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A New mouthwash for Chemotherapy Induced Stomatitis

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Background: Stomatitis is a disturbing side-effect of chemotherapy that disturbs patients and causes difficulties in patient's drinking, eating and talking, and may results in infection and bleeding.
Objectives: This study aimed to investigate the effect of *Yarrow* distillate in the treatment of chemotherapy-induced stomatitis.
Patients and Methods: This randomized controlled trial study was conducted during 2013. The study population consisted of all cancer patients with chemotherapy-induced oral stomatitis referred to Shahid Beheshti Medical Center, Kashan, Iran. The data collection instrument had two-part; a demographic part and another part recording the severity of the stomatitis at the first, seventh, and 14th days of the intervention based on a WHO criteria checklist in 2005. In this study, 56 patients diagnosed with cancer were randomly assigned into control and experimental groups in similar blocks according to their stomatitis severity. The experimental group gargled 15 mL of a routine solution mixed with Yarrow distillate 4 times a day for 14 days while the control group gargled 15 mL of routine solution. The severity of stomatitis was assessed at the beginning of the intervention, and then after 7 and 14 days of the study. Data were analyzed using chi-square and Fisher exact test, Mann-Whitney *U*, Kruskal-Wallis, and Friedman tests using SPSS 11.5 software.
Results: At first, the median score of stomatitis in the experimental group was 2.50 that significantly reduced to 1 and 0 in days 7 and 14 of the intervention, respectively (P value < 0.001). However, in the control group, the median score of stomatitis was 2.50, which significantly increased to 3 in days 7 and 14 (P value < 0.001).
Conclusions: *Yarrow* distillate-contained solution reduced stomatitis severity more than the routine solution. Therefore, we suggest using it in patients with chemotherapy-induced stomatitis.

Keywords: Yarrow distillate; Chemotherapy; Stomatitis; Cancer; Mouthwashes

1. Background

Cancer is an important challenge for the healthcare system (1, 2). Recent reports show that the rate of cancer is increasing with a fixed trend all over the world (1). Cancer has been known as the third major cause of mortality in Iran after the cardiovascular disease and accidents (3). Furthermore, it is the second cause of mortality in developed countries (4), and accounts for 13% to 25% of all deaths worldwide (1, 5).

Neoplasms are treated either to improve survival rate, or (if the treatment is impossible) to relief the symptoms, and to improve the quality of life. A combination of surgery, radiotherapy, chemotherapy, and biological treatments are usually used to achieve these objectives (2, 6). Chemotherapy is a common treatment that may result in longer periods of survival (7, 8). However, chemotherapy is accompanied with different problems; including bone marrow and immune system suppression; liver toxicity; complications in skin, central nervous system, urinary tract, and digestive tract such as inflammation of mouth and intestine mucosa (7, 8).

Stomatitis or oral mucositis is a typical chemotherapy-induced debilitating problem (9, 10) to such an extent that about 10% of the patients receiving adjuvant chemotherapy, 40% of the patients receiving neoadjuvant chemotherapy, and 80% of the patients being treated with stem cells suffer from this problem (11-13). Stomatitis-induced pain disturbs patients and makes it difficult to eat and drink, resulting in indigestion and dehydration (5, 9, 14). Stomatitis can also disturb speaking and communication with others, resulting in psychological and social problems (1, 7, 8). In addition, stomatitis is accompanied by a wide range of oral mucosa alterations such as infection and bleeding, which could result in systemic infection (7, 8).

In severe cases, it would increase the length of hospitalization and even make the physician to cease the chemotherapy (5, 9). Various methods and medications such as oral and dental hygiene, different types of mouthwash, applying ice and local anesthetics, magnesium-contained antacids, diphenhydramine, nystatin, prostaglandin E, granulocyte-macrophage colony-stimulating factor (GM-CSF), amphotericin, and chamomile essence are currently being used to treat stomatitis (2, 7, 8). Moreover, preventive measures are being taken, including receiv-

ing baking soda, normal saline, chlorhexidine, sucralfate, persica solution, allopurinol mouthwash, menthe distillate, and benzydamine solution (2, 7, 8, 15, 16). The most commonly used therapies often have no significant effect and sometimes cause additional problems (15). Given the side-effects of chemical drugs, complementary therapies in the forms of herbal products are increasingly used all over the world (17, 18).

Most of the ancient civilizations used different forms of herbal medicines. The Yarrow plant (also called *Achillea millefolium*) belongs to the Asteraceae family. It is a well-known herb and has been extensively used in ancient medicine for treating different diseases in general and burns and injuries in particular. One of the most important therapeutic effects of *Yarrow* plant is its antibacterial effect on a wide range of pathogens (19). The *Yarrow* fresh flowers have been used to treat respiratory problems (20). It was also employed as an anti-allergic (21), anti-congestion, and expectorant medicine (22). Its flowers' distillates contain chamazulene, cineol, and borneol (23) with anti-inflammatory and anti-spasmodic effects (24, 25), and also beneficial effects on nervous, cardiovascular and digestive systems (21).

Despite the historical background of this herb, reports about its therapeutic effects on wounds and injuries are rare (19). Aljancic et al. showed its significant inhibitory effect on *Candida albicans* and *Bacillus subtilis* in vitro. They also reported that, the flavonoids existed in *Yarrow* essence prevents the growth of *Aspergillus niger* (26). Sokmen et al. have also studied the antimicrobial effects of *Yarrow* distillate on 12 bacterial species and 2 types of yeast. They have reported that its aqueous extract had no antibacterial activity, the methanol one and the herb distillate had considerable antimicrobial activity though (27), in another study, no significant difference was observed in antimicrobial effects of aqueous and alcoholic extracts of *Yarrow* (19).

2. Objectives

The researchers' observations showed that cancer patients used Yarrow essence to alleviate their oral stomatitis. Therefore, the present study was designed to investigate the effect of *Yarrow* distillate-contained solution on the chemotherapy-induced stomatitis.

3. Patients and Methods

This was a triple-blind randomized trial study conducted on patients suffering from cancer with chemotherapy-induced oral stomatitis referring to Shahid Beheshti Hospital in Kashan, Iran, during 2013. They were under chemotherapy and received an anti-inflammatory drug (Dexamethasone 8 mg) as well. In this study, the patients, physician, and nurses (who gave the medications) remained blind to the intervention outcomes and allocation of the subjects to the intervention and control groups. The physician who examined patients' oral mucosa was also blind to the study and the intervention groups. In addition, the statistician who performed the data analysis was kept blinded to the allocation, as well.

Inclusion criteria were as follows: having chemotherapy-induced oral stomatitis; $\leq$ 20 years; 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 the beginning or during the study.

The study sample size was calculated using the results of a local study conducted by Shabanloei et al. (2007), in which S1, S2, μ1, and μ2 were equal to 3.62, 6.95, 14.75, and 3.18, respectively. 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 enrolled 28 patients for each group. Patients were recruited to the study by using the convenience sampling method. In the present study, 56 patients were selected based on the above-mentioned criteria and were randomly assigned into control and experimental groups in similar blocks based on stomatitis intensity. No patient was excluded, and no data missed during the study (Figure 1).

3.1. Intervention

The routine mouthwash was prepared by adding 1400 mg of lidocaine, 224 mg of dexamethasone, 35000 mg of sucralfate per liter to diphenhydramine solution. The diphenhydramine solution was purchased from Alborz Daroo Company, Ghazvin, Iran. Control group received the routine mouthwash while the patients in the experimental group received a mixture of the routing mouthwash and *Yarrow* distillate (50/50). Both bottles were similar in shape and size, distinguished only by a special code (bottle No. 1 and 2). The *Yarrow* 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 L of the distillate, 10 Kg of yarrow plant flowers 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.

All patients were trained individually, how to do mouth care, and use toothbrush and mouthwash. The patients were trained to wash their hands four times a day (after every meal: breakfast, lunch, dinner, and before going to bed) and brush their teeth with a soft toothbrush and toothpaste. According to the instruction, for 14 days, they had to hold 15 mL of the solution for 3 minutes in their mouth and then discard it. They were not allowed to wash their mouth or eat for an hour after mouth

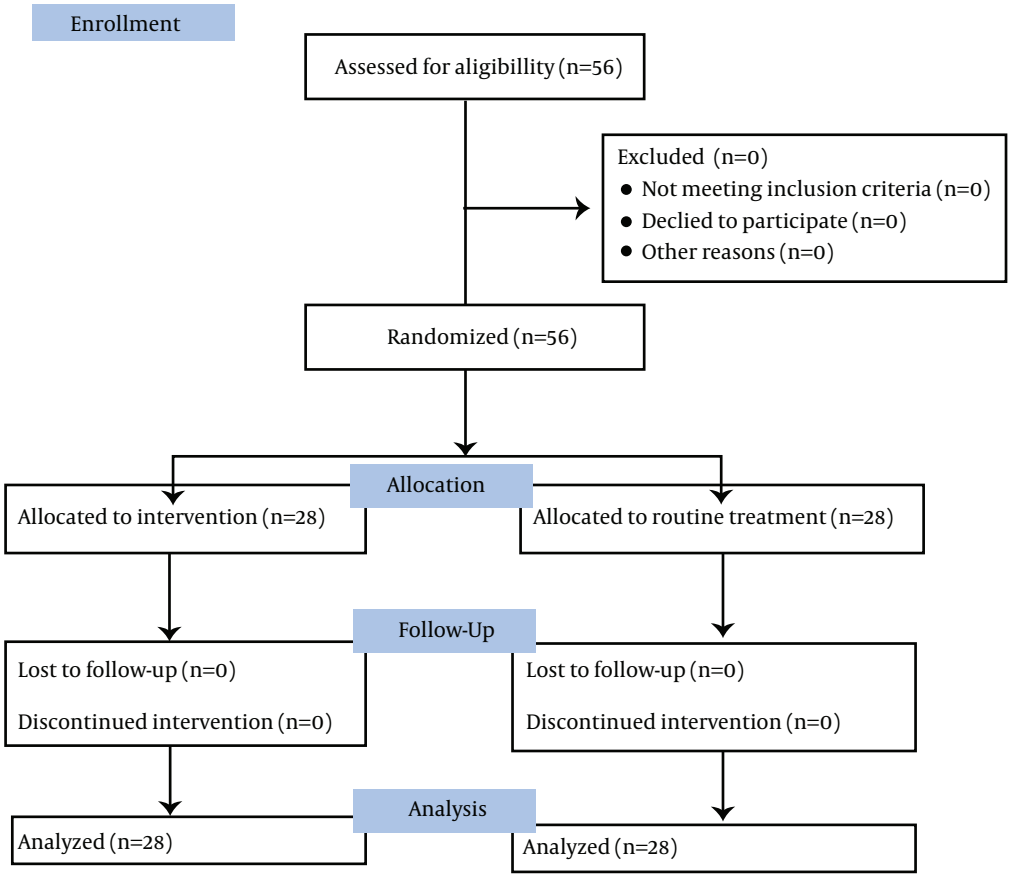

Figure 1. Consort Flow Diagram

washing. To ensure proper mouthwash use, patients or one of their companions were trained to mark a checklist. The checklist had 14 columns (days) and each column with four rows (four times a day).

3.2. Data Collection

The data were collected using a two-part instrument. The first part consisted of demographic questions (age, gender, marital status, and education level), time of cancer, chemotherapy information (type, cycle's number in before intervention and during the study), receiving an analgesic, smoking habit and artificial teeth. The second part of the instrument was a checklist used to record the severity of stomatitis at the first, seventh and 14^{th} days of the experiment. The severity of stomatitis was assessed based on WHO criteria (2005) as follows: grade 0 (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 stomatitis was scored according to its grade (i.e. ranging from 0 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 (28).

3.3. 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. The objectives of the study were explained to all the participants, and all of them signed a written informed consent before participation in the study. 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 Declaration of Helsinki.

3.4. Data Analysis

Data analysis was performed using SPSS version 11.5 software (SPSS Inc., Chicago, IL, and The USA). Descriptive statistics were used to describe and classify the data. Chi-square and Fisher exact tests were used to compare

the two groups in terms of gender, marital status, education level, time of cancer, smoking habit, using false teeth, number of chemotherapy cycles before intervention and during the study and receiving an analgesic drug. The Shapiro-Wilk test showed that the distribution of data was not normal. Friedman (in each group) and Mann-Whitney *U* tests (between two groups) were used to compare the stomatitis severity at three times: At the onset, 7, and 14 days after intervention. Also, the Mann-Whitney *U* test was used to compare the mean scores of stomatitis severity in the two genders. The Spearman correlation coefficient was also used to evaluate the relationship between stomatitis severity and age. A *P* value less than 0.05 was considered significant for all tests.

Table 1. Demographic Information of the Cancer Patients[a]

Variable	Group		P Value
	Experimental	Control	
Gender			0.99[b]
Female	16 (57.1)	16 (57.1)	
Male	12 (42.9)	12 (42.9)	
Marital status			0.778[b]
Married	19 (67.9)	18 (64.3)	
Single, Widow, Divorced	9 (32.1)	10 (35.7)	
Education level			0.592[b]
Illiterate	14 (50)	12 (42.9)	
Literate	14 (50)	16 (57.1)	
Artificial teeth			0.99[b]
Yes	17 (60.7)	17 (60.7)	
No	11 (39.3)	11 (39.3)	
Smoking habit			0.485[b]
Yes	4 (14.3)	6 (21.4)	
No	24 (85.7)	22 (78.6)	
Duration of Cancer, mo			0.763[c]
< 12	21 (75)	20 (71.4)	
> 12	7 (25)	8 (28.6)	
Chemotherapy cycles before intervention			0.946[c]
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)	
Chemotherapy cycles during the study			0.567[b]
1 time	20 (71.4)	18 (64.3)	
2 times	8 (28.6)	10 (35.7)	
Receiving an Analgesic			0.99[c]
Yes	5 (17.8)	5 (17.8)	
No	51 (82.2)	51 (82.2)	

[a] All data are presented as No. (%).
[b] chi-square.
[c] Fisher exact test.

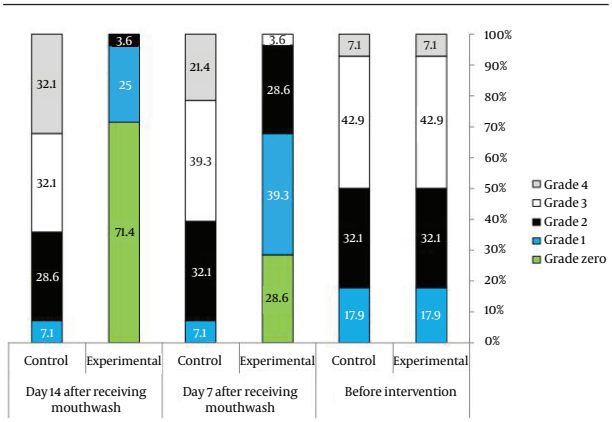

Figure 2. Comparison of the Severity of Stomatitis in Three Observations

Table 2. Comparison of Average Stomatitis Severity Scores in Three Observations

Severity of stomatitis	Group		*P* Value[a]	*Z* Value
	Control	Experimental		
	Median (Q3-Q1)	Median (Q3-Q1)		
Before intervention	2.50 (3-2)	2.50 (3-2)	1	0.000
Day 7 after receiving mouthwash	3 (3-2)	1 (2-0)	0.001	-5.26
Day 14 after receiving mouthwash	3 (4-2)	0 (1-0)	0.001	-6.41
P value[b]	0.001	0.001	-	-

[a] Mann-Whitney *U* test.
[b] Friedman test.

4. Results

Totally, 56 patients participated in this study. No significant difference was observed in terms of average age between the experimental (56.46 ± 14.32 y) and control group (55.54 ± 14.01 y) ($P = 0.807$). In total, 67.9% of the experimental group and 64.3% of the control group were married. There was no significant difference regarding false teeth, smoking habit, and other demographic information between the two groups (Table 1). The Spearman correlation coefficient showed no significant relationship between stomatitis severity and age (*P* value > 0.05). Also, the Mann-Whitney *U* test certified that gender had no effect on stomatitis severity before or during the study (*P* value > 0.05).

Before receiving the solutions, 42.9% and 32.1% of the patients in control and experimental groups had grade 3 and 2 stomatitis, respectively (Figure 2). The median score of stomatitis severity was equal (2.50) in both groups at the start of the study. The median scores of stomatitis in the experimental group significantly reduced to 1 and 0 in days 7 and 14 after the intervention, respectively (*P* value < 0.001). However, in the control group, the median score of stomatitis increased to 3 in days 7 and 14 (*P* value < 0.001) (Table 2).

5. Discussion

The present study was designed to investigate the effect of *Yarrow* distillate on chemotherapy-induced stomatitis. In this study, the stomatitis severity was significantly reduced in the experimental group receiving the solution contained *Yarrow* distillate. It was interesting to see that, more than 71% of the patients in this group were completely cured on 14th day of the experiment. Abedipour et al. have compared the effects of chlorhexidine and persica mouthwash -that contains *A. millefolium*- on preventing stomatitis in patients receiving chemotherapy and reported that both mouthwashes had similar effects. However, due to its better taste and smell, they recommended persica mouthwash as an alternative for chlorhexidine (7). Using different solutions and different forms of plant might be the reason for the different results seen between their study and ours i.e. we used *Yarrow* distillate in our routine mouthwash, but they used the extract of *Yarrow* in chlorhexidine solution.

Rashidi et al. have shown that *Yarrow* distillate was effective in treatment of rats' gastric ulcer. This effect was attributed to the antibacterial and healing properties of *Yarrow* (29). Among herbal plants, *Yarrow* has gained attentions due to its wide range of therapeutic effects. It is a known herb, which has been used for thousands of years for treatment of different disorders, especially wounds and infections. Researches indicate that the essential oil of the herb has inhibitory effects on various bacteria (21, 25). According to Aljancic et al. (1999), the flavonoids in *Yarrow* essence have antifungal effect (26). Some flavonoids (i.e. rutin, apigenin, luteolin, and acacetin) and bioactive ingredients of *Yarrow* essence (i.e. caffeic acid and salicylic acid) have antibacterial and anti-inflammatory effects (21, 25, 30). Sokmen et al. (2003) have extracted 32 separate ingredients from *Yarrow*, among which camphor and eucalyptol have significant inhibitory effects on *Candida albicans* and *Clostridium perfringens*. Also, borneol and piperitone in *Yarrow* essence are two other compounds with considerable bacterial inhibitory activity (31). This antibacterial and anti-fungal effect of *Yarrow* might be one of the reasons for the results we had in our experiment.

The routine mouthwash used in cancer clinic did not show any significant effect on the chemotherapy induced stomatitis in our study. In the present study, stomatitis severity increased in the control group during the experiment. In the control group, the number of the patients with grade 4 stomatitis increased from 7.1% to 21.4% on seventh and to 32.1% on 14th day of the experiment. The total percent of grade 3 and 4 was increased on seventh and 14th days of the experiment in control group as well. Clarkson et al. (2008), have reported that although allopurinol, granulocyte growth factors, immunoglobulin and herbal extracts are effective but sucralfate, lidocaine,

or diphenhydramine had no effect in treating chemotherapy-induced stomatitis (32).

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

Some limitations are accounted for this study. For example, the patients took the solutions at home where the researcher had no control over them. Moreover, the small sample size, disregarding 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, it would be better if the patients' mouths were checked daily in order to determine the treatment progress.

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Authors' Contributions

Study conception and design: Mohsen Adib-Hajbaghery, Leyla Soleymanpoor, Sedigheh Miranzadeh, and Majid Ehsani; Sampling, data collection, and preparing the manuscript draft: Leyla Soleymanpoor; and Data analysis, critical revision of the paper, and supervision of the study; Mohsen Adib-Hajbaghery.

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The authors declared that there were no conflicts of interests.

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