Original Article

Effect of Hydroalcoholic Extract of *Althaea officinalis* Root on Improving Chemotherapy-Induced Stomatitis: A Randomized, Double-Blind, Clinical Trial

Mohamad Sadegh Ghorbani, Mohsen Taghadosi, Hossein Akbari[1], Mehran Sharifi[2]

Trauma Nursing Research Center, Faculty of Nursing and Midwifery, Kashan University of Medical Sciences, [1]Department of Biostatistics and Epidemiology, Faculty of Health, Kashan University of Medical Sciences, [2]Department of Internal Medicine, Shahid Beheshti Medical Center, Kashan University of Medical Sciences, Kashan, Iran

ORCID:

Mohamad Sadegh Ghorbani: https://orcid.org/0000-0002-4937-2265;

Mohsen Taghadosi: https://orcid.org/0000-0001-9782-0862;

Hossein Akbari: https://orcid.org/000-0001-7486-8580;

Mehran Sharifi: https://orcid.org/0000-0003-2772-620x

Abstract

Background: Stomatitis is a common and serious side effect of chemotherapy. It is associated with multiple consequences such as pain, oral intake disorder, infection, bleeding, and failure of cancer treatments. **Objectives:** This study aimed to compare the improving effect of mouthwash containing hydroalcoholic extract of *Althaea* root and routine mouthwash on chemotherapy-induced stomatitis. **Methods:** This double-blind, randomized, controlled clinical trial was conducted on chemotherapy-induced stomatitis cases (n = 50) in the Oncology Department of Shahid Beheshti Hospital, Kashan, Iran, in 2016. Patients were assigned into two groups through permuted-block randomization. The control group was treated with 15 mL of routine mouthwash solution 4 times a day for 14 days whereas the experimental group was treated with a mixture of routine solution and *Althaea* root extract (50/50). The severity of stomatitis was assessed at baseline, 7th, and 14th days of intervention using the Worlds Health Organization's stomatitis evaluation checklist. Data analysis was conducted using the Chi-square and Fisher's exact tests and repeated measure analysis of variance. **Results:** At baseline, the mean score of stomatitis in the control group was 1.92 ± 0.70, which reduced to 0.96 ± 0.68 and 0.92 ± 0.64 on the 7th and 14th days after the intervention, respectively. In the experimental group, the mean score of stomatitis was 1.84 ± 0.74 at baseline, which reduced to 1.00 ± 0.82 and 0.44 ± 0.76 on the 7th and 14th days after the intervention, respectively (P = 0.015). **Conclusion:** Mouthwash solution containing *Althaea officinalis* root extract could improve stomatitis caused by chemotherapy more than the routine mouthwash solution. Thus, the mentioned herb has the potential to be used concurrently with chemotherapy agents to alleviate the occurrence of stomatitis.

Keywords: *Althaea, Cancer, Chemotherapy, Mucositis, Stomatitis*

Introduction

Stomatitis (oral mucositis) is one of the most common, acute, painful, and potential chemotherapy-induced complications. It is initiated shortly after the start of chemotherapy, and its peak occurs 7–10 days and sometimes up to 2 weeks after the treatment.[1-4] In general, 10%, 40%, and 80% of patients undergoing adjuvant chemotherapy, induction chemotherapy, and high-dose chemotherapy, respectively, affected by stomatitis.[5,6]

Stomatitis is frequently observed in medication regimens including cytarabine, bleomycin, fluorouracil, etoposide, doxorubicin, cisplatin, cyclophosphamide, and paclitaxel.[4] It not only causes discomfort for the patient[2] but also it may also interfere in food and liquid intake and causes malnutrition, dehydration, fatigue, weakness, weight loss, nausea, vomiting, and aspiration.[7,8] Stomatitis can also disrupt speaking and

Address for correspondence: Dr. Mohsen Taghadosi, Trauma Nursing Research Center, Faculty of Nursing and Midwifery, Kashan University of Medical Sciences, Kashan, Iran.
E-mail: taghadosi_m@kaums.ac.ir

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communication with others, resulting in psychological and social problems.[6] It may also be accompanied with oral mucosa infection and bleeding,[5] bacteremia, and septicemia.[9] These complications may result in prolonged hospitalization, the need for special care such as intravenous infusion, parenteral nutrition, and use of opioids, and barbiturates.[4,8,10] In severe cases, the patients may need to be feed through a gastric tube and or even gastrostomy.[10] Severe stomatitis may cause chemotherapy drug dose reduction, treatment refusal or discountation, increased costs, life quality reduction, and life-threatening problems.[7,8,11]

Currently, different strategies, such as management of local or systemic pain, antibiotics, debridement of mouth sores,[12] oral hygiene and mouthwashes, cryotherapy and low-level lasers,[3,7] antacids, and pharmacological agent such as diphenhydramine, nystatin, sucralfate, prostaglandin E, granulocyte-colony stimulating factor, amphotericin, acyclovir,[5,13] are used to improve stomatitis. However, most of these treatments have no significant results and sometimes even cause side effects.[13]

One of the most common treatments of stomatitis is the use of mouthwash. Chemical mouthwashes have side effects such as brown staining of the teeth, changes in taste sense, and bitter taste. Patients often experience difficulty in tolerating irritation caused by chemical mouthwashes because of their weakened immune system.[14]

Interest in assessing therapeutic effects of herbal mouthwashes has increased dramatically due to their low complications.[12] *Althaea officinalis* L. is one of the common medicinal herbs and of the *Malvaceae* family, which has been used for the treatment of various diseases.[15] This plant is commonly known as marshmallow or *Althaea*. Leaves, flowers, and roots of this plant have medicinal properties.[16] *Althaea* root (sodden or its extract) is used in cases of gum abscesses, fever, inflammation of oral mucosa, dry throat, severe cough, asthma, bronchitis, gastric ulcer, wound healing, remedy of skin irritations, constipation, abdominal cramps, urinary tract stones, hyperthyroidism, and reduction of blood sugar and fat.[16-19]

Well-known compounds of the roots of *Althaea* include flavonoids, polysaccharides, and mucin.[17] Polysaccharides and flavonoids in *Althaea* root have antioxidant and anti-inflammatory properties, stimulating the immune system, and producing antibacterial effects.[19,20] Walter *et al*. demonstrated that the antibacterial effect of roots, leaves, and flowers of *Althaea*.[21] Shah *et al*. reported that the antibacterial, antifungal, antiviral, and anti-inflammatory activities of ethanol extract of *Althaea* root.[19] Al-Snafi also reported that the anti-inflammatory, analgesic, and antiulcer properties of *Althaea* root on rats, as well as the positive effect of 20% ointment containing aqueous extract of *Althaea* root on external ear itching in rabbits.[16] Meanwhile, Motaharinia showed that *Althaea* flower and root extract have a less antifungal effect on *Malassezia furfur* compared with ketoconazole.[22]

In local observations, the researchers observed that some patients used *Althaea* flowers or roots to alleviate their oral ulcers. As regard to the observed positive effects, this question comes to mind that "can extract of *Althaea* root improve the chemotherapy-induced stomatitis?"

Objectives

The objective of the present study was designed to evaluate the improving effect of hydroalcoholic extract of *Althaea* root on the severity of chemotherapy-induced stomatitis.

Methods

Study design and participants

This study was designed as a double-blind, randomized, controlled clinical trial. The patients and the nurses, who gave mouthwash to the patients, were blinded to the intervention outcomes and allocation of the participants to the two groups.

The study population consisted of patients with cancer and chemotherapy-induced stomatitis (with Grades 1–3), who were gradually referring to the oncology center of Shahid Beheshti Hospital, Kashan, Iran, in 2016. After registration, the patients were randomly assigned into two groups through permuted-block randomization [Figure 1]. According to the reference[23] and oncologist confirmation, herbal medication was produced in the formulation section of Barij Essence pharmaceutical company, was packed in the same bottles and was coded by using permuted-blocked randomization method. The manual method of randomization was used to create blocks of 4 with letters A and B, which were constructed according to a random number table.

The sample size formula and parameters were derived from the study conducted by Barahimi *et al*. who studied the effect of honey on chemotherapy-induced stomatitis and reported that the recovery rate in the experimental and the control groups was, respectively, 31% (p1) and 20% (p2).[23] Then, considering the Type I and Type II errors as 0.05 and 0.10, and a maximum difference of 35% between the two groups, 50 (25 in each group) were determined to be needed for the study.

The inclusion criteria were as follows: patients undergoing chemotherapy without simultaneous radiation therapy,

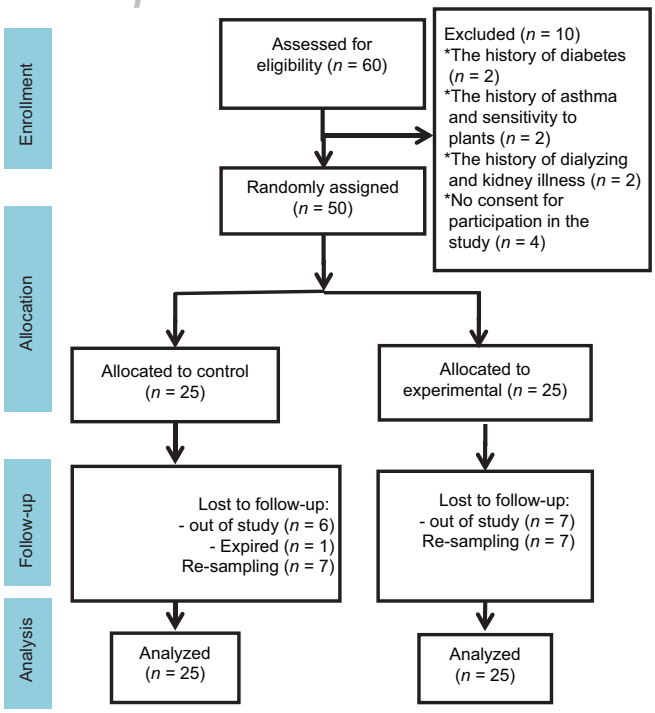

Figure 1: Consort flow diagram of the study

suffering from stomatitis (Grades 1–3), age ≥20 years, complete consciousness, satisfaction of participation in the study, lack of a known comorbidity such as kidney, liver, and immune deficiency, and any known hypersensitivity; and receiving no systemic antibiotics and antifungal drugs at the start of the study. The exclusion criteria were as follows: fever, irregular use of the mouthwash regarding time and amount, and receiving systemic antibiotics or antifungal drugs during the study and the use of another mouthwash during the study.

Data collection instruments

The data collection instrument consisted of two parts. The first part included questions on patients' age, sex, marital status, education level, having artificial teeth, and questions about the duration of cancer, chemotherapy, and receiving an analgesic and anti-inflammatory drugs.

The second part was a standard checklist that measured stomatitis severity at the 1st, 7th, and 14th days of the intervention based on the Worlds Health Organization criteria.[10] The severity of stomatitis was graded from 0 to 3. The content validity and reliability of the Persian translation of the checklist were confirmed by Ashktorab *et al*., and its reliability was 0.93.[13]

Intervention

The control group received the routine mouthwash.[23] Approximately 100 mL of the routine mouthwash contained 5 mL (100 mg) of 2% lidocaine, 12 mL of nystatin drop (1 vial or 1,200,000 U), 28 mL (70 mg) of diphenhydramine syrup, and 55 mL (4950 mg) of aluminum-magnesium-simethicone (Al-mg-s) syrup. Lidocaine ampoule, nystatin drops, Al-mg-s, and diphenhydramine syrup were purchased from Exir Co. Emad Darman Pars Co., Soha Co., and Alhawi Co., Tehran, Iran, respectively.

The experimental group received a combination of half of the routine mouthwash and *Althaea* root extract with a concentration of 8% (50/50). Approximately 100 mL of this solution contained 2.5 mL (50 mg) of 2% lidocaine, 6 mL of nystatin drops (½ vial or 600,000 U), 14 mL (35 mg) of diphenhydramine syrup, 27.5 mL (2475 mg) of Aluminium Mg-S syrup, and 50 mL of *Althaea* root extract. Mouthwashes with the same ratio reached the final volume of 840 mL (for 14 days of use) and then poured into identical dark bottles, regarding shape and size, which were identified and known only by a special code.

After botanist confirmation and shade drying, *Althaea* root was milled into powder form by Barij Essence Pharmaceutical Company, Kashan, Iran. The powder was poured into a percolator after being wetted with solvent (96% ethanol). Subsequently, 96% ethanol was added to it, and its extract was received with the ratio of 1:1 after 48 h. Its solvent was isolated as much as possible by a condenser under vacuum. It was then placed in front of airflow in wide trays so that the solvent was completely evaporated and turned into dried extract. The extracted powder was sterilized by ultraviolet radiation and maintained at 4°C until further use. The extraction ration of the extract and root powder was 8%.[17,24]

In this research, all patients were trained individually with oral care procedures and the use of toothbrushes and mouthwash by the researcher through face-to-face training methods. The patients in both groups were trained to wash their hands 4 times a day (after breakfast, lunch, and dinner and before bedtime), brush their teeth with a soft toothbrush and a gentle toothpaste, and gargle 15 mL of the mouthwash solution every time for 3 min (keep the solution in their mouth and then pour it out) for 14 days.

The patients were requested not to wash their mouth or eat anything until 1 h after rinsing with the mouthwash. To ensure the proper implementation of the mouthwash, patients or his/her companions were trained to mark a control sheet (consisting of 14 rows [days] and four columns [4 times a day]). The patients were requested to return the bottle to the refrigerator after every mouth rinse. If the mouthwash was not used in accordance with the instructions, the patient was excluded from the study and replaced with a new subject.

Ethical considerations

This study was approved by the Ethics Committee of Kashan University of Medical Sciences under the code "IR.KAUMS.REC.1395.10." It was also registered at the Iranian Registry of Clinical Trials (IRCTs) under the number "IRCT201307274655N4". The study goals were explained to all participants, and their written informed consent was obtained. All patients were free to participate in the study. According to the Helsinki declaration, they were assured that their personal and treatment information would remain confidential.

Data analysis

Data were analyzed using SPSS-16 (IBM Company). To compare the two groups, Chi-square and Fisher's exact tests were used for categorical data. The Kolmogorov-Smirnov test was used to determine the normal distribution of quantitative variables and the normality was approved. The analyses were conducted based on the intention-to-treat approach. Independent *t*-test was used for comparison of means between the two groups. Finally, repeated measures analysis of variance was used to analyze the effect of time and treatment groups on changes in stomatitis severity $P < 0.05$ was considered significant.

Results

The average age in the experimental and control groups were 53.96 ± 15.48 and 49.48 ± 16.80 years, respectively. No statistically significant difference was found between the personal and clinical features of the two groups [$P \geq 0.05$; Table 1].

Table 1: Demographic and clinical characteristics of cancer patients undergoing chemotherapy[a]

Variable	Experimental	Control	*P*
Gender			
Male	11 (44)	11 (44)	0.999[b]
Female	14 (56)	14 (56)	
Marital status			
Married	23 (92)	18 (72)	0.182[c]
Single, widow, and divorced	2 (8)	7 (28)	
Education level			
Illiterate	3 (12)	4 (16)	0.774[b]
Under the diploma	12 (48)	10 (40)	
College education	10 (40)	11 (44)	
Artificial teeth			
Yes	13 (52)	8 (32)	0.087[b]
No	12 (48)	17 (68)	
Age, years	53.96 ± 15.48	49.48 ± 16.80	0.332[d]
Duration of cancer and morbidity, years	7.96 ± 7.00	9.72 ± 13.48	0.565[d]
Chemotherapy cycles, course	7.48 ± 6.27	7.04 ± 5.51	0.792[d]

[a]Data presented as *n* (%) or mean ±SD, [b]Chi-square test; [c]Fisher exact test; [d]Independent *t*-test. SD: Standard deviation

Table 2: Comparison of the mean stomatitis severity in the study groups

Group	Time		
	Baseline	7th day	14th day
Experimental	1.84 ± 0.74	1.00 ± 0.82	0.44 ± 0.76
Control	1.92 ± 0.70	0.96 ± 0.68	0.92 ± 0.64
P[a]	0.698	0.851	0.020

[a]Independent *t*-test. Effect of time (P=0.001) and effect of time and group (P=0.015) by repeated measure analysis of variance

At baseline, the mean score of stomatitis severity in the experimental group was 1.84 ± 0.74, which reduced to 1.00 ± 0.82 on the 7th day after the intervention and 0.44 ± 0.76 on the 14th day, respectively. In the control group, the mean score of stomatitis was 1.92 ± 0.70, and which was reduced to 0.96 ± 0.68 on the 7th day and 0.92 ± 0.64 on the 14th day after the intervention, respectively.

The independent *t*-test showed no significant difference between the two groups before the intervention and the 7th day regarding stomatitis severity ($P \geq 0.05$); however, a statistically significant difference was observed on the 14th day [$P < 0.05$; Table 2].

Repeated measurement analysis of variance showed the effect of time on the severity of stomatitis ($P = 0.001$) which explains the severity of stomatitis changed during the time in the two groups. Furthermore, interaction effects of time and group on the severity of stomatitis were statistically significant ($P = 0.015$). Thus, changes in the severity of stomatitis were not similar in both groups, and a reduction in stomatitis severity was statistically significant in the experimental group than in the control group [Table 2 and Figure 2].

Discussion

The severity of stomatitis showed a further reduction in the experimental group, which used the mouthwash containing *Althaea* root extract compared with the control group with the routine mouthwash. However, *Althaea* root extract-contained solution composed half of the component of the routine solution.

The reduction in stomatitis severity in two groups during the 1st week was almost the same. However, the reduction in stomatitis severity in the experimental group was more than the control group by the end of the 2nd week. The better effects seen in the experimental group might be attributed to antimicrobial,[25] anti-inflammatory,[16] and immune system supporting[19] effects of the ingredients

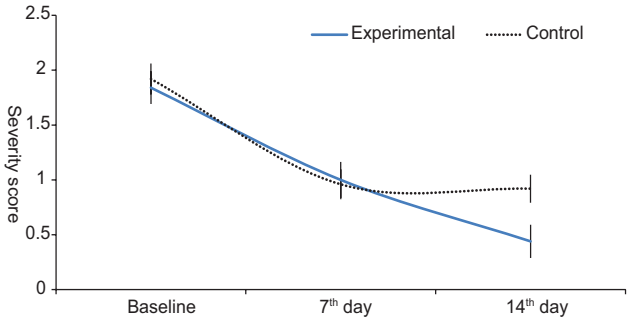

Figure 2: Comparing the mean and standard error of severity of stomatitis during the intervention in both groups

of *Althaea* root extract. Some earlier studies have also demonstrated that the antimicrobial effect of hexane extract of *Althaea* root on a number of Gram-positive and Gram-negative bacteria and oral fungus.[25] In the study of Dehghan *et al.*, the ethanol extract of *Althaea* root was effective in inhibiting the growth of *Streptococcus pyogenes*, and 50 mg/ml extract had an effective equivalent to penicillin.[20] In a study, the methanol extract of *Althaea* root significantly reduced pathogenic bacteria (aerobic and anaerobic) living in the oral cavity.[16] In another study, the hydroalcoholic extract of *Althaea* had more bactericidal and bacteriostatic effects than the hydroalcoholic extract of chamomile.[26] Chamomile mouthwash is reportedly effective in the prevention and alleviation of chemotherapy-induced stomatitis.[4,8] However, *Althaea* root extract is more effective than chamomile, or at least shares the same efficacy, in improving and alleviating stomatitis. *Althaea* root contains ingredients such as flavonoids, polysaccharides, mucin, scopoletin, and pectin.[27] Flavonoids and polysaccharides found in *Althaea* root have confirmed antioxidant, anti-inflammatory, anti-allergic, antibacterial, and antiviral effects.[27,28] The polyphenolic and flavonoid contents of *Althaea* root exert their inhibitory effects on bacterial growth by producing hydrogen peroxide and consequently decreasing the microbial load of the oral cavity.[20] In a previous study by Jafari *et al.*, the aqueous extracts of *Althaea* root and flower reduced the symptoms of hand skin allergy caused by latex.[24] This reduction was possibly due to the anti-inflammatory and protective effects of *Althaea* root. Broujeni *et al*. demonstrated that the solution containing *Althaea* and ginger reduces cough attacks and chest pain caused by tracheobronchitis in patients by reducing inflammation.[29] Antibacterial, antiviral, and anti-inflammatory features of *Althaea* may have decreased the symptoms of tracheobronchitis.

The *Althaea* plant is rich in antioxidants, which can deactivate free radicals, and exerts protective effects. About 69% of *Althaea* antioxidant activity is related to alpha-tocopherol combination.[20,30]

The anti-inflammatory features of *Althaea* root are due to the bioadhesive polysaccharide layer covering the surface of inflamed and damaged epithelial lining of the oral mouth, thereby leading to enhanced protection and hydration of oral mucosal tissues against chemical, physical, and biological stress. The formation of this bioadhesive layer on human epithelial tissue is demonstrated by fluorescence histology.[24,31]

Among herbal plants, *Althaea* is a well-known plant that has gained attention due to its wide range of therapeutic effects. It has been used for thousands of years for the treatment of different disorders especially wounds, infections, fever, and bronchitis.

The antimicrobial, anti-inflammatory, and protective properties of *Althaea* root extract might explain some of the results observed in our study. Toxicity, allergic reactions, or other side effects were not observed on using this mouthwash during the study.

In this study, the routine mouthwash used in the control group also reduced stomatitis severity. Therefore, the combination of lidocaine, diphenhydramine, Al-mg-s, and nystatin was effective in improving stomatitis.

Conclusion

The findings showed that the severity of stomatitis has been further reduced in the experimental group using mouthwash containing the *Althaea* root extract compared to the control group using routine mouthwash, despite the doubling of the routine mouthwash compounds. Considering the availability and safety of the *Althaea* plant compared to chemical drugs, this solution is recommended for the treatment of chemotherapy-induced stomatitis along with other existing therapies.

Since the *Althaea* root extract was combined with the routine solution in this study, it is suggested to use the extract alone in future studies to reveal the therapeutic effects of *Althaea* as well. Furthermore, the effects of hydroalcoholic and aqueous extracts of *Althaea* root or flower in combination with other mouthwashes should be studied to achieve more effective mouthwash.

Some limitations of the current study were as follows: the small sample size, disregarding other variables such as teeth problems (decayied, broken, and implanted), history of oral disease, and a significant decrease in one of the paraclinical parameters such as white blood cells and platelets. The possibility of false reports by the patients should also be considered. If possible, the future

studies to be done in the hospital setting, monitoring of the mouthwashes use by the patients would be done more precisely. Moreover, it would be better if the patients' mouths are checked daily to determine the treatment progress.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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