

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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Study protocol

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Abstract

Background and purpose: Stomatitis or oral inflammation is one of the common complications in patients undergoing chemotherapy, which causes pain, discomfort, infection and long-term hospitalization. The only way to prevent this condition is to use a suitable mouthwash and maintain oral hygiene. The purpose of this study is to investigate the effect of Cordia myxa mouthwash on preventing stomatitis in patients undergoing chemotherapy.

Method: 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% Cordia myxa formulation in 20 cc of water, and they will be asked to put the solution in their mouth, swirl it in their mouth for a minute and then spit it out. In the control group, in addition to betadine mouthwash, sterile water placebo (having the same taste and smell) will be used. Patients will brush their mouths with a soft toothbrush and the same toothpaste 3 times a day after breakfast, lunch, and dinner followed by mouthwash use for 14 days. Data will be collected using a demographic information questionnaire and the oral stomatitis severity checklist. The data will be analyzed based on statistical tests using SPSS version 22.

Discussion: This study is expected to shed light on the effectiveness of Cordia myxa mouthwash in improving the severity of stomatitis among leukemia patients. To the best of our knowledge, no valid scientific research has so far been conducted on this very topic. If this intervention proves effective in improving access and adherence to treatment, it would be a step forward in addressing a chronic health problem that is common among leukemia patients undergoing chemotherapy. Given its natural essence and the fact that it is not associated with any complications, the Cordia myxa mouthwash can be used safely alongside the main treatment to prevent and reduce the severity of mouth ulcers caused by chemotherapy.

Introduction

Leukemia is a type of blood cancer that is caused by the excessive production of white blood cell-forming tissues, which leads to a significant increase of premature or abnormal WBCs in the blood circulation [1, 2]. Chemotherapy is a systemic and common method to treat leukemia. Side effects of chemotherapy, however, lead to 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 that occurs in almost 40% of patients undergoing chemotherapy [4].

Chemotherapy causes inflammation and ulceration through tissue damage caused by a sequence of chemical, metabolic, and biological events that occur in several steps. Stomatitis usually starts in the first week after starting the treatment and reaches its peak in the second week [3]. These oral ulcers can cause pain, dysphagia, eating problems, swallowing, speaking, increased hospitalizations [5], weight loss, local infection [6], physical limitations, psychological discomfort, and patients' impaired quality of life [7]. Also,

the disrupted oral mucosa caused by stomatitis can be fatal for patients, because it creates the main path for the entry of pathological microorganisms and leads to various infections, including fatal septicemia [8]. In addition, patients with high-grade mucositis should reduce their chemotherapy regimen, which causes a delay in cancer treatment and leads to a worse prognosis [9].

Despite the devastating clinical consequences of oral mucositis, there is no effective treatment to prevent or reduce it in patients, and oral and gastrointestinal mucositis remains a significant challenge for patients undergoing cancer treatment. The few interventions supported by solid evidence are not necessarily applicable to all types of oral mucositis, nor are their effects on tissues completely clear, leading to arbitrary protocols with large 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 results have not been clearly confirmed [10].

One of the medicinal plants whose therapeutic effect has long been proven is the Assyrian plum, known scientifically as *Cordia myxa* L. It is the most common species of the genus *Cordia*, which belongs to the Boraginaceae family and is generally found in tropical, semi-arid regions. *Cordia myxa* grows in tropical and dry to moist deciduous forests. In traditional (ancient) medicine, it is used to treat throat and chest complaints, relieve the gallbladder, quench thirst, relieve voice hoarseness, and to treat heartburn as well as bladder and intestinal ulcers [11]. Different parts of the plant such as the fruit, the bark, the leaves and the seeds are used as an anti-fever, anti-oxidant, anti-diabetic, anti-ulcer, immune system modulator, and anti-cancer drug. This plant has also been used as a medicine for impotency, stomach pain, asthma, oral ulcers, bronchitis, diarrhea, cardiovascular diseases, rheumatism, and tooth decay [12-15]. Pyrrolizidine alkaloids, flavonoids, saponins, terpenes and sterols have been reported to exist in the fruit, leaves, seeds and bark of this plant [16, 17]. Recently, the presence of rutin along with p-coumaric acid or caffeic acid has been reported in *Cordia myxa*. Rosmarinic acid shows various biological activities such as antioxidant, anti-inflammatory and neuroprotective effects [18]. *Cordia myxa* has antimicrobial, anti-inflammatory, analgesic and diuretic effects and is used to treat digestive, respiratory, genitourinary, cardiac, vascular and blood disorders [19].

In Iran, *Cordia myxa* L. grows in the tropical and subtropical regions in the south and southwest of this country [20]. The fruit and leaves of this plant are available at a very modest price in the south and southwest of Iran. Since no similar research has so far been conducted on the effects of this fruit on the prevention of oral ulcers, the present study aims to investigate the effect of *Cordia myxa* mouthwash on the incidence and severity of stomatitis in leukemia patients undergoing chemotherapy.

Methods

Design and setting

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

Participants

Using the following statistical formula and assuming $p_1=0.73$, $p_2=0.38$, $\alpha=0.05$, $\beta=0.20$ and an attrition rate of 15%, we will set the sample size to be $n= 60$ for both intervention and control groups.

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

Patients meeting the following criteria will be eligible to participate in this study: being aged 18 or above, being recently diagnosed with acute leukemia, receiving the same chemotherapy regimen for two weeks, having full consciousness, not having ulcers in the mouth area, asthma, diabetes, allergies or other allergy diseases, not using narcotic drugs or other mouthwash solutions, and not receiving radiotherapy. Exclusion criteria will include: change in chemotherapy regimen or systemic infection during the study.

Randomization and blinding/masking

Patients will be selected based on the inclusion criteria and then assigned to intervention and control groups using permutation block randomization method. To this aim, a randomization list will be prepared by a statistician and provided to the researcher (first author). In this list, random assignment of patients to intervention and control groups with codes A and B will be available to the first author. The sequence will be concealed in consecutively numbered opaque envelopes. Each envelope will be opened at the time of the intervention.

Control of bias

In this study, both the researcher (first author) and the patients will be blinded to group allocation. Patients will be unaware of group assignment. The pharmacologist will label the main drug and placebo using codes C and D, respectively, and will then give them to the first author to implement the intervention. The physician responsible for the assessment of oral stomatitis will also be blinded to the group assignment.

Intervention protocol

Soft toothbrushes will be provided to the two groups, and they will be taught how to brush their teeth correctly. Afterwards, the correct way of using the mouthwash will be taught to the patients of both groups. In the oncology departments of the hospital in which this study is going to be carried out, betadine 1% mouthwash solution (5 cc of betadine in 500 cc of saline) is routinely used to prevent stomatitis. In addition to receiving the routine 1% betadine mouthwash, patients of the intervention group will be instructed to pour 30 drops of 5% mucilage formulation of Cordia myxa in 20 cc of water, put it in their mouth, swirl it in the mouth for one minute, and then spit it out. The patients will be asked not to take anything by mouth for 1 hour after using the mouthwash. In addition to the betadine mouthwash,

the control group will be given sterile water placebo (having the same taste and smell) in a glass with a dropper. For 14 days, the patients will brush their mouths with a soft toothbrush and the same toothpaste 3 times a day after breakfast, lunch and dinner and then use the mouthwash. On the first, seventh, and fourteenth days, the mouths of the patients will be examined individually by the attending physician, and the evidence will be recorded according to the WHO stomatitis checklist.

Ethical consideration

This study will receive approval from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref ID: IR.AJUMS.REC.1398.752). Before assignment of patients into study groups, they will be briefed on the study objectives and their informed consent will be obtained. The participants will be ensured that they will remain anonymous throughout the study, that their information will remain confidential, and that they could withdraw from the study any time they wish. Patients who will not be part of the intervention group will also benefit from essential hospital services and treatments. Moreover, the study will be registered in the Iranian Registry of Clinical Trials (IRCT20180511039610N2).

Outcome assessment. Variables and measurement instruments

In order to evaluate the study objectives, the oral area will be evaluated by a specialist doctor to check for oral mucositis on the first, seventh, and the fourteenth days in both the intervention and control groups.

The independent variables are as follows:

- Condition or group: mouthwash with 5% Cordia myxa mucilage formulation in addition to 1% betadine mouthwash (intervention group) or sterile water placebo mouthwash in addition to 1% betadine mouthwash (control group).
- Demographic data: age, sex, marital status, educational attainment, chemotherapy regimen, use of painkillers.

The dependent variable includes evaluation of oral mucositis:

Oral mucositis evaluation

The checklist for determining the severity of inflammation of the oral mucosa (stomatitis) will be based on the criteria of the World Health Organization and the National Cancer Institute (NCI) [21].

According to the criteria of the World Health Organization, stomatitis is classified as follows:

Grade 0: No stomatitis. Grade 1: The oral mucosa is characterized with erythema and soreness, which may also involve the inner part of the cheeks, but there is no ulceration at this stage. Grade 2: There are ulcers in the mouth, but the patient is able to eat. Grade 3: There are ulcers with extensive erythema, and the patient is unable to eat solid foods and needs a liquid diet. Grade 4: The inflammation and ulcers are so extensive that oral feeding is not possible and the patient is only able to receive liquids.

The NCI scale is a graded scale as follows: 0. No visible change. 1. Presence of erythema. 2. Patchy ulcers up to 1.5 cm in diameter; 3. Patchy ulcers with a diameter greater than 1.5 cm. 5. Ulcers characterized with necrosis and bleeding. In this study, oral mucositis will be considered severe when classified as Grade 3 or 4 according to the NCI and/or WHO scales.

Data analysis

Data will be expressed as mean and standard deviation for continuous quantitative variables with normal distribution, as median and interquartile range for quantitative variables with non-normal distribution, and as frequency and percentage for qualitative variables. The normality of the data distribution will be checked using the Shapiro-Wilk test. Baseline outcomes on the first, seventh, and fourteenth days will be compared between the control group and the intervention group using t-test or the Wilcoxon test. Also, in order to evaluate the trend of oral ulcer presentation on the first, seventh and fourteenth days, Friedman's repeated measurement analysis or GEE will be used, depending on the normality of the data.

Significance level will be set at 0.95 in order to determine significant differences between variables. Therefore, p-values less than 0.05 are considered statistically significant. SPSS 23.0 statistical software will be used for data analysis.

Discussion

The expected result is to prevent the occurrence of stomatitis or reduce the percentage of its occurrence through an intervention based on *Cordia myxa* mouthwash, as a complementary treatment approach. The *Cordia myxa* mouthwash is safe, easy to use, and does not interfere with other treatments or interventions. Therefore, it can be easily used in the routine nursing care of patients undergoing chemotherapy in hospital or at home. Using this mouthwash can reduce the costs of treating oral stomatitis. However, little is known about its effects and cost-effectiveness. In addition, this treatment is not supported by the Ministry of Health and Medical Education of Iran. This study will expand our knowledge about the usefulness of the *Cordia myxa* mouthwash and provides evidence for its use against stomatitis, which will have very important implications for public policy makers as well as oncologists.

The results of Ebrahimi Hemmati Keikha et al. showed that the mucilage of *Cordia myxa* could prevent the growth of 8 strains of Gram-negative and Gram-positive pathogenic bacteria in laboratory conditions to a large extent [22]. Nariya et al. (2011) also investigated and studied the antibacterial and antifungal effect of the bark of a species of the *Cordia myxa* tree. Their results showed that the bark of this species has antifungal and antibacterial activity [23].

Declarations

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Authors' contributions

MJ, SM, BS, AS,AAD, MSK, SAM: investigation, wrote the manuscript, and writing—review and editing. MJ, SM, BS, AS,AAD: conceptualization methodology and writing—review and editing. MJ, SM, BS, AS,AAD, MSK, SAM: writing—review and editing.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

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. Written informed consents will also obtain from the participants. 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).

Consent to publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest about this working.

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