A New mouthwash for Chemotherapy Induced Stomatitis

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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-containing 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-
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; ≤ 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 $S_1$, $S_2$, $\mu_1$, and $\mu_2$ 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 Da-roo 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 Ardalah, Kashan, Iran by Barij Esans Company, Kashan, Iran. In order to prepare 20 L of the distillate, 10 Kg of yarrow plant flowers with $50 \text{ L}$ 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
Enrollment

Assessed for eligibility (n=56)

Excluded (n=0)
- Not meeting inclusion criteria (n=0)
- Declined to participate (n=0)
- Other reasons (n=0)

Randomized (n=56)

Allocated to intervention (n=28) Allocated to routine treatment (n=28)

Follow-Up

Lost to follow-up (n=0) Discontinued intervention (n=0)

Analysis

Analyzed (n=28) Analyzed (n=28)

Figure 1. Consort Flow Diagram

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 14th 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/29/5j1/2571 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

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

*All data are presented as No. (%).

b Chi-square.

Fisher exact test.
However, in the control group, the median value < 0.001). However, in the control group, the median

Also, the Mann-Whitney

ship between stomatitis severity and age (P

correlation coefficient showed no significant relation-

mation between the two groups (Table 1). The Spearman

correct correlation showed no significant relationship

to between stomatitis severity and age (P value > 0.05).

Also, the Mann-Whitney U test certified that gender had

do 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 stomati-

tis. In this study, the stomatitis severity was significantly

reduced in the experimental group receiving the solu-
tion 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. Abedi-
pour et al. have compared the effects of chlorhexidine and
persica mouthwash -that contains A. millefolium- on
preventing stomatitis in patients receiving chemother-

apy 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 re-

sults seen between their study and ours i.e. we used Yar-
row distillate in our routine mouthwash, but they used
the extract of Yarrow in chlorhexidine solution.

Rashidi et al. have shown that Yarrow distillate was ef-

ective 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 at-
tentions 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 flavo-

noids (i.e. rutin, apigenin, luteolin, and acacetin) and bio-

active 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 cam-

phor and eucalyptol have significant inhibitory effects on

Candida albicans and Clostridium perfringens. Also,
borneol and pipertone in Yarrow essence are two other
compounds with considerable bacterial inhibitory activ-

ity (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 experi-

ment. 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 allo-
purinol, granulocyte growth factors, immunoglobulin
and herbal extracts are effective but sucralfate, lidocaine,

| Severity of stomatitis | Group          | P Valuea | Z Valueb |
|------------------------|---------------|----------|----------|
|                        | 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 |

* Mann-Whitney U test.

b Friedman test.

4. Results

Totally, 56 patients participated in this study. No sig-

nificant 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 infor-
mation between the two groups (Table 1). The Spearman

Table 2. Comparison of Average Stomatitis Severity Scores in

Three Observations

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

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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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