three observations.

Group	Time	Mean difference of oral mucositis severity	*P* value
Experimental			
Before intervention	Day 7 after intervention	1.32 ± 0.13	0.001
	Day 14 after intervention	2.07 ± 0.13	0.001
Day 7 after intervention	Day 14 after intervention	0.75 ± 0.11	0.001
Control			
Before intervention	Day 7 after intervention	−0.35 ± 0.09	0.002
	Day 14 after intervention	−0.50 ± 0.09	0.001
Day 7 after intervention	Day 14 after intervention	−0.14 ± 0.06	0.04

Table 5
The relationship between oral mucositis severity and age, cigarette numbers per day and Chemotherapy cycles carried out in cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013.[a]

Group	Age	Cigarette number per day	Number of chemotherapy cycles
Experimental			
Severity of oral mucositis before intervention	−0.05	0.27	0.14
Severity of oral mucositis in day 7	−0.13	−0.05	0.01
Severity of oral mucositis in day 14	−0.08	–	0.03
Control			
Severity of oral mucositis before intervention	−0.25	−0.15	−0.03
Severity of oral mucositis in day 7	−0.27	−0.25	−0.04
Severity of oral mucositis in day 14	−0.19	−0.25	0.08

[a] All data presented as correlation coefficient.

Ethical considerations

The study was approved by the Research Council and Research Ethics Committee of Kashan University of Medical Sciences, No.: P/29/5/1/2571 dated 16 Sep. 2013. All the patients signed a written informed consent before participation in the study; for illiterate patients the form was read by the researcher. All the patients were informed that participation in the study is voluntary and were assured that their personal information would be treated confidentially. Researchers were committed to consider the participants' rights in accordance to the principles explained in the Helsinki Declaration.

Data analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS, v. 11.5). Descriptive statistics were used to describe and classify the data. Chi-square and Fisher's exact tests were used to compare the two groups in terms of demographic information, type of cancer, smoking habit, using artificial teeth, chemotherapy regime, number of chemotherapy cycles and, receiving an analgesic drug.

The Friedman (in each group) and Mann–Whitney *U* tests (between two groups) were used to compare the stomatitis severity at three times before, 7 and 14 days after intervention. Moreover, the Mann–Whitney *U* test was used to compare the mean scores of OM severity in the two genders, in patients with and without smoking habit, and in patients with and without artificial teeth. Furthermore, Kruskal–Wallis test was used to compare the severity of OM in different cancer types and chemotherapy regimens. The Spearman correlation coefficient was also used to evaluate the relationship between the severity of OM and number of

Table 6
Comparison of mean oral mucositis severity in terms of gender, artificial teeth, smoking habit and cancer type in cancer patients who referred to Shahid Beheshti Hospital, Kashan in 2013.[a]

Group	Severity of oral mucositis					
	Before intervention	*P* value	Day 7	*P* value	Day 14	*P* value
Experimental						
Gender		0.92[b]		0.86[b]		0.65[b]
Male	2.42 ± 0.90		1.08 ± 0.79		0.25 ± 0.45	
Female	2.38 ± 0.88		1.06 ± 0.92		0.38 ± 0.61	
Artificial teeth		0.23[b]		0.37[b]		0.43[b]
Yes	2.24 ± 0.90		0.94 ± 0.74		0.24 ± 0.43	
No	2.64 ± 0.80		1.27 ± 1.01		0.45 ± 0.68	
Smoking habit		0.60[b]		0.42[b]		0.18[b]
Yes	2.25 ± 0.5		0.75 ± 0.95		0.001 ± 0.001	
No	2.42 ± 0.92		1.12 ± 0.85		0.38 ± 0.57	
Type of cancer		0.73[c]		0.70[c]		0.47[c]
Gastrointestinal	2.63 ± 0.51		1.38 ± 0.74		0.50 ± 0.53	
Leukemia	2.11 ± 1.05		0.89 ± 0.92		0.22 ± 0.44	
Lung	2.33 ± 0.57		0.67 ± 0.57		0.01 ± 0.01	
Bone	2.00 ± 10.41		1.00 ± 1.41		0.50 ± 0.70	
Kidney	–		–		–	
Breast	2.67 ± 1.03		1.17 ± 0.98		0.33 ± 0.81	
Control						
Gender		0.92[b]		0.44[b]		0.35[b]
Male	2.42 ± 1.08		2.58 ± 1.08		2.67 ± 1.15	
Female	2.38 ± 0.71		2.88 ± 0.71		3.06 ± 0.77	
Artificial teeth		0.49[b]		0.60[b]		0.76[b]
Yes	2.29 ± 0.77		2.71 ± 0.68		2.88 ± 0.85	
No	2.55 ± 1.03		2.82 ± 1.16		2.91 ± 1.13	
Smoking habit		0.63[b]		0.54[b]		0.86[b]
Yes	2.50 ± 1.22		2.83 ± 1.47		2.83 ± 1.47	
No	2.36 ± 0.79		2.73 ± 0.70		2.91 ± 0.81	
Type of cancer		0.49[c]		0.44[c]		0.29[c]
Gastrointestinal	2.29 ± 0.75		2.57 ± 1.13		2.71 ± 1.11	
Leukemia	2.57 ± 0.97		3.00 ± 0.81		3.14 ± 0.90	
Lung	2.50 ± 0.70		3.00 ± 0.01		3.50 ± 0.70	
Bone	3.00 ± 1.41		3.50 ± 0.70		3.50 ± 0.70	
Kidney	1.83 ± 0.98		2.17 ± 0.75		2.17 ± 0.75	
Breast	2.75 ± 0.50		3 ± 0.81		3.25 ± 0.95	

[a] All data presented as Mean ± SD.
[b] Mann–Whitney *U*.
[c] Kruskal–Wallis test.

chemotherapy cycles or numbers of cigarette per day and age. A *P*-value less than 0.05 was considered significant for all tests.

Results

The number of patients' participated in this study was 56. No significant difference was observed in terms of mean age between the experimental (56.46 ± 14.32) and control group (55.54 ± 14.01) ($P = 0.8$). In total, 67.9% of the experimental group and 64.3% of the control group were married. There was no significant difference between the two groups regarding artificial teeth, smoking habit, type of cancer, chemotherapy regimens and other demographic information (Table 1).

Before receiving the mouthwashes, 42.9% and 7.1% of the patients in control and experimental groups were in grade 3 or 4 OM, respectively. In the days 7 and 14 after the intervention, 3.6% and 0% of the experimental group were in of grade 3 or 4 OM, respectively. However, at this times, the rate of patients with grade 3 or 4 OM were increased to more than 60% in the control group (Table 2).

The mean score of OM severity was equal (2.39 ± 0.87) in both groups at the start of the study. The mean severity score of OM in the experimental group was reduced to 1.07 ± 0.85 and 0.32 ± 0.54 in days 7 and 14 after the intervention, respectively (*P* value < 0.001). However, in the control group, the mean severity score of OM was increased to 2.75 ± 0.88 and 2.89 ± 0.95 in days 7 and 14, respectively (*P* value < 0.001) (Table 3 and Fig. 2).

However, Friedman and Wilcoxon tests showed the significant differences ($p < 0.001$) between the mean severity score of OM in control and experimental group at the three assessment times as well (Tables 3 and 4).

The Spearman correlation coefficient showed no significant relationship between the severity of OM and age, daily cigarette smoking, or number of chemotherapy cycles ($P > 0.05$) (Table 5). Also, the Mann–Whitney *U* test certified that none of the factors such as gender, dentures or smoking habits had any effect on severity of OM before or during the study (Table 6). Although the mean score of OM of women, especially in the control group was higher than that in men but none of them were statistically significant. Kruskal–Wallis test showed no significant difference between the mean score of OM severity in patients with different types of cancer and chemotherapy regimens (Tables 6 and 7).

Discussion

The present study was designed to investigate the effect of adding *A. millefolium* distillate on mouthwash on chemotherapy-induced OM. In this study, the severity of OM was significantly reduced in the experimental group receiving the *A. millefolium*-contained solution. It was interesting that more than 71% of the patients in this group were completely healed at day 14 of the experiment. No previous studies are available on using *A. millefolium* to treat OM due to cancer chemotherapy. However, findings of the present study was consistent with a study that used

Table 7
The comparison of mean and standard deviation of oral mucositis severity scores in terms of chemotherapy regimens.[a]

Chemotherapy regimens in the two groups	Before intervention	*P* value[b]	Day 7	*P* value[b]	Day 14	*P* value[b]
Experimental		0.29		0.23		0.15
AMETAB	2.40 ± 0.54		1.20 ± 0.44		0.20 ± 0.44	
AMETAB + AK + PD	3.00 ± 0		2.00 ± 0		1.00 ± 0	
AMETAB + AK + AA	3.25 ± 0.50		1.75 ± 0.95		1.00 ± 0.81	
AK + AA	2.00 ± 1.22		0.80 ± 0.83		0.2 ± 0.44	
PD + AK + AA	2.00 ± 0.81		0.25 ± 0.50		0.01 ± 0.001	
PD + AK	2.17 ± 0.98		1.00 ± 0.89		0.17 ± 0.40	
AMETAB + AA	2.67 ± 0.57		1.33 ± 1.15		0.33 ± 0.57	
Control		0.26		0.51		0.40
AMETAB	2.00 ± 0.81		2.25 ± 0.50		2.50 ± 1.00	
AMETAB + AK + PD	3.00 ± 1.00		3.00 ± 1.00		3.33 ± 1.15	
AMETAB + AK + AA	2.67 ± 0.57		3.00 ± 1.00		3 ± 1.00	
AK + AA	2.38 ± 1.06		2.88 ± 0.99		3 ± 1.06	
PD + AK + AA	2.75 ± 0.50		2.75 ± 0.50		2.75 ± 0.50	
PD + AK	1.33 ± 0.57		2.00 ± 1.00		2.00 ± 1.00	
AMETAB + AA	2.67 ± 0.57		3.33 ± 1.15		3.67 ± 0.57	

[a] All data presented as Mean ± SD.
[a] Kruskal Wallis Test.

another complex mouthwash (Traumeel S®) containing different herbal materials, including *A. millefolium* and reported that it was effective in treating OM after hematopoietic stem cell transplantation (Oberbaum et al., 2001). In another study, the healing effects of *A. millefolium* on treatment of rats' gastric ulcer have been confirmed. This effect was attributed to the antibacterial and healing properties of *A. millefolium* (Rashidi et al., 2005).

In the present study, the routine mouthwash used in cancer clinic (which was a mixture of Lidocaine, Dexamethasone, Sucralfate and Diphenhydramine) did not show any significant effect on the chemotherapy induced OM. Consequently, the severity of OM was increased in the control group during the experiment. In a recent study, it has reported that although Allopurinol, granulocyte growth factors, immunoglobulin's and herbal extracts are effective but sucralfate, lidocaine, or diphenhydramine had no effect in treating chemotherapy-induced OM (Clarkson et al., 2008).

The findings of this study revealed that neither in the experimental group nor in the control group, there was no significant relation between stomatitis severity and factors such as, gender, age, and cancer type. However, some of previous studies have reported that gender and age could affect the severity of chemotherapy induced OM so that females, older people and children are more vulnerable to severe OM (Cheng et al., 2004; Eilers, 2004; Vokurka et al., 2006). This discrepancy might be explained by the fact that our patients did not include any children or very older people. Beside, the different OM severity seen between men and women is clinically important even though it was not statistically significant.

The findings of this study revealed that neither in experimental group, nor in control group, there was no significant difference between the severity of OM in different chemotherapy regimens. This finding may be attributed to the diversity of chemotherapy regimens in our patients. Then a small number of patients were under treatment with each type of regimen and this small number was not enough to detect differences in the severity of OM.

Limitations of the study

The small sample size, not studying other variables such as teeth problems (decay, break, and implant), history of oral disease, and white blood cell (WBC) count may limit the generalizability of the findings. Also, if the patients' mouths were checked daily in order to determine the treatment progress, more precise data would have been generated.

Conclusion

Since the mixture of *A. millefolium* distillate with the routine solution used in this study could decrease the severity of OM due to chemotherapy and had no side effects, this solution might be used for all patients during chemotherapy. Given the *A. millefolium* distillate was mixed with ward's routine solution, it is suggested that *A. millefolium* distillate alone be used to clearly define its effect on improvement of OM. Also the mixture of *A. millefolium* distillate with other types of mouthwash should be tested to optimize the effect of this plant.

Conflicts of interest

None declared.

Acknowledgments

This article is the report of a Master's thesis, funded by Kashan University of Medical Sciences with the grant number 9282. We would like to thank the research deputy of Kashan University of Medical Sciences for its funding, as well as the management of Shahid Beheshti Hospital, head nurse of oncology and chemotherapy department, and Kashan Barij Esans Company's laboratory for their cooperation. All the patients who patiently participated in the study were also appreciated.

References

Abedipour, A., Abedsaeedi, J., Salehi, M., Ebrahimi, E., 2006. Comparison of persica and Chlorhexidine mouthwashes in prevention of stomatitis in patients receiving chemotherapy. Iranian Journal of Nursing Research 1 (1), 41–46.
Adib-Hajbaghery, M., Hoseinian, M., 2014. Knowledge, attitude and practice toward complementary and traditional medicine among Kashan health care staff, 2012. Complementary Therapies in Medicine 22 (1), 126–132.
Aggarwal, B.B., Prasad, S., Reuter, S., Kannappan, R., Yadev, V.R., Park, B., et al., 2011. Identification of novel anti-inflammatory agents from Ayurvedic medicine for prevention of chronic diseases: “reverse pharmacology” and “bedside to bench” approach. Current Drug Targets 12 (11), 1595–1653.
Aljancic, I., Vajs, V., Menkovic, N., Karadzic, I., Juranic, N., Milosavljevic, S., et al., 1999. Flavones and Sesquiterpene Lactones from Achillea a trata subsp. m ultifida: antimicrobial Activity. Journal of Natural Products 62 (6), 909–911.
Arora, H., Pai, K.M., Maiya, A., Vidyasagar, M., Rajeev, A., 2008. Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis

in oral cancer patients. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 105 (2), 180–186 e181.
Ashktorab, T., Yazdani, Z., Mojab, F., Majd, H., Madani, H., 2010. Preventive effects of an oral rinse Peppermint essence on chemotherapy-induced oral mucosistis. Koomesh 12 (1), 8–13.
Avritscher, E.B., Cooksley, C.D., Elting, L.S., 2004. Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. Seminars in Oncology Nursing 20 (1), 3–10.
Cheng, K.K., Chang, A.M., Yuen, M., 2004. Prevention of oral mucositis in paediatric patients treated with chemotherapy: a randomised crossover trial comparing two protocols of oral care. European Journal of Cancer 40 (8), 1208–1216.
Clarkson, J.E., Worthington, H.V., Eden, O., 2008. Interventions for treating oral mucositis for patients with cancer receiving treatment. Australian Dental Journal 53 (4), 363–365.
Düsman, E., Almeida, I. V. d., Coelho, A.C., Balbi, T.J., Düsman Tonin, L.T., Vicentini, V.E.P., 2013. Antimutagenic effect of medicinal plants Achillea millefolium and Bauhinia forficata in vivo. Evidence-Based Complementary and Alternative Medicine 2013, 893050.
Eilers, J., 2004. Nursing interventions and supportive care for the prevention and treatment of oral mucositis associated with cancer treatment. Oncology Nursing Forum 31 (4), 13–23.
He, M., 2011. Interventions for preventing oral mucositis in patients with cancer receiving treatment. Clinical Nurse Specialist 25 (6), 284–285.
Lalla, R.V., Bowen, J., Barasch, A., Elting, L., Epstein, J., Keefe, D.M., et al., 2014. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 120 (10), 1453–1461.
Nemeth, E., Bernath, J., 2008. Biological activities of yarrow species (Achillea spp.). Current Pharmaceutical Design 14 (29), 3151–3167.
Oberbaum, M., Yaniv, I., Ben-Gal, Y., Stein, J., Ben-Zvi, N., Freedman, L., et al., 2001. A randomized, controlled clinical trial of the homeopathic medication TRAUMEEL S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. Cancer 92, 684–690.
Orav, A., Arak, E., Raal, A., 2006. Phytochemical analysis of the essential oil of Achillea millefolium L. from various European countries. Journal of Asian Natural Product Research 20 (12), 1082–1088.
Pavesi, V.C., Lopez, T.C., Martins, M.A., Sant'Ana Filho, M., Bussadori, S.K., Fernandes, K.P., et al., 2011. Healing action of topical chamomile on 5-fluouracil induced oral mucositis in hamster. Supportive Care in Cancer 19 (5), 639–646.
Pires, J.M., Mendes, F.R., Negri, G., Duarte-Almeida, J.M., Carlini, E.A., 2009. Antinociceptive peripheral effect of Achillea millefolium L. and Artemisia vulgaris L.: both plants known popularly by brand names of analgesic drugs. Phytotherapy Research 23 (2), 212–219.
Potting, C., Uitterhoeve, R., Reimer, O., Scholte, W., Van Achterberg, T., 2006. The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: a systematic review. European Journal of Cancer Care 15 (5), 431–439.
Rashidi, I., Taherimoghadam, M., Mozaffari, A., 2005. Study of anti-inflammatory and healing effects of Achillea millefolium in the treatment of indomethacin-induced gasthic ulcer in rat. The Journal of Qazvin University of Medical Sciences 8 (33), 9–13.
Saeidnia, S., Gohari, A., Mokhber-Dezfuli, N., Kiuchi, F., 2011. A review on phytochemistry and medicinal properties of the genus Achillea. DARU Journal of Pharmaceutical Sciences 19 (3), 173–186.
Saeidnia, S., Gohari, A.R., Yassa, N., Shafiee, A., 2005. Composition of the volatile oil of Achillea conferta DC. from Iran. DARU Journal of Pharmaceutical Sciences 13 (1), 34–36.
Shabanlouei, R., Ahmadi, F., Vaez, G.J., Hajizadeh, E., Javadzadeh, Y., 2006. Effect of chamomile mouthwash in the prevention of chemotherapy-induced stomatitis. Journal of Rehabitation 7 (2), 70–75.
Sökmen, A., Sökmen, M., Daferera, D., Polissiou, M., Candan, F., Ünlü, M., et al., 2004. The in vitro antioxidant and antimicrobial activities of the essential oil and methanol extracts of Achillea biebersteini Afan. (Asteraceae). Phytotherapy Research 18 (6), 451–456.
Sökmen, A., Vardar-Ünlü, G., Polissiou, M., Daferera, D., Sökmen, M., Dönmez, E., 2003. Antimicrobial activity of essential oil and methanol extracts of Achillea sintenisii Hub. Mor. (Asteraceae). Phytotherapy Research 17 (9), 1005–1010.
Tajik, H., Jalali, F.S.S., 2009. Comparative evaluation of antimicrobial efficacy of aqueous and alcoholic extracts of yarrow against pathogenic microorganisms. Urmia Medical Journal 19 (4), 302–309.
Vera-Llonch, M., Oster, G., Ford, C.M., Lu, J., Sonis, S., 2007. Oral mucositis and outcomes of allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies. Supportive Care in Cancer 15 (5), 491–496.
Vokurka, S., Bystrická, E., Koza, V., Scudlová, J., Pavlicová, V., Valentová, D., et al., 2006. Higher incidence of chemotherapy induced oral mucositis in females: a supplement of multivariate analysis to a randomized multicentre study. Supportive Care in Cancer 14 (9), 974–976.
Yarom, N., Ariyawardana, A., Hovan, A., Barasch, A., Jarvis, V., Jensen, S.B., et al., 2013. Systematic review of natural agents for the management of oral mucositis in cancer patients. Supportive Care in Cancer 21 (11), 3209–3221.