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The Effect of *Cordia myxa* Mouthwash on the Incidence and Severity of Stomatitis in Leukemia Patients Undergoing Chemotherapy: A Protocol Study

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Abstract

Background: Stomatitis, or oral inflammation, is one of the common complications in patients undergoing chemotherapy, causing pain, discomfort, infection, and prolonged hospitalization.

Objectives: The purpose of this study is to investigate the effect of *Cordia myxa* mouthwash on preventing stomatitis in patients undergoing chemotherapy.

Methods and Result: This study will be a double-blind, single-center, randomized controlled clinical trial focusing on 60 patients undergoing chemotherapy. The samples will be randomly divided into intervention and control groups. In addition to receiving the routine Betadine mouthwash, participants in the intervention group will receive a solution of 30 drops of 5% *C. myxa* formulation in 20 cc of water, and they will be asked to put the solution in their mouth, swirl it for a minute, and then spit it out. In the control group, in addition to Betadine mouthwash, a sterile water placebo (with the same taste and smell) will be used. The data will be analyzed based on statistical tests using SPSS version 22.

Conclusions: If this intervention proves effective in improving access and adherence to treatment, it would represent a step forward in addressing a chronic health problem common among leukemia patients undergoing chemotherapy. Given its natural essence and the fact that it is not associated with any complications, *C. myxa* mouthwash can be used safely alongside the main treatment to prevent and reduce the severity of mouth ulcers caused by chemotherapy.

Keywords: Stomatitis, Chemotherapy, Mouthwash, *Cordia myxa*, Nursing

1. Background

Leukemia is a type of blood cancer caused by the excessive production of white blood cell-forming tissues, leading to a significant increase in premature or abnormal WBCs in the blood circulation (1, 2). Chemotherapy is a systemic and common method to treat leukemia. However, the side effects of chemotherapy result in adverse anatomical and functional conditions, such as dysphagia, vomiting, diarrhea, malnutrition, arthralgia, bleeding, anemia, and mucositis (stomatitis) (3).

Oral mucositis is one of the most common complications, occurring in almost 40% of patients undergoing chemotherapy (4). Chemotherapy induces inflammation and ulceration through tissue damage caused by a sequence of chemical, metabolic, and

biological events that occur in several stages. Stomatitis typically begins within the first week of treatment and peaks in the second week (3). These oral ulcers can cause pain, dysphagia, difficulties in eating, swallowing, speaking, increased hospitalizations (5), weight loss, local infection (6), physical limitations, psychological discomfort, and impaired quality of life for patients (7).

Moreover, the disrupted oral mucosa caused by stomatitis can be fatal for patients, as it provides a pathway for the entry of pathogenic microorganisms, leading to various infections, including life-threatening septicemia (8). Additionally, patients with high-grade mucositis often need to reduce their chemotherapy regimen, resulting in delays in cancer treatment and a worsened prognosis (9).

Despite the devastating clinical consequences of oral mucositis, there is no effective treatment to prevent or reduce it in patients. Oral and gastrointestinal mucositis remains a significant challenge for individuals undergoing cancer treatment. The few interventions supported by solid evidence are not universally applicable to all types of oral mucositis, nor are their effects on tissues fully understood. This lack of clarity leads to varied and often arbitrary protocols with significant differences between medical centers (9). Although some complementary and alternative medicines, such as medicinal herbs, have been used to prevent and treat stomatitis, their therapeutic effects have not been conclusively confirmed (10).

One medicinal plant with a long history of proven therapeutic effects is the Assyrian plum, scientifically known as *Cordia myxa* L. It is the most common species within the genus *Cordia*, belonging to the *Boraginaceae* family, and is generally found in tropical and semi-arid regions. *C. myxa* grows in tropical, dry, and moist deciduous forests. In traditional (ancient) medicine, it is used to treat throat and chest ailments, relieve gallbladder issues, quench thirst, relieve hoarseness, and treat heartburn, as well as bladder and intestinal ulcers (11). Different parts of the plant, such as the fruit, bark, leaves, and seeds, are utilized for their anti-fever, antioxidant, anti-diabetic, anti-ulcer, immune-modulating, and anti-cancer properties. Additionally, this plant has been used as a remedy for impotence, stomach pain, asthma, oral ulcers, bronchitis, diarrhea, cardiovascular diseases, rheumatism, and tooth decay (12-15).

The fruit, leaves, seeds, and bark of this plant contain pyrrolizidine alkaloids, flavonoids, saponins, terpenes, and sterols (16, 17). Recently, the presence of rutin, along with p-coumaric acid or caffeic acid, has been identified in *C. myxa*. Rosmarinic acid, which is also present, exhibits various biological activities such as antioxidant, anti-inflammatory, and neuroprotective effects (18). *Cordia myxa* possesses antimicrobial, anti-inflammatory, analgesic, and diuretic effects and is used to treat disorders of the digestive, respiratory, genitourinary, cardiac, vascular, and blood systems (19). Both in acute and chronic phases, the hydro-alcoholic extract of *C. myxa* fruit has demonstrated analgesic and anti-inflammatory properties (20). In 2001, Al-Awadi et al. showed that experimental colitis could be treated using the *C. myxa* fruit preparation 170, which possesses anti-inflammatory qualities. The dichloromethane and ethyl acetate fractions of *C. myxa* showed notable anti-inflammatory effectiveness, with inhibition percentages of 45.16% and 40.26%, respectively, which were relatively close to that of indomethacin (51.61%) when comparing the complete ethanol extract and various fractions of *C. myxa* leaves (21).

In Iran, *C. myxa* L. grows in tropical and subtropical regions, particularly in the south and southwest of the country (22). The fruit and leaves of this plant are readily available at an affordable price in these regions.

2. Objectives

Since no similar research has been conducted on the effects of this fruit on the prevention of oral ulcers, this study aims to investigate the effect of *C. myxa* mouthwash on the incidence and severity of stomatitis in leukemia patients undergoing chemotherapy.

3. Methods and Results

3.1. Design and Setting

The present study is a double-blind, randomized controlled clinical trial conducted on leukemia patients undergoing chemotherapy in the oncology departments of Baqaei 2 Hospital, affiliated with Ahvaz Jundishapur University of Medical Sciences in Ahvaz.

3.2. Participants

Using the following statistical formula and assuming parameters ($P_1 = 0.73$), ($P_2 = 0.38$), ($\alpha = 0.05$), ($\beta = 0.20$),

and an anticipated attrition rate of 15%, the sample size has been set at (n = 60) for both the intervention and control groups.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 [P_1(1-P_1)+P_2\,(1-P_2)]}{(P_1-P_2)^2}$$

Patients meeting the following criteria will be eligible to participate in this study: Aged 18 or older, recently diagnosed with acute leukemia, receiving a consistent chemotherapy regimen for two weeks, fully conscious, without ulcers in the mouth area, and without conditions such as asthma, diabetes, allergies, or other allergic diseases. Additional criteria include not using narcotic drugs or other mouthwash solutions and not receiving radiotherapy. Withdrawal criteria will include any change in chemotherapy regimen or occurrence of systemic infection during the study.

3.3. Randomization and Blinding/Masking

Patients who meet the inclusion criteria will be assigned to either the intervention or control group using the permutation block randomization method. A randomization list will be prepared by a statistician and provided to the first author. In this list, patients will be randomly assigned to the intervention and control groups, labeled as codes A and B, and made available to the first author. The sequence of assignments will be concealed in consecutively numbered opaque envelopes, with each envelope opened only at the time of intervention.

3.4. Control of Bias

In this study, both the researcher (first author) and the patients will be blinded to group allocation. Patients will remain unaware of their group assignment. A pharmacologist will label the primary drug and placebo with codes C and D, respectively, and will then provide them to the first author for intervention. The physician responsible for assessing oral stomatitis will also be blinded to the group assignments.

3.5. Intervention Protocol

Both groups will be provided with soft toothbrushes and instructed on proper brushing techniques. Additionally, both groups will be taught the correct way to use the mouthwash. In the oncology departments where this study will be conducted, a 1% Betadine mouthwash solution (5 cc of Betadine in 500 cc of saline) is routinely used to prevent stomatitis.

In the intervention group, in addition to the routine 1% Betadine mouthwash, patients will be instructed to add 30 drops of a 5% mucilage formulation of *C. myxa* to 20 cc of water. They will then place this solution in their mouths, swirl it for one minute, and spit it out. Patients will be advised to avoid eating or drinking anything for 1 hour after using the mouthwash.

In the control group, in addition to the Betadine mouthwash, patients will receive a placebo—sterile water with the same taste and smell—delivered in a glass with a dropper.

For a period of 14 days, patients in both groups will brush their teeth using a soft toothbrush and the same toothpaste three times daily, after breakfast, lunch, and dinner, followed by the designated mouthwash. On days one, seven, and fourteen, an attending physician will examine the mouths of all patients individually, recording findings using the World Health Organization (WHO) stomatitis checklist.

3.6. Ethical Considerations

This study will be approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref ID: IR.AJUMS.REC.1397.110). Before assignment to study groups, patients will be briefed on the study objectives, and informed consent will be obtained from each participant. They will be assured of their anonymity throughout the study, that all personal information will remain confidential, and that they may withdraw from the study at any time if they wish. Patients who are not part of the intervention group will continue to receive all essential hospital services and treatments. Additionally, the study will be registered in the Iranian Registry of Clinical Trials (IRCT20180511039610N2, Registration date: 2018-10-24). Outcome Assessment: Variables and Measurement Instruments

To evaluate the study objectives, a specialist doctor will assess the oral area for signs of mucositis on days one, seven, and fourteen in both the intervention and control groups.

3.7. Independent Variables

- Condition or group: Use of mouthwash with a 5% *C. myxa* mucilage formulation in addition to a 1% Betadine

mouthwash (intervention group) or a sterile water placebo mouthwash in addition to a 1% Betadine mouthwash (control group).

- Demographic data: Age, sex, marital status, educational attainment, chemotherapy regimen, and use of painkillers.

3.8. Dependent Variable

- Evaluation of oral mucositis: The primary dependent variable is the severity of oral mucositis.

3.9. Oral Mucositis Evaluation

The severity of oral mucositis (stomatitis) will be assessed using a checklist based on criteria from the WHO and the National Cancer Institute (NCI) (23). According to WHO criteria, stomatitis is classified as follows: Grade 0: No stomatitis; grade I: Erythema and soreness of the oral mucosa, potentially involving the inner cheeks, but without ulceration; grade II: Presence of ulcers in the mouth; however, the patient is still able to eat; grade III: Ulcers accompanied by extensive erythema; the patient is unable to eat solid foods and requires a liquid diet; grade IV: Severe inflammation and ulcers that make oral feeding impossible; the patient is limited to liquid intake only.

This grading will help objectively assess the severity and progression of oral mucositis in each patient.

The NCI Scale is a graded scale for assessing oral mucositis severity as follows: Zero indicates no visible change, 1 indicates the presence of erythema, 2 denotes patchy ulcers up to 1.5 cm in diameter, 3 indicates patchy ulcers larger than 1.5 cm in diameter, and 4 represents ulcers with necrosis and bleeding. In this study, oral mucositis will be considered severe if classified as Grade 3 or 4 on either the NCI or WHO Scales.

The secondary outcomes include the difference in the score between the initial and final evaluations on the HADS survey (Hospital Anxiety and Depression Scale), a 14-question survey assessing anxiety and depression. Additionally, another secondary outcome is the difference in the quality of life score, as defined by the EQ-5D survey, between the initial evaluation and the assessment conducted three months post-surgery.

Data will be expressed as mean and standard deviation for continuous quantitative variables with a normal distribution, as median and interquartile range for quantitative variables with a non-normal distribution, and as frequency and percentage for qualitative variables. The normality of data distribution will be assessed using the Shapiro-Wilk test, while homoscedasticity will be checked using the Fisher-Snedecor test. Comparisons between independent groups will be analyzed using the χ^2 or Fisher's exact test for categorical variables. Baseline outcomes on the first, seventh, and fourteenth days will be compared between the control and intervention groups using the *t*-test or the Mann-Whitney test, depending on data distribution.

To evaluate the trend of oral ulcer presentation on the first, seventh, and fourteenth days, Friedman's repeated measures analysis or generalized estimating equations (GEE) will be employed, based on data normality. The significance level is set at 0.95 to identify significant differences between variables; thus, P-values less than 0.05 will be considered statistically significant. Data analysis will be conducted using SPSS 23.0 statistical software. If the frequency of missing data exceeds 5%, additional analyses will be performed using imputation methods.

4. Discussion

The expected result is to prevent the occurrence of stomatitis or to reduce its incidence through an intervention using *C. myxa* mouthwash as a complementary treatment. The *C. myxa* mouthwash is safe, easy to use, and does not interfere with other treatments or interventions, making it feasible for incorporation into routine nursing care for patients undergoing chemotherapy, both in hospital and at home. The use of this mouthwash could potentially lower the costs associated with treating oral stomatitis. However, its effects and cost-effectiveness remain largely unstudied, and it is not yet supported by the Ministry of Health and Medical Education of Iran. This study aims to expand our knowledge about the benefits of *C. myxa* mouthwash, providing evidence for its effectiveness against stomatitis. These findings could have significant implications for public policymakers as well as oncologists.

The results of Hemati et al. indicated that the mucilage of *C. myxa* significantly inhibited the growth of eight strains of gram-negative and gram-positive pathogenic bacteria under laboratory conditions (24). Similarly, Nariya et al. investigated the antibacterial and antifungal effects of the bark of a *C. myxa* species, demonstrating that the bark possesses both antifungal and antibacterial properties (25).

One limitation of the present study is the potential for genetic variability in patients' susceptibility to nausea and vomiting, which is beyond the researcher's control. Another limitation is the small sample size, as the study was conducted in only one hospital. Additionally, factors such as psychological stress, genetics, nutritional imbalances, immune and hormonal changes, and allergies are all recognized as important contributors to the etiology of mouth ulcerations.

Footnotes

Authors' Contribution: Research conception and design: M. J., S. M., B. S., A. A. D., and A. S.; data collection: B. S. S. A. M., and M. S. K.; analysis and interpretation of data: S. M., B. S. S., A. M., and M. S. K.; drafting of the manuscript: M. J., S. M., B. S., A. A. D., A. S., S. A. M., and M. S. K.; review and editing: M. J., S. M., B. S., A. A. D., and A. S. All authors contributed to the article and approved the submitted version.

Clinical Trial Registration Code: The author will observe the ethical principles of research work of the Declaration of Helsinki. This investigation was registered in the Iranian Registry of Clinical Trials Center (IRCT20180511039610N2).

Conflict of Interests Statement: The authors declare that they have no conflict of interest about this working.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: At first, a written permit will obtain to conduct the research, and the proposal was approved under the code IR.AJUMS.REC.1397.110 by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences.

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Informed Consent: Written informed consents will also obtain from the participants.

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