

ORIGINAL ARTICLE

The Effect of Aloe Vera Solution on Chemotherapy-Induced Stomatitis in Clients with Lymphoma and Leukemia: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Stomatitis is the most common complication of chemotherapy. This study aimed to assess the effect of aloe vera solution on stomatitis and its pain intensity in patients undergoing chemotherapeutic procedures.

Methods: In this randomized controlled clinical trial, 64 patients with Acute Myeloid Leukemia and Acute Lymphocytic Leukemia undergoing chemotherapy were randomly divided into a control and an intervention group. The intervention group patients were asked to wash their mouths with 5 ml of aloe vera solution for two minutes three times a day for 14 days. The control group patients, however, used only the ordinary mouthwashes recommended in hematologic centers. The patients' mouths were examined by two assistants on days 1, 3, 5, 7, and 14. The intensity of stomatitis was recorded according to WHO stomatitis intensity checklists and pain was evaluated using Visual Analog Scale. The data were analyzed by SPSS statistical software, version 18.

Results: The results showed that aloe vera solution mouthwash significantly reduced the intensity of stomatitis and its pain in the intervention group compared to the control group. On the first day, no significant difference was found between the two groups regarding the mean intensity of stomatitis ($P=0.178$) and pain ($P=0.154$). However, a significant difference was observed between the two groups in this regard on other days (days 3-14: $P=0.001$ for stomatitis intensity, $P=0.001$ for pain).

Conclusions: Aloe vera solution can improve the patients' nutritional status, reduce stomatitis and its pain intensity, and increase the patients' satisfaction.

Trial Registration Number: IRCT2014092819318N1

KEYWORDS: Aloe vera; Chemotherapy; Leukemia; Lymphoma; Stomatitis

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INTRODUCTION

Nowadays, along with increased life span, mortalities caused by chronic diseases such as cancers have also increased.¹ Cancer is a pathogenic process that is caused by increase and multiplication of abnormal body cells.^{1,2} According to the information provided by World Health Organization (WHO) in 2005, 7.6 million out of all the 58 million cases of death all around the world were caused by cancer (13%). In Iran, cancer is the third cause of death after cardiovascular disease and accidents.³ Blood cancer or different types of leukemia comprise about 8% of all human population cancers and are known as the fifth common cancers all around the world. Two main types of these cancers are Acute Myeloid Leukemia (AML) and Acute Lymphocytic Leukemia (ALL).⁴ American Association of Cancer has estimated that 31500 individuals are diagnosed with one type of leukemia each year and approximately 21500 of them will die.⁵ Iran's cancer registry center also reported 4393 new cases of blood malignancies in 2008, 805 (18.3%) and 432 (9.8%) cases who were diagnosed with ALL and AML, respectively. Although the prevalence of acute leukemia is estimated to be 3% lower than that of other cancers, this group of cancers is the main cause of death in individuals below 39 years old.⁶

Scientific improvements have increased the efficacy of cancer treatments.⁷ Chemotherapy is one of the most common treatments for cancer and consists of the use of cytotoxic drugs to cure the disease. Chemotherapy is the first line therapy of leukemia and lymphomas and is a systematic therapy compared to topical treatments, such as surgery and radiation therapy.¹ Yet, it has numerous side effects,^{8,9} the most common of which being stomatitis or oral cavity mucositis. In general, 40% of patients under chemotherapy, 70% of patients under bone marrow transplantation, and almost all patients under radiation therapy are affected by stomatitis.⁸ Stomatitis is an inflammatory reaction in the oral cavity along with intermediate redness and swelling and

can be painful. It can also lead to problems, such as infection, mucosal hemorrhage, food intake and nutritional disturbance, and restlessness.¹⁰ Studies have shown that based on the patients' opinions, pain was the most annoying sign of stomatitis.¹ Overall, 76-86% of patients with stomatitis have pain, which can cause malnutrition.¹¹ Clinically, the effect of chemotherapy on the oral mucosa begins shortly after administration, peaks on days 7-10, and can last for 14 days.^{3,12} The best way to overcome stomatitis is its prevention.¹³ To date, in most hematology units, normal saline and sodium bicarbonate are used as mouthwash before the occurrence of signs and solutions, such as diphenhydramine syrup, nystatin droplet, lidocaine, and chlorhexidine which are used after appearance of oral signs. Each of these solutions has some side effects and, thus, may not satisfy the patients completely.^{9,7} Herbal drugs have been increasingly used since the last decades because of their appropriate effects and low side effects.⁷ Aloe vera or Sabr-e-Zard has been used for 2000 years as a topical drug for skin disorders.¹⁴ This plant belongs to lylyasae family and its appearance is like cactus. It is grassy, durable, and fleshy.^{15,16}

Up to now, no clinical trials have assessed the effect of aloe vera on chemotherapy-induced stomatitis in Iran. Considering the increase in the prevalence of cancer and the number of patients undergoing chemotherapy and effects of aloe vera on wound healing, the present study aimed to evaluate the effectiveness of aloe vera in the intensity of stomatitis and its pain. It was hypothesized that receiving aloe vera solution would decrease the intensity of stomatitis and its pain in the patients undergoing chemotherapy.

MATERIALS AND METHODS

This randomized controlled clinical trial aimed to assess the effect of aloe vera solution on the intensity of stomatitis and its pain between August 11th and October 23rd, 2014. According to the study objectives and the previous studies

conducted on the issue¹⁷ and considering the power of 80% and $\alpha=0.05$, a 64-subject sample size (32 in each group) was determined for the study using NCSS software and the following formula:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

The study participants were between 18 and 88 years old, suffered from ALL and AML, and had referred to Nemazee educational hospital and chemotherapy unit of Shahid Motaharri Clinic. The inclusion criteria of the study were the patients' willingness to cooperate, age above 18 years, confirmation of AML and ALL, and being under chemotherapy. On the other hand, the exclusion criteria were suffering from any other underlying diseases; being addicted to cigars, tobacco and opioid drugs; having a history of sensitivity to aloe vera; developing any kind of sensitivity to

any material during the study; developing any acute condition during the study; and unwillingness to continue participation in the study. The participants were selected through convenience sampling. In so doing, any patient who met the inclusion criteria and signed the written informed consent was enrolled in the study. Then, the participants were divided into intervention (N=32) and control (N=32) groups through block randomization (Figure 1).

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethic code: CT-9374-7114). At the first step, all the participants were provided with information about the study objectives and procedures. They were also reassured about the voluntary nature of the study and confidentiality of their information. Then, written informed consents for taking part in the study were obtained from all the participants.

A demographic data sheet was used to gather the participants' demographic information,

CONSORT Flow Diagram

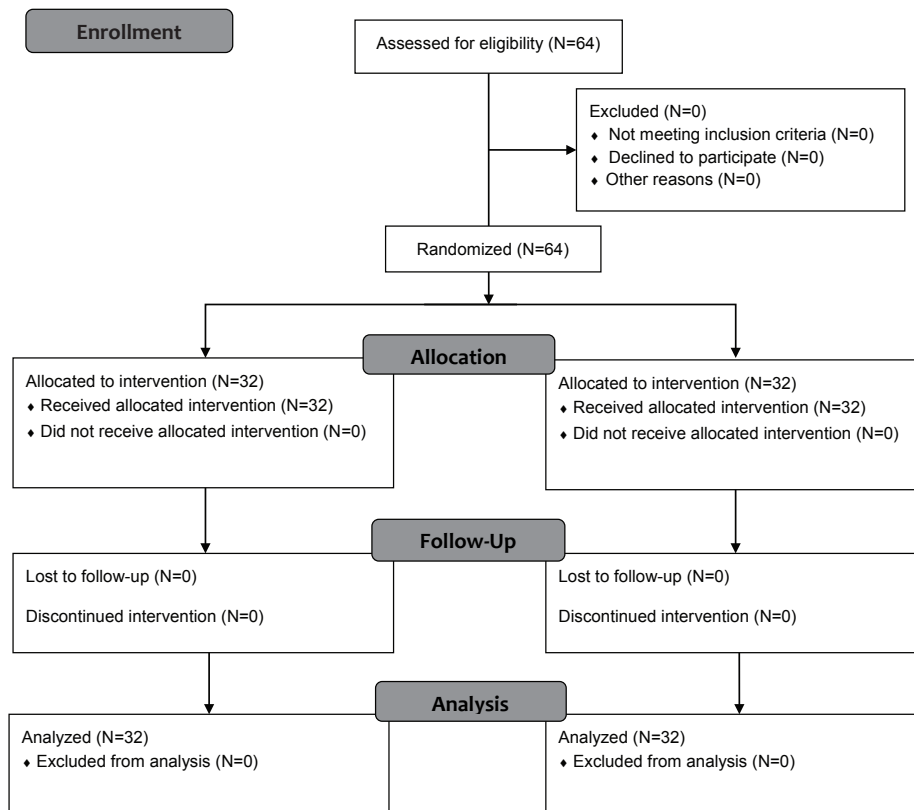


Figure 1: Flow diagram of the participants

including age, sex, occupation, marital status, education level, and type of disease. In addition, “WHO stomatitis intensity survey checklist” was used to assess the intensity of stomatitis and Visual Analog Scale (VAS) was used to evaluate the intensity of pain in the patients. WHO stomatitis intensity survey checklist is a 5-point scale in which zero is considered as no stomatitis, 1 represents pain and erythema without wounds, 2 refers to the case where wound and erythema exist but the patient is able to eat solid food, 3 is existence of extensive wound and erythema and inability to eat solid food, and 4 is the most severe condition with mucosal bleeding, extensive inflammation, and complete inability to eat and drink. This checklist was provided by WHO and its reliability and validity were confirmed in several investigations.¹⁸ In Iran, Brahimi et al. performed an investigation entitled “The effect of honey on stomatitis recovery of patients undergoing chemotherapy in hospitals affiliated to Shaheed Beheshti Medical University” and determined the validity of this scale using content validity method. Besides, they confirmed the reliability of the scale by $r=0.81$.⁷

VAS is a standard tool for measuring pain intensity. This instrument is a 10 cm ruler in which zero shows no pain and 10 represents intolerable pain. VAS is a quick, simple, stable, and valid tool that has been used in many investigations and medical clinics.¹⁹ The validity and reliability of this instrument have also been confirmed in many previous studies.^{20,21}

In the intervention group, the patients used aloe vera mouthwash in addition to routine treatments. This solution was prepared by Barij Essance Co., Kashan, Iran and delivered to the researcher. The patients were asked to wash their mouths with 5 ml of the solution for 2 minutes 3 times a day and avoid eating and drinking for 30 minutes after that for 2 weeks. In the control group, on the other hand, routine mouthwashes, including normal saline, chlorhexidine, and nystatine, were used according to the physician’s prescription.

The control group patients were also asked to use the routine mouthwashes 3 times a day and avoid eating and drinking for the next 30 minutes for 2 weeks. The patients’ mouths were examined for stomatitis by two assistants on days 1, 3, 5, 7, and 14. These two assistants were not aware of the goal and type of the intervention. The intensity of stomatitis in both groups was evaluated using WHO stomatitis intensity survey checklist. Also, the patients were asked to report their pain intensity between 0 and 10 in these 5 visits.

All data analyses were performed using SPSS statistical software, version 18 and $P<0.05$ was considered as statistically significant. At first, Kappa coefficient between the two assistants in the 5 visits was measured by Kappa test, revealing agreement between the two assistants ($P=0.001$). Therefore, the data were analyzed by one of the assistants. The demographic data were analyzed using Chi-square and independent T-test. In addition, Mann-Whitney non-parametric test, independent T-test, and Friedman test were used to compare the two groups regarding the intensity of pain and stomatitis.

RESULTS

The study participants’ demographic information is presented in Table 1. Accordingly, no significant difference was found between the two groups regarding the mean age. Also, the results of Chi-square test indicated no significant difference between the intervention and control groups in terms of sex, marital status, education level, and type of disease ($P>0.05$). However, the results of Fisher’s exact test revealed a significant difference between the two groups concerning occupation ($P=0.01$). Yet, due to randomization, this could not affect the main variables.

Based on Table 2, no significant difference was found between the two groups with respect to the mean intensity of stomatitis and pain on day 1. However, a significant difference was observed in this regard on days 3 to 14.

The results of Friedman test are presented

Table 1: Comparison of the control and intervention groups regarding the demographic variables

Group	Control	Intervention	P value
Quantitative variable	Mean±SD	Mean±SD	
Age(year)	47.78±18.28	46.25±18.17	0.738
Qualitative variables	N (%)	N (%)	
Sex (Male)	19 (29.7)	19 (29.7)	1.000
Occupation (Employee)	20 (42.2)	14 (21.8)	0.010
Education level (Diploma and above)	21 (32.8)	14 (21.9)	0.136
Marital status (Single)	7 (10.9)	8 (12.5)	0.955
Type of disease			
AML	17 (26.6)	10 (15.6)	0.076
ALL	15 (23.4)	22 (34.4)	

Note: Significant at $\alpha=0.05$

Table 2: Comparison of the two groups regarding the mean intensity of pain and stomatitis on days 1, 3, 5, 7, and 14

Group	Control		Intervention		P value	
	Mean±SD		Mean±SD			
Days	Stomatitis	Pain	Stomatitis	Pain	Stomatitis	Pain
Day 1	0.312±0.592	0.156±0.627	0.125±0.336	0.001±0.001	0.178	0.154
Day 3	1.406±0.559	1.812±1.424	0.500±0.508	0.187±0.737	0.001	0.001
Day 5	1.843±0.447	3.468±1.480	0.937±0.504	0.781±1.337	0.001	0.001
Day 7	2.000±0.439	4.00±1.502	1.125±0.553	1.125±1.431	0.001	0.001
Day 14	0.593±0.498	0.812±1.148	0.938±0.296	0.031±0.176	0.001	0.001

Note: Significant at $\alpha=0.05$

in Table 3. In this test, the effect of passage of time on the intensity of stomatitis was assessed regardless of the study groups. The results showed that the intensity of stomatitis significantly changed over time.

According to Table 4, a significant difference was found between the two groups regarding the intensity of stomatitis between days 3 and 14 ($P<0.05$). The results also showed a significant difference between the two groups concerning pain intensity between days 3 and 14 ($P=0.013$).

DISCUSSION

Stomatitis or oral mucositis is a side effect of chemotherapy and requires medical and nursing interventions. Unfortunately, oral care standards have been used incorrectly in these patients and may not even exist in many organizations. On the other hand, most clinical interventions are variable and limited data are available in this regard. Therefore, in the present study, the intervention method was designed

based on stomatitis development process and standard tools were used to survey the intensity of stomatitis and its pain.⁸ The findings of this study showed higher levels of stomatitis and pain in the control group compared to the intervention group. This implies that safe and simple methods can be used to decrease the intensity of stomatitis and its pain during chemotherapy.

One of the most important spiritual responsibilities that has always been suggested in moral medicine is avoiding causing harm and pain to individuals. The present study findings also showed that aloe vera was significantly effective in reducing the intensity of stomatitis and its pain in the intervention group compared to the control group. According to the results, no significant difference was found between the intervention and control groups at the first visit ($P>0.05$), but a significant difference was observed between the two groups in the next visits ($P=0.001$). These results were in line with those of many studies performed on

Table 3: Comparison of the mean intensity of pain and stomatitis during the study according to the results of Friedman test

Days	Stomatitis	Pain
	Mean±SD	Mean±SD
Day 1	0.218±0.486	0.078±0.447
Day 3	0.953±0.699	1.00±1.391
Day 5	1.390±0.657	2.125±1.947
Day 7	1.562±0.663	2.562±2.053
Day 14	0.343±0.478	0.421±0.905
P value	0.001	0.001

Note: Significant at $\alpha=0.05$

Table 4: Comparison of the two groups regarding the mean intensity of stomatitis and pain on days 3 and 14

Difference between days 3 and 14	Intervention	Control	P value
	Mean±SD	Mean±SD	
Stomatitis Intensity	0.406±0.559	0.812±0.644	0.009
Pain intensity	0.156±0.627	1.00±1.759	0.013

Note: Significant at $\alpha=0.05$

aloe vera as a wound healer and oral mucosal protector. However, no investigations have been performed on the effect of aloe vera on chemotherapy-induced stomatitis.^{15,17,22-24}

In a double-blind clinical trial on 40 patients with recurrent oral aphthous-induced stomatitis, aloe vera gel was used in one group, while lubricant gel containing 2% normal saline was used in the other group. The patients' mouths were examined on days 0, 3, 7, and 10 and the lesions' width and pain were recorded. The results indicated that aloe vera significantly reduced the intensity, width, and pain of stomatitis.¹⁷

Another trial compared the effects of aloe vera and triamcinolone acetonide 1% mouthwashes on oral lichen planus disease in 46 patients. The patients were examined on days 8 and 16 and after completing the course of treatment.²³ The results of that study demonstrated that aloe vera was as effective as triamcinolone in treatment of oral lichen planus disease, which is compatible with the findings of the current study.

One other research evaluated the effect of aloe vera gel on cesarean section wound healing. In that study, 90 women undergoing cesarean section were divided into two groups receiving either aloe vera gel or routine treatment for dressing their wounds. Wound

healing was assessed 24 hours and 8 days after the cesarean operation and the results revealed the positive effect of aloe vera gel on healing the wounds, which is in agreement with the results of our investigation.²⁵

One other research was performed on 58 patients with head and neck cancer undergoing radiotherapy to compare the effects of aloe vera solution and placebo on radiotherapy-induced mucositis. The findings revealed that the intensity of mucositis was lower in the aloe vera group, but the difference was not statistically significant. According to the researchers, the main limitations of that study were its small sample size, patients' heterogeneity, and large distribution of the primary sites.²² In the present study, the researchers tried to eliminate those limitations and the results indicated a significant difference between the intervention and control groups concerning the intensity of stomatitis and its pain.

Another study assessed the effect of chamomile on stomatitis intensity in 42 cancer patients undergoing chemotherapy. In that research, the patients were divided into two groups. The control group patients were asked to wash their mouths with water 4 times a day for 16 days, while the intervention group had to do so using chamomile solution.

Stomatitis intensity and pain were evaluated in 4 periods of 4 days. The results showed no significant difference between the control and chamomile groups in the first period. However, chamomile was significantly effective in healing and preventing stomatitis between the second and the fourth period.⁸

Considering the above mentioned points, the study hypothesis was confirmed. Thus, it can be concluded that aloe vera could be effective in reducing stomatitis intensity and pain.

CONCLUSION

This study showed that aloe vera solution was effective in decreasing stomatitis intensity and pain. Hence, besides other methods, aloe vera mouthwash can be useful in preventing and treating stomatitis in patients with chemotherapy-induced stomatitis without any side effects. Thus, it is recommended to be used in order to achieve appropriate oral hygiene in patients undergoing oral toxic treatments and chemotherapy.

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Conflict of Interest: None declared.

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