



ORIGINAL ARTICLE

Effect of Aqueous Extract of Sage on Prevention of Pain Due to Stomatitis in Children with Leukemia Under Chemotherapy

Khodayar Oshvandi¹, Fariba Ebrahimi Horyat², Ramezan Kalvandi³, Hossein Esfahani⁴, Arash Khalili^{5*}

¹Professor, Department of Medical and Surgical Nursing, Mother and Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran

²Masters of Pediatric Nursing, Hamadan University of Medical Sciences, Hamadan, Iran

³Hamadan Agricultural and Natural Resources Research and Education Center, Hamadan, Iran

⁴Department of Pediatric Nursing, Mother and Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

⁵Mother and Child Care Research Center, Hamadan University of Medical Sciences, Hamadan, Iran

ARTICLE INFO

Article History:

Received: 25.06.2021

Accepted: 29.08.2021

Keywords:

Aqueous extract of the sage
Stomatitis
Chemotherapy
Children

*Corresponding author:

Arash Khalili,
Mother and Child Care Research
Center, Hamadan University of
Medical Sciences, Hamadan, Iran
Tel: +98 9173412530
Email: arash5920@yahoo.com

ABSTRACT

Background: prevention of stomatitis can significantly reduce the cost of treatment and even increase the survival rate of patients. considering large side-effects of chemotherapy induced stomatitis, the aim of current study was to investigate the effect of sage aqueous extracts on the prevention of pain associated with stomatitis in children with chemotherapy-dependent leukemia admitted to hematology department of Be'sat Hospital in Hamadan during 1396. **Methods:** This double-blind and clinical study was conducted on children admitted to hematology department of Be'sat Hospital, Hamedan; during 1396. The mouth of all patients before and after the intervention was checked and recorded in the checklist in terms of severity of pain caused by stomatitis.

Results: Current study was conducted on 60 children aged 6 to 14 years old. Comparison of the severity of the pain in the intervention group before intervention was not significant but after the intervention it was significant ($P < 0.001$). Comparison of pain intensity in the control group before intervention was not significant but after the intervention it was significant ($P < 0.001$). Comparison of pain intensity between intervention and control groups before intervention was not significant but after intervention, it was significant ($P < 0.001$).

Conclusion: According to results of current study, the aqueous extract of the sage has a significant effect on pain relief from stomatitis in patients undergoing chemotherapy.

Please cite this article as: Oshvandi K, Ebrahimi Horyat F, Kalvandi R, Esfahani H, Khalili A. Effect of Aqueous Extract of Sage on Prevention of Pain Due to Stomatitis in Children with Leukemia Under Chemotherapy. IJBC 2021; 13(3): 67-71.

Introduction

Cancer is one of the most common and disabling diseases, and can be considered a cancer of the child if it is diagnosed under the age of 15 years. Among cancers, leukemia is one of the most common malignancies in childhood. The incidence of cancer in this age group is approximately 129 per million children.¹ The first goal is to treat cancer, and if this primary goal can't be met, the goal is to relieve symptoms and maintain quality of life for the remainder of the patient's life. Treatments

involve surgery, biological treatments (Immunotherapy and gene therapy), bone marrow transplantation and chemotherapy.²

Oral stomatitis, on the other hand, is one of the most common problems in children undergoing chemotherapy and reduces quality of life in children. According to the American National Leukemia Organization, symptoms of stomatitis is visible in approximately 40% of people undergoing chemotherapy, especially in patients who receives bleomycin, doxorubicin, cyclophosphamide,

methotrexate, 5-FU, and Danurubicin.³ The peak of these side effects is on the oral cavity within first 7 to 10 days of chemotherapy and is usually parallel with medication effects on the bone marrow. The severity of side effect varies for each medication and is specific for each drug.⁴ The incidence of stomatitis varies and depends on the type of treatment and type of leukemia, so that, adverse outcomes of stomatitis include increase hospitalization, consequently increase treatment costs, the patient's unwillingness to have enough nutrition, the need for complete intravenous feeding, and the use of Drugs.⁵ Therefore, prevention of stomatitis is important for affected children and their parents, and the main goal in nursing children is to improve the care of children and their families.⁶ Stomatitis is very painful. Moreover, a relationship between interference in the nutrition of patients as well as their daily life, anorexia, fatigue, fever, irritability, bad smelling breath, and so on was observed in severe cases.⁷ The only way to treat and prevent chemotherapy induced stomatitis is to recommend proper oral hygiene and using suitable oral mouthwash.⁸

considering many complications of chemotherapy induced stomatitis, prevention of stomatitis can significantly reduce the cost of treatment and even increase the survival rate of patients. In the meantime, current treatment using for stomatitis includes mouthwashes with warm water or diluted Normal Saline, nicotine drops, a cocktail solution (a combination of nicotine drops, diphenhydramine syrup, MG aluminum syrup), brushing teeth with a soft toothbrush, and in severe infections, using topical or systemic antibiotics can be effective in reducing this complication.⁹ Potential disadvantages of these treatments involve a long stay in hospital, a patient's unwillingness to eat, weakness, family concerns about the treatment process, medical costs, psychological involvement of other family members, etc.¹⁰ Therefore, to reduce the hospitalization time of these patients, lots of herbal mouthwashes are used following their low level of complications nowadays.¹¹

Among medicinal herbs, the *Salvia* plant, known as sage, is more important because of its anti-cellular activity against cervical, skin and breast cancer.¹² Some of most important effects include steroidal anti-inflammatory properties in oral and throat infections, injuries to other parts of the body, best blood glucose reducer, cardiopulmonary suppressants, milk in mothers who want to lose their milk, Treating all types of fever, treating chronic coughing, improving memory, enhancing senses, treating colds, and so on. Sage is used as a nutritional ingredient in foods and beverages and also in herbal medicines and therapeutic uses.¹³ Therefore, considering high oral complications following stomatitis and considering that in addition to the chemical mouthwash, herbal mouthwash can also affect its control¹⁴ the aim of current study was to survey the effect of extract of sage in preventing pain following stomatitis in children with leukemia under chemotherapy admitted to the hematology department of Be'sat Hospital in Hamadan during 1396.

Materials and Methods

This study was approved by Hamedan university of medical science (IR. MSHA. REC. 1395. 450). The clinical trial code is (IRCT2017011732025N1). This double-blind clinical trial study was conducted by two-group design, with pre-test and after test- groups. The population of current study was 60 children aged 6 to 14 years old admitted to the hematological department of Be'sat Hospital, Hamedan, Iran during 1396. These children were undergoing chemotherapy and the diagnosis of leukemia was certain for them for the first time. Sixty patients with chemotherapy-induced leukemia were randomly assigned for each experimental group (mouthwash with aqueous extract of sage, cocktails solvent of the department 30 persons) and control (mouthwash with cocktail solvent 30 persons). all caregivers of patients signed a written permission letter for their willingness to participate in the study, Before the intervention. Demographic patient's data including age, sex, duration of disease, place of residence, educational level of parents, occupation of parents and number of children of the family were completed in questionnaire. Patient's mouth was examined by the physician in terms of severity of stomatitis and the severity of pain. Data were noted in special and standard WHO checklist before the intervention. To wash mouth in experimental group, the aqueous extract of sage was used 3 times a day. in addition, their mouth was washed besides the routine treatment (cocktail solution, which is a combination of nicotine drop, aluminum syrup, AJS, and Diphenhydramine). The extract of the sage plant was provided to the patients. This extract was purchased from the medical company Tebe Sabz-e- Bou Ali Sina at a specific concentration.¹⁵ 3 drops of extract were diluted in 2 cc water.^{11,16} Patients entered the diluted extract into the mouth after brushing after each meal (3 times a day). they rolled it out for a minute, exclude it and did not eat anything for up to 1 hour. Patients in control group gargled their mouth with cocktail 3 times a day for two weeks with a drop-glass with 2 cc of cocktail solution. using mouthwash was done after breakfast, lunch and dinner after brushing. The method of using mouthwashes and proper time was taught to mothers by the researcher. A special checklist was provided to mothers about the time of using mouthwashes. A special checklist was provided to mothers for the duration of using mouthwash. At the end of the period of using mouthwash (second week), the physician examined patients in terms of the severity of pain and the researcher completed the relevant checklist with the doctor's opinion.

Admission criteria include ages 6 to 14 years old, the child is admitted to hematological department of Be'sat Hospital in Hamedan, the child is afflicted with leukemia, the child or caregiver is teachable and speaks Farsi, the child has done chemotherapy at least once and admitted to prevent stomatitis by the physician, s/he has no sensitivity to the sage drug, sage is not ill-tasting for the child, the child is afflicted to stomatitis.

Exclusion criteria include the inclination of participants to continue to participate in the study, leave the study for any reason Such as death, displacement, and so on.

The formula proportional to the difference between the mean of the two different societies was used to determine the population. Considering the statistical power: 95%, the error level: 0.05, the variance: 6.40 and 15.84, the mean 0.8 and 4.3,¹⁵ respectively, the sample size was calculated as 27. It was calculated 30 persons for each group because the sample loss has considered 10%.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2} = \frac{(1.96 + 4.64)^2 (6.40 + 15.84)}{(4.13 - 0.8)^2} = 26.05 \approx 27$$

Data acquiring tool in current study has two parts:

A. Demographic questionnaire: Demographic data includes patient name, age, sex, type of leukemia, duration of leukemia, place of residence, native or non-native status, father's occupation, mother's occupation, parental education, number of children.

B-Grading Pain Based on Wong & Baker Scale:

Wong & Baker facial scale was used in current study to measure pain. This tool was introduced by these authors in 1998. It includes two parts of the face and number. The scoring method was:

Scores 0-1, 1-2, 3-4, 5-6, 7-8, 9-10 mean without pain, low pain, little more, much more pain, severe pain and most severe pain respectively.

The second part is a facial value includes six pictures of the child's face. Each picture shows a different amount of pain. The left side of the scale illustrates the lack of pain and the right image was the most severe type of pain. This section was used for children who can not count or do not understand the meaning of numbers. Validity and reliability of this tool was approved by foreign and

Iranian studies.¹⁷

All ethical standards, such as obtaining permits, written consent, confidentiality of information, use of information for research purposes were considered. Data were entered SPSS (version 16). Tests Descriptive statistics, Chi-square, independent T-test, Mann-Whitney and covariance analysis were used to evaluate correlation and comparison of groups in the case of establishing the assumptions. Otherwise Alternative tests were used.

Statistical Analysis

Data were entered SPSS (version 19) and analyzed by Fisher test and Chi- square test.

Results

Current study was conducted on 60 children aged 6 to 14. Different demographic variables were compared in two groups. To compare quantitative variables in two groups, independent T-test was used to establish the normality assumption.

Table 1 shows the similarity of demographic characteristics of groups. 66.7% of participants lived in villages around Hamedan and 70% of mothers of children under chemotherapy had under diploma degree. Table 2 shows that there was no significant difference between two groups before the intervention. After intervention, the severity of pain was significantly different between two groups ($P < 0.001$). Table 3 showed that there was significant difference between the pain severity level before and after intervention in the control group ($P < 0.001$). Table 4 showed that there was significant difference in the intensity of pain before and after the intervention ($P < 0.001$).

Table 1: demographic specifications of patients

Variable	Specifications	Control		Intervention		P
		Number	Percentage	Number	Percentage	
Sex	Male	14	46.7%	14	46.7%	0.999
	Female	16	53.3%	16	53.3%	
Mother's occupation	Employee	2	6.7%	2	6.7%	0.999
	House wife	28	93.3%	28	93.3%	
Place of residence	City	19	63.3%	21	70.0%	0.584
	Village	11	36.7%	9	30.0%	
Mother's education	Illiterate	4	13.3%	5	16.7%	0.774
	Under-diploma	21	70.0%	21	70.0%	
	Assistant	4	13.3%	2	6.7%	
	Expert and higher	1	3.3%	2	6.7%	

Table 2: Comparison of pain intensity in the test and control groups before and after the intervention.

Specification		Control		Intervention		P
		Number	Percentage	Number	Percentage	
Pre- intervention	No pain	0	0	0	0	0.249
	Low pain	14	46.7%	10	33.3%	
	A bit more pain	16	53.3%	18	60.0%	
	Much more pain	0	0	2	6.7%	
Post- intervention	No pain	10	33.3%	24	80.0%	0.001
	Low pain	20	66.7%	6	20.0%	
	A bit more pain	0	0	0	0	
	Much more pain	0	0	0	0	

Table 3: Comparison of pain intensity in the control group before and after intervention.

Severity of pain	Before intervention		After intervention	
	Number	Percentage	Number	Percentage
Painless	0	0	10	33.3%
Low pain	14	46.7%	20	66.7%
A bit more pain	16	53.3%	0	0
Much more pain	0	0	0	0
Chi-square test	P<0.001			

Table 4: Comparison of pain intensity in the intervention group before and after intervention.

Severity of pain	Before intervention		After intervention	
	Number	Percentage	Number	Percentage
Painless	0	0	24	80%
Low pain	10	33.3%	6	20%
A bit more pain	18	60%	0	0
Much more pain	2	6.7%	0	0
Chi-square test	P<0.001			

Discussion

This study was conducted to evaluate the effect of aqueous extract of sage on prevention of stomatitis- induced pain in children with leukemia admitted to hematologic department of Be'sat Hospital. The only way to treat and prevent chemotherapy induced stomatitis is to recommend oral hygiene and proper oral mouthwash.⁸ Results showed that pain intensity was not significant before intervention. The comparison of pain severity between two groups was significant after intervention. This result was as consistent as results of Mirzadeh,¹⁸ Alijani Renani,³ Sha'ban Luyi¹¹ and VeKorka et al.¹⁹ It was not as consistent as results of Ezgi et al.²⁰ This inconsistency could be related to the study method because he applied the aqueous extract of the sage in the composition with tea. This agent could have a potential change in the amount of extract used and, as a result, has different effect.

Table 3 shows significant difference between the degree of pain before and after the intervention in the control group. These results were as consistent as results of Mirzadeh,¹⁸ Sha'ban Luyi¹¹ VeKorka et al.¹⁹ All of studies indicated that there was significant relationship between the amount of stomatitis- induced pain after applying the extract. The effect of this extract could reduce the stomatitis- induced pain. these results were not as consistent as results of Alijani Renani.³ The reason of this inconsistency can be defined as the amount of substance consumed was at a much higher concentration (about 10 times). Also, it was not as consistent as results of Kaviani et al.¹⁵ The reason of this inconsistency can be defined as difference between desired population (population of their study were pregnant women).

Table 4 shows significant difference between the severity of pain before and after the intervention in the test group. It was as consistent as results of Mirzadeh,¹⁸ Alijani Renani,³ Shaaban Luyi¹¹ and Vekorka et al.¹⁹ it was not as consistent as results of Kaviani et al.¹⁵ The reason of inconsistency can be defined as difference in the type of study population (they studied pregnant women. The study way was totally difference with current study due to differences in dosage of the medication and duration

of usage. Different outcomes were not unexpected. These results were also different with the study of Ezgi et al.²⁰ It can be defined as utilizing very high dose of the drug in their study, because the drug was used in combination with tea and beverage, therefore, the researcher had to use high dose of medication to see the effects of the medicine in studies.

Conclusion

According to results of current study, aqueous extract of sage as mouth wash and gargle can reduce the severity of stomatitis- induced pain in children undergoing chemotherapy. Moreover, it can be used as an effective method for preventing pain in these patients. Therefore, utilizing this extract is recommended in children under chemotherapy.

Conflict of Interest: None declared.

References

- Harrison TM. Family-centered pediatric nursing care: state of the science. *J Pediatr Nurs.* 2010;25(5):335-43. doi: 10.1016/j.pedn.2009.01.006.
- Hockenbery M, Wilson D. Wong's nursing care of infant and children. 9th ed. Canada: Elsevier Mosby Publishers; 2011.
- Alijani Renani H, Keikhai B, Ghadimi Mahani H, Latifi M, Baraz pordanjani SH. [Effect of Chamomile Mouthwash for Preventing Chemotherapy-Induced Stomatitis in Children]. *J Mazandaran Univ Med Sci.* 2012;21(86):19-25.
- Smeltzer SC, Hinkle JL, Bare BG, Cheever KH. Brunner and suddarths text book of medical surgical nursing. In: Jila Abed Saedi, Translator. 12th ed. Tehran, Iran: Nashre jame'eneqar; 2010. p. 205-57.
- Valizadeh I, Hosseinpour-Feizi A, Joonbakhsh F. [Comparing the quality of life in children with cancer in Tabriz children medical and training center reported by themselves and their parents, 2013]. *Journal of Clinical Nursing and Midwifery.* 2014;3(1):1-8.

6. Bowden V, Greenberg C. Children and their families (The continuum of care). 2nd edition. USA: Lippincott William & Wilkins Co.; 2010.
7. Asselin BL. Epidemiology of childhood and adolescent cancer. Nelson Textbook of Pediatrics. 2012. pp. 2416-2418e1.
8. Langhorne ME, Fulton JS, Otto SE. Oncology Nursing, 5th ed. USA: Mosby; 2007. pp. 505-23.
9. Bjork M, Nordstrom B, Wiebe T, Hallstrom I. Returning to a changed ordinary life - Families' lived experience after completing a child's cancer treatment. Eur J Cancer Care. 2011;20(2):163-9. doi: 10.1111/j.1365-2354.2009.01159.x. PubMed PMID: 20345458.
10. Bellm LA, Cunningham G, Durnell L, Eilers J, Epstein J.B, Fleming T, et al. 2002. Defining clinically meaning-ful outcomes in the evaluation of new treatment for oral mucositis: oral mucositis patient provider advisory board. Cancer Invest. 20(5-6): 793-800. doi: 10.1081/cnv-120002497. PubMed PMID: 12197238.
11. Shabanlouie R, Ahmadi F, Vaez Gharamaleki J, Hajizadeh E, Javadzadeh Y. [The effect of chamomile mouthwash in the prevention of chemotherapy-induced stomatitis]. J Rehab. 2006; 7(25): 70-5.
12. Rotblatt M, Zimen I. Evidence-based herbal medicine. 2nd ed. Philadelphia: Hanley and Belfus; 2002. p. 67-80.
13. Xavier CP, Lima CF, Fernandes-Ferreira M, Pereira-Wilson C. Salvia fruticosa, Salvia officinalis, and rosmarinic acid induce apoptosis and inhibit proliferation of human colorectal cell lines: the role in MAPK/ERK pathway. Nutr Cancer. 2009; 61(4):564-71. doi: 10.1080/01635580802710733. PubMed PMID: 19838929.
14. Slamenová D, Masterová I, Lábaj J, Horváthová E, Kubala P, Jakubíková J, et al. Cytotoxic and DNA-damaging effects of diterpenoid quinones from the roots of *Salvia officinalis* L. on colonic and hepatic human cells cultured in vitro. Basic Clin Pharmacol Toxicol. 2004;94(6):282-90. doi: 10.1111/j.1742-7843.2004.pto940605.x. PubMed PMID: 15228500.
15. Kaviani M, Maghbool SH, Azima S, Tabaei MH. Effects of salvia officinalis on the severity of labor pain in nulliparous women. Nurs Midwifery J. 2014;12(2):79-85.
16. Sadeghi A.H, Bakhshi M, Behboodi M.Z, Goodarzi S, Haghani H. Effect of sage extract on hot flashes in postmenopausal women. Journal of Complementary Medicine. 2013;2(4):324-35.
17. Imanshahidi M, Hosseinzadeh H. The pharmacological effects of *Salvia* species on the central nervous system. Phytother Res. 2006; 20(6):427-37. doi: 10.1002/ptr.1898.
18. Miranzadeh S, Adib-Hajbaghery M, Soleymanpoor L, Ehsani M. Effect of adding the herb *Achillea millefolium* on mouthwash on chemotherapy induced oral mucositis in cancer patients: A double-blind randomized controlled trial. Eur J Oncol Nurs. 2015; 19(3): 207-13.
19. Vokurka S, Bystricka E, Scudlova J, Mazur E, Visokaiova M, Vasilieva E, et al. The risk factors for oral mucositis and the effect of cryotherapy in patients after the BEAM and HD-L-PAM 200 mg/m² autologous hematopoietic stem cell transplantation. Eur J Oncol Nurs .2011;15(5):508-12. doi: 10.1016/j.ejon.2011.01.006. PubMed PMID: 21310656.
20. Yayla EM, Izgu N, Ozdemir L, Erdem SA, Kartal M. Sage tea-thyme-peppermint hydrosol oral rinse reduces chemotherapy-induced oral mucositis: A randomized controlled pilot study. Complement Ther Med. 2016;27:58-64.