



## ORIGINAL ARTICLE

## Comparative Effect of Chamomile Mouthwash and Topical Mouth Rinse in Prevention of Chemotherapy-Induced Oral Mucositis in Iranian Pediatric Patients with Acute Lymphoblastic Leukemia

Fatemeh Pourdeghatkar, MSc; Minoo Motaghi\*, PHD; Bahram Darbandi, MD; Adel Baghersalimi, MD

Islamic Azad University Isfahan (Khorasgan), University Blvd, Arghavanieh, Jay Street East, Isfahan, Iran  
17th Sharivar Hospital, Guilan University of Medical Sciences, Rasht, Iran

## ARTICLE INFO

## Article History:

Received: 10.02.2017

Accepted: 29.06.2017

## Keywords:

Chamomile  
Methotrexate  
Mouthwash  
Oral mucositis

## \*Corresponding author:

Minoo Motaghi, PhD;  
Department of Nursing, Isfahan  
(Khorasgan) Branch, Islamic Azad  
University, Isfahan, Iran.  
Email: [m.motaghi912@gmail.com](mailto:m.motaghi912@gmail.com)

## ABSTRACT

**Background:** Oral mucositis afflicts more than 3/4 of patients with cancer under chemotherapy. In acute cases it could lead to brain damage caused by hypoxia and even death due to airway obstruction and reduction of chemotherapy drug dose. We aimed to compare the effects of topical mouth rinse and chamomile mouthwash in prevention of oral mucositis caused by chemotherapy in children with cancer.

**Methods:** The study was a randomized double-blind clinical trial on 62 children aged 6-15 years with acute lymphoblastic leukemia under chemotherapy. The participants were divided randomly into two groups. The first group used topical mouth rinse and the second group started to use chamomile mouthwash a day before chemotherapy through 14 days. Mucous membrane status was assessed before starting the treatment (one day before chemotherapy), 7th and 14th day and it was reviewed based on WHO oral mucositis check list assessment and then registered by the researcher.

**Results:** The results showed that the frequency of severity of oral mucositis in both groups did not have any significant difference 7 days after chemotherapy ( $P=0.46$ ). The severity of oral mucositis in those who had used chamomile mouthwash 14 days after chemotherapy was significantly lower than those who used topical mouth rinse ( $Z=3.23$ ,  $P=0.001$ ).

**Conclusion:** In short term, using chamomile mouthwash and topical mouth rinse to prevent oral mucositis is effective in children with cancer.  
Iranian Registry of Clinical Trials: IRCT2015040821658N1.

Please cite this article as: Pourdeghatkar F, Motaghi M, Darbandi B, Baghersalimi A. Comparative Effect of Chamomile Mouthwash and Topical Mouth Rinse in Prevention of Chemotherapy-induced Oral Mucositis in Iranian Pediatric Patients with Acute Lymphoblastic Leukemia. IJBC 2017; 9(3): 84-88.

## Introduction

Survival of pediatric cancer patients has been dramatically increased as a result of multimodality approaches such as surgery, radiotherapy, and intensive chemotherapy.<sup>1</sup> In the United States, acute leukemia comprises about 27% of childhood cancers.<sup>2</sup> Systemic chemotherapy has been used to eradicate leukemic cells; various protocols with different cytotoxic potentials have been used for childhood ALL.<sup>3</sup>

IC-BFM 2002 protocol is prescribed for childhood ALL and has been used in children with ALL aged 1 to 18 years. This protocol was conducted in clinical trials since 2002 and today it is one of the most important protocols for treatment of childhood ALL.<sup>4</sup>

Most of the chemotherapeutic agents inhibit cellular proliferation and hence have unfavorable side effects on healthy tissues that proliferate rapidly such as bone marrow and gastrointestinal mucosa. Oral mucositis is

one of the main complications of chemotherapy which is debilitating in cancer patients and occurs commonly following chemotherapy or radiation therapy.<sup>3</sup>

Oral mucositis is defined as inflammatory changes which occur in buccal and labial mucosa, the inferior surface of the tongue, sublingual folds and soft palate. In early stages the first clinical sign is a white-milky layer which severe scarring develops after 1-2 weeks with loss of epithelial structure.<sup>5</sup> On the other hand, reduced doses of chemotherapy or any delay in treatment could cause serious problems and might increase mortality to 40% in patients undergoing chemotherapy.<sup>6</sup> In physiologic conditions, the normal oral mucosa and natural salivary activity are two important barriers to prevent the invasion of microorganisms. These barriers will be impaired by the occurrence of oral mucositis.<sup>7</sup> Among chemotherapeutic agents in childhood ALL, methotrexate and cytarabine cause bone marrow suppression and are commonly associated with oral and intestinal mucositis.<sup>8</sup> Mucositis usually develops 3-5 days after starting chemotherapy and reaches its peak after 7-14 days.<sup>9</sup> There is no standard approach for prevention and management of oral mucositis in children and all currently used approaches are still under survey in clinical trials. The most important factor to prevent damage to the oral mucosa is maintaining oral hygiene.<sup>10</sup>

German chamomile is one of the most widely used herbs in pharmaceutical products worldwide and chamomile mouthwash is produced from the extract of this plant.<sup>11</sup> This plant contains chamazulene, alpha bisabolol, bisabolol oxides, spiro ethers, and flavonoids which have anti-inflammatory, antibacterial and antifungal properties.<sup>12</sup>

Mazokopakis et al. has reported a case of methotrexate-induced oral mucositis in a patient with rheumatoid arthritis who was treated successfully with chamomile mouthwash.<sup>13</sup>

There are also other products such as local anesthetic agents, antibiotics, antacids, nystatin and sucralfate which are used for relief of oral mucositis or the pain itself.<sup>14</sup> There is a report that allopurinol mouthwash has been able to relieve the severity of stomatitis and associated pain.<sup>15</sup>

In this study we aimed to assess the efficacy of topical mouth rinse with compounds of (sucralfate, allopurinol, bicarbonate 7.5% and serum half-saline) which has been used in this study and in return they have used mainly chamomile mouthwash to prevent mucositis resulted by chemotherapy.

## Materials and Methods

### Study Design

This study was a randomized, double-blind clinical trial which compared the effects of chamomile mouthwash with topical mouth. The powdered pill (sucralfate, allopurinol) combined with sodium bicarbonate 7.5% and half-saline serum were given to the test group as a topical mouthwash for prevention of oral mucositis elicited by chemotherapy in children with ALL. 62 children (31 patients received

topical mouth rinse and 31 patients received chamomile mouthwash treatment) aged 6-15 years old, admitted to 17 Shahrvivar hospital of Rasht city were enrolled into this study. All the patients were receiving protocol 2002 BFM.

The content and methods of this study were approved by the Research Council and Research Ethics Committee (approval no: IR.MUI.REC.1394.4.38) of Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran, before initiation of data collection. After text review regarding the safety of chamomile mouthwash and topical mouth rinse and clarifying the research goals to children and their parents, all the parents 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 kept confidentially. Researchers were committed to consider the participants' rights in accordance to the principles explained in the Helsinki Declaration.

One day prior to the start of the treatment with methotrexate and cytarabine, the questionnaire including the demographic data was completed by the investigator and the patients' mouth was assessed for the presence of any mucositis or ulcer based on the oral mucositis check list of WHO.

### World Health Organization's Oral Mucositis Check List

In this scale, zero has been defined as lack of oral mucositis, grade 1 as sore and erythema, grade 2 as ulceration and erythema in the mouth while being able to eat solid food, grade 3 ulcer and extensive erythema in the mouth and ability to just drink liquids and grade 4 as mucositis to the extent that there is inability to eat or drink even liquids.

### Instruments

Toothbrush and toothpastes were given to both groups and they were taught how to brush properly. Also, the precise way of mouthwash application (chamomile or topical mouth rinse) was taught and they were asked to record the frequency of mouthwash usage in a check list prepared by investigator in order to control and follow up.

The test group started to gargle the mouthwash a day before chemotherapy continued for 14 days, every day after brushing, three times a day (morning, afternoon, evening) and every time 20 cc (without any dilution) for a minute so that all parts of the mouth, gums and tongue be smeared. They didn't eat up for an hour after mouth rinsing and all other treatments were continued other than the consumption of chamomile.

The control group used chamomile mouthwash available in pharmacies (30 ml drop Matrika mouthwash barijessans/kashan, Iran) for mouth rinse since the day before chemotherapy for 14 days afterwards, every day after brushing, three times a day (morning, noon, night). Thus, they diluted 30 drops of solution in 20 cc water and then gargled for a minute so that all parts of mouth, gums and tongue smeared. They didn't eat up either for an hour after mouthwash and previous standard treatment of doctor continued other than topical mouth rinse consumption.

### Data Collection/Procedure

Data were collected between July to December 2015. The study started since the day before chemotherapy until 14 days thereafter. The patient's mucosal status and existence of any kind or degree of mucositis in the mouth or throat were recorded according to executive protocol by the investigator before starting treatment (one day before chemotherapy) and then on seventh and fourteenth day based on oral mucositis check list assessment of WHO.

### Data Analysis

Data were analyzed by statistical software of SPSS version 11, using descriptive statistics and chi-square test, T-test, Mann-Whitney-Wilcoxon tests.

### Results

Evaluation of unit's distribution according to sex and age of divided groups is shown in Table 1. Chi-square test showed that the frequency of sex in both groups were not significantly different ( $\chi^2=0.07$ ,  $P=0.79$ ) and independent t-test showed that there was not a significant difference between two groups in terms of mean age ( $t=0.28$ ,  $P=0.78$ ).

### The Frequency of Oral Mucositis in Terms of Severity on Seventh and Fourteenth Day after Chemotherapy

On seventh days after chemotherapy, forty-one patients (66%) were free from oral mucositis, twelve patients (19%) showed grade 1, five patients (8%) grade 2, three patients (5%) grade 3 and one patient (2%) experienced grade 4 oral mucositis, whereas 14 days after chemotherapy, thirty-four patients (55%) were free of oral mucositis (grade 0), seventeen patients (27.5%) had grade 1, five patients (8%) grade 2, two patients (3%) grade 3 and four patients (6.5%) experienced grade 4 oral mucositis. (Figure 1)

### The Frequency of Severity of Oral Mucositis in Two Groups on Seventh Days after Chemotherapy

The results of this study showed that the frequency and severity of oral mucositis in two groups, seven days after chemotherapy was not significantly different ( $P=0.46$ ). In other words, in short term, (7 days) the effect of topical mouth rinse and chamomile mouthwash on oral mucositis caused by chemotherapy was not different.

### The Frequency and Severity of Oral Mucositis in Two Groups on Fourteenth Days after Chemotherapy

The results showed that the frequency and severity of oral mucositis, 14 days after chemotherapy was significantly less in those who had used chamomile mouthwash than control group who had used topical mouth rinse. ( $Z=3.23$ ,  $P=0.001$ , table 2).

**Table 1:** Distribution of sex and the mean age of the subjects in both groups

Personal records	Groups	Local mouthwash		Chamomile mouthwash	
		Number	Percentage	Number	Percentage
		Average	SD	Average	SD
Age		9.7	3.01	9.9	2.9
Sex	Boy	17	54.8	18	58/1
	Girl	14	45/2	13	41/9
Overall		31	100	31	100



Grade 1



Grade 2



Grade 3



Grade 4

**Figure 1:** Oral mucositis and ulcers in different grades.



**Table 2:** Frequency distribution of oral mucositis in two groups, 7 and 14 days after chemotherapy

Mucositis severity	7 days after local mouthwash consumption		14 days after local mouthwash consumption		7 days after chamomile mouthwash consumption		14 days after chamomile mouthwash consumption	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Without mucositis	20	64.5	11	35.5	21	67.7%	23	74.2%
Grade 1	4	12.9	11	35.5	8	25.8%	6	19.2%
Grade 2	3	9.7	4	12.8	2	6.5%	1	3.3%
Grade 3	3	9.7	1	3.3	0	0	1	3.3%
Grade 4	1	3.2	4	12.8	0	0	0	0
Overall	31	100	31	100	31	100	31	100

## Discussion

This study showed that the frequency and severity of oral mucositis in two groups, seven days after chemotherapy was not significantly different ( $P=0.46$ ). However, in the previous studies reported from Iran,<sup>16</sup> They reported that there was a significant difference in number of patients with oral mucositis on the day 7, in group of patients who had used chamomile as mouthwash in comparison to the control group ( $P=0.01$ ). According to the investigator, the observed difference in their study could be explained by comparing the chamomile mouthwash with a placebo (sterile water); while in our study chamomile mouthwash was compared to a topical mouth rinse comprised of sucralfate, allopurinol, bicarbonate 7.5% and serum half-saline. In our study, the severity of oral mucositis on seventh day after chemotherapy was lower in the chamomile mouthwash group; however, it was not significant.

The severity of oral mucositis, 14 days after chemotherapy, was significantly lower in group of patients who had used chamomile rather than topical mouth rinse. The results of our study in this longer period did not match with the previous study.<sup>12</sup> It seems that the difference could be due to the age of the subjects in this study who were children with ALL; aged 6-15 year, but in Fiedler's study; the average age of the participants was 64.3 years old. In addition, the type of chemotherapy could have some contributions since in Fiedler's study it was 5-Fluorouracil, while it consisted of methotrexate and cytarabine in our study. Another study from Iran has reported lower rate of occurrence of oral mucositis on seventh day after chemotherapy in patients treated with chamomile mouthwash. ( $P=0.01$ ). However, on 14<sup>th</sup> day of chemotherapy, the incidence of oral mucositis in patients treated with chamomile mouthwash was not significantly different with the placebo group<sup>16</sup> ( $P=0.5$ ). In that study, the pathophysiology of the mucositis process was mentioned as the reason for the discrepancy. They also stated the symptoms and intensity of mucositis from fourth day and its subsidence almost after 2 weeks; while in the present study the mucositis severity on day 7 and 14 after chemotherapy in the group of patients using chamomile mouthwash had no significant difference based on statistical analysis. According to Adamson and colleagues, the most important side effect of methotrexate was bone marrow suppression with oral and intestinal mucositis. Meanwhile, the most adverse effect of

cytarabine is reported to be bone marrow suppression with gastrointestinal mucosal injuries that occur between days 5-14 after treatment.<sup>9</sup>

Fiedler conducted a study to assess the efficacy of chamomile mouthwash on prevention of stomatitis caused by 5- Fluorouracil. It showed that chamomile mouthwash had no beneficial effect on incidence of oral mucositis induced by 5- Fluorouracil ( $P=0.32$ ).<sup>12</sup>

The beneficial effect of chamomile mouthwash on oral mucositis caused by methotrexate has been reported in a patient with rheumatoid arthritis.<sup>13</sup> In our study, the severity of oral mucositis 14 days after chemotherapy, in the group who consumed topical mouth rinse, was significantly more than 7 days after chemotherapy [ $Z=2.05$  ( $P=0.04$ )]. In other words, the severity of mucositis at the day 14 after chemotherapy was more than what was observed on 7th day of chemotherapy. In another study, the topical mouth rinse of various combinations failed to prevent the occurrence of oral mucositis in children with cancer.<sup>8</sup> In this research the topical mouth rinse had less effect in preventing mucositis compared to smectite cream glycerin, and also no serious adverse effects were observed in both groups.<sup>8</sup> Sucralfate is suggested as an effective topical mouth rinse. Its effect on the pain following tonsillectomy in children aged 6-12 has been investigated and has showed positive results.<sup>17</sup>

Allopurinol has also been proposed as a topical mouth rinse and it was one of the ingredients of our topical mouth rinse. The efficacy of allopurinol mouthwash on prevention of chemotherapy-induced oral mucositis has been studied.<sup>15</sup> It showed that allopurinol mouthwash could significantly decrease severity of oral mucositis and its associated pain.

## Conclusion

Based on the results of this study, chamomile mouthwash in comparison to topical mouth rinse (sucralfate, allopurinol, bicarbonate 7.5% and serum half-saline) is an effective compound in prevention of oral mucositis in children with cancer.

**Conflict of Interest:** None declared.

## References

1. Kuiken NS, Rings EH, Tissing WJ. Risk analysis, diagnosis and management of Gastrointestinal mucositis in pediatric cancer patients. Crit Rev

- Oncol Hematol 2015; 94(1):87-97. doi: 10.1016/j.critrevonc.2014.12.009. PubMed PMID: 25560731.
2. Farahmand M, Almasi-Hashiani A, Mohammad Beigi A, Raei-Dehaghi M, Ajdari A. The epidemiology of childhood hematopoietic and reticuloendothelial cancer based on Fars province cancer registry data system from 2001 to 2008. *daneshvarmed* 2011; 18(94): 27-34.
  3. Benjamin I, Griggs R, Wing E, Fitz G, Andreoli T. Andreoli and Carpenter's Cecil Essentials of Medicine. 8<sup>th</sup> ed. Saunders/Elsevier; 2010.
  4. Sary J, Zimmermann M, Campbell M, Castillo L, Dibar E, Donska S, et al. Intensive Chemotherapy for Childhood Acute Lymphoblastic Leukemia: Results of the Randomized Intercontinental Trial ALL IC-BFM 2002. *J Clin Oncol* 2014; 32(3):174-84. doi: 10.1200/JCO.2013.48.6522. PubMed PMID: 24344215.
  5. Chen SC, Lai YH, Huang BS, Lin CY, Fan KH, Chang JT. Changes and predictors of radiation-induced oral mucositis in patients with oral cavity cancer during active treatment. *Eur J Oncol Nurs* 2015; 19(3):214-9. doi: 10.1016/j.ejon.2014.12.001. PubMed PMID: 25586214.
  6. Cheng KKF, Chang AM, Yuen MP. Prevention of oral mucositis in paediatric patients treated with chemotherapy a randomized crossover trial comparing two protocols of oral care. *Eur J Cancer* 2004; 40:1208-16. doi: 10.1016/j.ejca.2003.10.023.
  7. Miller M, Pharm D, Donald D, Hagemann T. Prevention and treatment of oral mucositis in children with cancer. *J Pediatr Pharmacol Ther.* 2012; 17(4):340-50. doi: 10.5863/1551-6776-17.4.340. PubMed PMID: 23413048. PubMed Central PMCID: PMC3567887.
  8. Lin JX, Fan ZY, Lin Q, Wu DH, Wu XY, Chen YR, et al. A comparison of dioctahedral smectite and iodineglycerin cream with topical mouth rinse in treatment of chemotherapy induced oral mucositis: a pilot study. *Eur J Oncol Nurs* 2015; 19(2):136-41. doi: 10.1016/j.ejon.2014.10.006. PubMed PMID: 25465773.
  9. Adamson pc, Bagatell R, Balis F. General principles of chemotherapy in pizzo pa, poplack dg. Principles and practice of pediatric oncology. Philadelphia: Lippincott Williams and Wilkins Inc; 2011.
  10. Briggs J. Prevention and treatment of oral mucositis in cancer patients. *Best Pract.* 1998; 2(3): 1-6. Available from: <http://oralcancerfoundation.org/wp-content/uploads/2016/09/mucositis.pdf>
  11. Balazes T, Tisserand R. German chamomile. *International Journal of Aromatherapy* 1998; 9(1):15-21. doi: 10.1016/S0962-4562(98)80043-X.
  12. Fidler P, Loprinzi CL, O'Fallon JR, Leitch JM, Lee JK, Hayes DL, et al. Prospective evaluation of a chamomile mouthwash for prevention of 5- FU induced oral mucositis. *Cancer.* 1996; 77(3):522-5. doi: 10.1002/(SICI)1097-0142(19960201)77:3<522::AID-CNCR14>3.0.CO;2-6. PubMed PMID: 8630960.
  13. Mazokopakis EE, Vrentzos GE, Papadakis JA, Babalis DE, Ganotakis ES. Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis. *Phytomedicine* 2005; 12(1-2):25-7
  14. *Esmaeeli D Javid GH, Emami AH, Ataie-Fashtami L, Safaeinodahi SR, Merikh-Baiat F, Fateh M, et al.* Low Level Laser Therapy in Management of Chemotherapy-Induced Oral Mucositis: Prophylaxis or Treatment? *J Lasers Med Sci* 2011; 2(1).
  15. Shabanlooe R, Ahmadi F, Vaez gharamaleki J, Hajizadeh E, Javadzadeh Y. The effects of allopurinol mouthwash in the prevention of chemotherapy induced stomatitis. *Tehran Univ Med J* 2007; 65(9): 71-76
  16. Alijani H, Keikhai B, Ghadimi 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
  17. Jahanshahi J, Pazira S, Farahani F, Hashemian F, Shokri N, Karkhaneh B, et al. Effect of topical sucralfate vs clindamycin on post tonsillectomy pain in children aged 6 to 12 years: A triple-blind randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2014; 140(8):698-703. doi: 10.1001/jamaoto.2014.979. PubMed PMID: 24946226.