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Efficacy of Aloe Vera in Prevention and Treatment of Chemotherapy-Induced Oral Mucositis in A group of Egyptian Children with Acute Leukemia: A Randomized controlled trial

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Aim: The aim of the study was to evaluate the efficacy of Aloe Vera (AV) in prevention and treatment of chemotherapy-induced oral mucositis(CIOM) in a group of Egyptian children suffering from acute leukemia in terms of appearance and severity.

Materials and Methods: A randomized controlled trial (RCT) was conducted over a period of 2 months at Nasser Institute Hospital for Research and Treatment (NIH). The study included 40 patients undergoing treatment for acute lymphoblastic leukemia (ALL). They were assigned into two groups; in the intervention group (20 patients) applied 70% AV gel topically three times daily, starting three days before chemotherapy and over a period of two months. While, the control group did not receive this treatment; instead, they used routine mouthwashes prescribed by their physicians, including chlorhexidine or nystatin.

Results: At baseline, all the cases in both groups were free from oral mucositis (OM) .After 2 months, a significantly higher percentage of cases in the control group (85%) were affected in comparison to the study group (15%) ($p<0.001$). For the study group, the mean onset was 19 days , while for the control group, the mean was 13 days. All cases with OM in study group presented with lower grades of severity than the control group.

Conclusion: AV had a significant effect in preventing CIOM and notably reduces both the duration and severity of symptoms compared to the control group. These findings suggest that AV gel could be a valuable therapeutic option for managing CIOM

Keywords: Aloe Vera, Oral Mucositis, Acute Lymphoblastic Leukemia, Acute leukemia.

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Introduction

Acute leukemia is the most common childhood cancer, comprising 25% of all cancers in individuals under 20 years, with ALL accounting for about 75% of cases. ALL affects the bone marrow, leading to an overproduction of immature lymphocytes, particularly prevalent between ages of 2 and 6 years.[1] The annual incidence reported by the National Cancer Institute, Cairo University, Egypt is approximately four cases per 100,000 children per year.[2] A significant adverse effect of cancer treatments (chemo and radio) therapy is OM, which presents as painful erythema and ulcerations in the oral mucosa. OM impacts essential functions like chewing and swallowing, affecting patients' quality of life.[3] It arises from complex biological interactions, with 40-76% of patients undergoing treatment likely to experience this condition.[4]

The United States Food and Drug Administration (US-FDA) has not approved a single agent for treating OM. The reduction of symptoms and the prevention of OM complications, including dietary support, pain control, prophylaxis and/or secondary infection care, are considered the key corner stone of OM management.[5]

Many interventions have been proposed for managing OM ; however, none of the current therapeutic options can completely prevent or cure it , highlighting the ongoing need for safe and effective treatments.[6] Recent clinical practice guidelines have reviewed the use of antimicrobial agents (chlorhexidine), anti-inflammatory agents (benzydamine), cytoprotective agents (glutamine), biological response modifiers (palifermin), physical therapies (cry therapy and laser), anesthetics, and analgesics (management of pain)., and natural compounds.[7,8] Despite these therapeutic options, there is a notable lack of scientific evidence regarding their effectiveness and side effects in pediatric patients.9 Children are particularly vulnerable to OM, and not all treatments may be appropriate for this demographic.[9]

Currently, herbal products are being widely researched and used with therapeutic purposes because they are considered more economical, relatively safe, and generally have low toxicity.[10] However the effectiveness and safety of these herbal medicines still need to be scientifically proven.[11]

Among these herbal products is AV which became one of the alternative therapies that can be used to treat various conditions due to its anti-inflammatory, antioxidant, antibacterial, antifungal, and other beneficial properties.[12] AV is indeed recognized for its ability to support the healing process, particularly in conditions like ulceration or wounds.[13] The specific use of AV in treating oral mucosa issues, especially those caused by Candida albicans or Herpes simplex virus type 1, is of particular interest. Its antimicrobial properties can help reduce secondary infections that commonly occur alongside oral inflammation. AV also has a role in treating local inflammation, potentially easing discomfort from ulcers or sores in the mouth, speeding up recovery, and preventing further infections.[12,13]

Although AV shows potential, there have been only a handful of studies investigating its effectiveness in treating chemotherapy-induced oral mucositis. The current study threw the light on the efficacy of AV gel in prevention and treatment of CIOM in a group of Egyptian children suffering from acute leukemia in terms of appearance and severity. A null hypothesis was tested where there is no difference between AV and control groups of CIOM in terms of appearance and severity.

Subjects And Methods

Study design and clinical considerations

This study was designed as parallel arm randomized controlled trial with 1: 1 allocation ratio. The was registered at Clinical Trial.gov in January 2025 with a registration number (NCT06757270) and reporting followed the Consolidated Standards of Reporting Trials (CONSORT)[14](Figure 1). Fourty Egyptian children were recruited from the pediatric oncology department at NIH for Research and Treatment from march 2023 to march 2024. The trial was conducted over a period of 2 months .They undergoing treatment for ALL. Patients were randomized into two groups: the study group, patients applied 70%AV gel topically three times daily, starting three days before chemotherapy and over a period of two months. The control group did not receive such treatment; instead, they used routine mouthwashes prescribed by their physicians, including chlorhexidine or oracure gel when OM appeared. Randomization was performed using the computer software (research randomizer program: *https://www.randomizer.org*).It was an open-label trial where no blinding was used.

Sample size calculation:

A power analysis was designed to have adequate power to apply a two-sided statistical test of the null hypothesis that there is no difference between both groups. By adopting an alpha (α) level of 0.05 (5%), a beta (β) level of 0.20 (20%) i.e. power=80%, and an effect size of (0.931) calculated based on the results of a previous study; the predicted sample size (n) was found to be a total of (40) cases. Sample size calculation was performed using G*Power version 3.1.9.4.[15,16]

Ethical Regulations :

The study protocol was approved by the Research Ethics Committee, Faculty of Dentistry, Ain Shams University (FDASU-REC) in feb. 2021 (EecIM 022203).

Parents of eligible children were informed, in full details, about the purpose of the study and any possible side effects. Prior to enrollment of children in the study, parents were asked to sign a written informed consent in simple Arabic language which was approved by the FDASUREC.

The informed consent included information about the risks and benefits of AV. The form explicitly indicated that whenever AV used, it can prevent the appearance of CIOM or delay it. Care givers were informed that they had the right to withdraw at any point during treatment without any penalty or loss of any benefits before starting the trial. They were also notified that the privacy of participants and the confidentiality of the collected data will be maintained at each stage of the research from recruitment to follow up. To achieve that, all information pertinent to each participant was entered into the database with a numerical code.

Eligible children were informed about the nature of the study using age appropriate language and those who were 7 years or older were asked to give an assent to participate in the trial.[17,18] The assent form was written in Arabic language using simplified phrases to clarify key steps and was also approved by the Ethical Committee.

Eligibility criteria for study participants:

1-Inclusion Criteria:

- Patients suffering from ALL.
- Patients scheduled for chemotherapy treatment.
- Patients who range from 3 to 13 years old.
- Both genders.
- Patients with no previous history of any chemotherapy or radiotherapy treatment.

Exclusion Criteria

- Patients scheduled for radiotherapy treatment.
- Existence of any signs or symptoms of OM
- Unwilling to participation in the study.
- Patients with any other systemic diseases or other neoplasms.

Study groups:

- The study included two arms:

Study arm (Group I): (n=20) Intervention group, patients used 70% AV gel.(Preventive protocol)[15]; patients began the study phase on the 3rd day before the chemotherapy by topically applying the preventive agent 3times/d/8h.

Children were instructed not to drink, eat, or gargle for 30 minutes after each application of gel to allow the agent to be kept in adherence with the oral mucosa as long as possible.

Control arm (Group II): (n=20) control group with no intervention. On the other hand, routine mouthwashes, including cholorhexidine, and nystatine were used according to the physician's prescription.

Gel Preparation:

The preparation was carried out at the Nawah Scientific Lab. The provided AV leaves were washed and cut from the bottom, and then stood upright for 10 minutes to clear the yellow plant latex. Furthermore, the other thin tip was cut and discarded, and the rest of the leaf was cut horizontally into multiple small pieces facilitating the removal of the top part of each piece, and then the gel was withdrawn with a smooth knife. Finally, the colorless gel was extracted and homogenized at 8000 rpm and then filtered in order to remove the fibers. The resulting solution was stored at -80 0C until gel preparation.The gel consists of 2.5% Hydroxyethyl cellulose (HEC) (w/w), 0.1% potassium sorbate (w/w), 0.01% sodium meta-bisulfite (w/w), 0.1% sucralose (w/w), 5% sorbitol (w/w), 70% AV gel (w/w) was stirred until homogenous then the weight completed to 400 g with water. The gel was sterilized using UV before packing in Esco - LVG-4AG-F8.

Application of AV gel

Children in the study group together with their caregivers received a demonstration on how to apply the gel to specific areas of the mouth, including lips, the lateral borders of the tongue, floor of the mouth, buccal and labial mucosa, and palate in order to cover oral mucosa that may be affected through the chemotherapy.[8] The caregiver was instructed to apply the gel for their children in front of the investigator for the first application; the rest of applications were carried out by the parents or caregivers themselves. Sponge sticks made by the investigator were used to apply the AV agent topically. The researcher provided parents with appropriate training on how to apply the gel to all targeted oral surfaces. Oral hygiene instructions were given to all children either in study group or control group. They were instructed to brush teeth 3times/day, under parents/caregivers supervision. Parents whose children were unable to use toothbrush and tooth paste, were instructed to use gauze to clean the child's mouth 3 times/day.

Follow up and Assessment

All participants were evaluated daily by the investigator throughout the 2 months of the study . The assessment of oral mucosa was done using torch as a light source and tongue depressors in order to evaluate OM (Figure 1) regarding their presence and grading following World Health Organization (WHO) grading scale.[19]

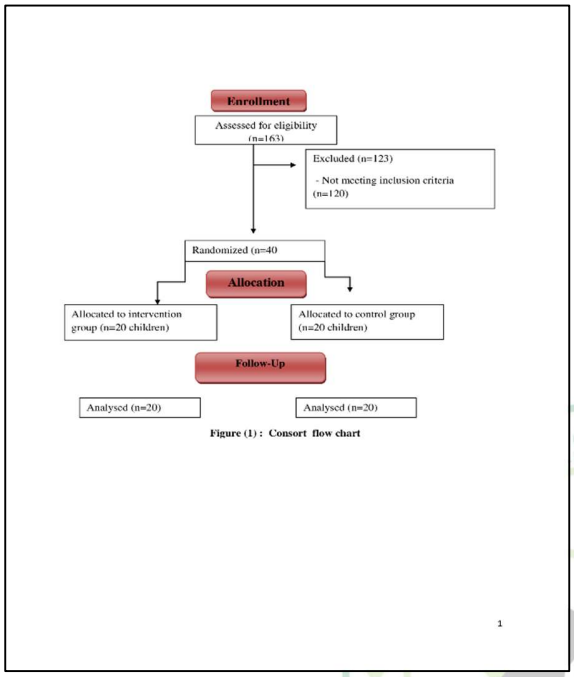

Figure (1) : Consort flow chart

0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life threatening)	Ulcers ,Oral alimentation impossible

Statistical analysis :

Categorical data were analyzed using McNemar's and chi-square tests for inter and intragroup comparisons respectively. Numerical data were presented as mean with 95% confidence intervals (CI), standard deviation (SD), median, minimum (min.) and maximum (max.) values. They were examined for normality by viewing distribution and using Shapiro-Wilk's test. Age data were found to be normally distributed and were analyzed using independent t-test. The significance level was set at $p<0.05$ within all tests. Statistical analysis was performed with R statistical analysis software version 4.4.1 for Windows.[20]

Results:

Demographic data:

1- The study was conducted on 40 equally and randomly allocated cases to each studied group. In both groups, there were 15 males and 5 females. The mean age of children in the study group was (8.18±4.13) years; in the control group, it was (8.75±2.45) years. There was no statistical significant difference between groups regarding gender (p=1) and age (p=0.595).

Mucositis incidence:

Intergroup comparison:

At baseline, all the cases in both groups were free. After 2 months, a significantly higher percentage of OM in the control group (85%) compared to the study group (15%) ($p<0.001$).

Mucositis onset:

Descriptive statistics for mucositis onset are presented in table (1) , which revealed that the onset of mucositis was delayed in cases of the study group .

Table (1): Descriptive statistics for mucositis onset among study groups .

Group	Mean ±SD	SD	Median	Min.	Max.	95% CI	
						Lower	Upper
Study (days)	19.00 ±5.29	5.29	21.00	13.00	23.00	13.01	24.99
Control (days)	13.65 ±3.32	3.32	14.00	8.00	20.00	12.07	15.22

Mucositis duration:

In the study group, There were 2 cases presented with a duration range between (1 to 5 days) and one case where the duration was 6 days.While in the control group, there were 13 cases where the duration range to above 5 days and 4 cases the duration range from (1 to 5days).

Mucositis grade:

All cases with OM in study group presented lower grades of severity than the control group. (Figure 2,3)

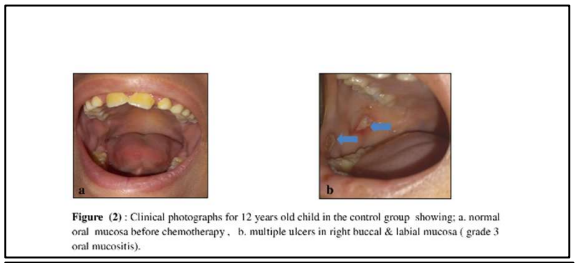

Figure (2) : Clinical photographs for 12 years old child in the control group showing; a. normal oral mucosa before chemotherapy , b. multiple ulcers in right buccal & labial mucosa (grade 3 oral mucositis).

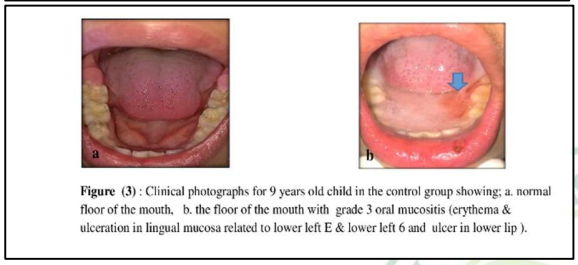

Figure (3) : Clinical photographs for 9 years old child in the control group showing; a. normal floor of the mouth, b. the floor of the mouth with grade 3 oral mucositis (erythema & ulceration in lingual mucosa related to lower left E & lower left 6 and ulcer in lower lip).

Descriptive statistics for mucositis grade are presented in table (2).

Table (2): Descriptive statistics for mucositis grade among study groups.

Mucositis grade	No. (%)	
	Study	Control
1	1 (33.33%)	2 (11.76%)
2	2 (66.67%)	10 (58.82%)
3	0 (0.00%)	5 (29.41%)

Discussion

ALL is the most common cancer in children, and one of the most frequent side effects of its chemotherapeutic treatment is mucositis which occurs in about 40% of patients overall. It results from the systemic effects of chemotherapeutic drugs. It ranges from erythematic to severe ulceration. Symptoms of OM vary from pain and discomfort to inability to tolerate food or fluids. It may also limit the patient's competence to accept (chemo or radio) therapy.[21]

Considering the complexity of CIOM pathogenesis, it is not surprising that there is no single way effective for its prevention. Interventions that point to only one definite step of the pathological mechanism of CIOM cannot prevent it from vigorous occurrence.[22]

In our study, we evaluated the efficacy of AV in prevention and treatment of CIOM in children suffering from ALL. ALL was chosen because it is the most common type of cancer found in children, significantly impacting their lives and families. According to the American Cancer Society, leukemia accounts for about 28% of all cancers in children under 15, making it a critical area of research and awareness.

The current study was conducted prospectively on 40 patients receiving treatment for ALL at NIH for research and treatment. The age of the children included in the study was between 3 years to 13 years. Children who were below 3 years were excluded to standardize the protocol of treatment for all patients and the patients below 3years old receive a different protocol than older patients. The study included children aged from 3 to 13 to achieve the required sample size .All children were free of any signs or symptoms of OM at the start point to be able to effectively evaluate the efficacy of AV for preventing and treating CIOM compared to the control group with no intervention.

In an attempt to find an effective preventive agent and treatment with a relatively innocuous agent for CIOM, we decided to study the use of AV gel. This decision was based on a fact that there is a growing interest in the therapeutic benefits of herbal medicine on cancer therapy-induced oral mucositis due to their reduced side effects, cost, and better availability compared to synthetic drugs .Herbal agents exert their effects via several mechanisms of action consisting of analgesic, antioxidant, antifungal, anti-inflammatory, antiseptic, and anti carcinogenic activities. [23]

Aloe vera (AV)-based preparations contain various active compounds, including folic acid, iron, vitamins and electrolytes , that have positive effects on general health.[24] Its formula shows moisturizing, emollient, anti-inflammatory, and immune-modulatory properties.[25] It has been studied for the

prevention and treatment of many mucocutaneous conditions, without any adverse effects . [26]

AV consists of more than 75 active components such as, such as anthraquinones (e.g., emodin and aloin), polysaccharides (e.g., lignins), mucopolysaccharides, glycosaminoglycans (e.g., hyaluronic acid, acemannan, and heparin), minerals, vitamins, and enzymes.[27]

Anthraquinones[28] were proved to have antioxidant and anti-inflammatory properties. They can potentially help reduce inflammation and oxidative stress that contribute to mucositis. Polysaccharides[29] are known for their immune-boosting properties and may support tissue repair, increase absorption, and stimulate collagen production, helping to prevent or reduce the severity of mucositis. Hyaluronic acid, acemannan and heparin are the main mucopolysaccharides[30]found in AV. Acemannan activates macrophages to bind and destroy microorganisms. Nevertheless, hyaluronic acid plays an important role in collagen synthesis and fibroblast activity.[31]Mucopolysaccharides,glycosamino glycans[32] activate mucosa protective barrier, reduce irritation and allergies, and prevent cellulites. They also moisturize and prevent xerostomia, a predisposing factor for CIOM.

In the current study, AV in the form of gel was chosen. Mucoadhesive gel preparations are generally more effective for oral mucosal ulceration lesion therapy .[33]The use of mouthwash preparations for OM therapy will be more effective to cover a large area of lesions [34],while the gel will be more effective because it can be directly and easily applied on localized lesions .[35]

AV gel was manufactured by Nawah Scientific Lab. This gel was composed of various components; 2.5% Hydroxyethyl cellulose 0.1% potassium sorbate, 0.01% sodium meta-bisulfite, 0.1% sucralose, 5% sorbitol and 70% AV gel.

Sponge sticks were made by the investigator and were used to facilitate application of AV gel and ensure gentleness on the oral mucosa when mucositis appeared, as the aim was to reduce discomfort and promote healing. No specific type of toothpaste was recommended for patients, as the goal was simply to maintain oral hygiene.

Children began the study phase on the 3rd day before the chemotherapy to assess the role of AV in prevention of CIOM. The goal of prevention could be achieved either by decreasing the grade of mucositis, delaying its onset, or preventing its appearance. The AV was topically applied 3 times daily every 8 hours. Children were instructed not to drink, eat, or gargle for 30 minutes after each application of gel to allow the agent to be kept in adherence with the oral tissues as long as possible.

The proper assessment of the oral mucosa is of great importance before initiating chemotherapy and throughout the treatment course. In our study we used the WHO Grading scale on the basis of its simplicity, validity and having both the subjective and objective data combined. The WHO mucositis scale is a standardized grading system; it was used to assess the severity of OM. It was developed as part of the WHO handbook in 1979 to help clinicians standardize reporting and track outcomes related to cancer treatment. The scale was used to determine the level of mucositis based on clinical observations and the patient's ability to tolerate solid and liquid foods.[53]

According to the interpretation of the current study findings, there was a significantly higher percentage of cases in the control group (85%) compared to the study group (15%) ($p<0.001$) after 2 months. The study demonstrated that 70% AV gel prevented the occurrence of 85% of OM in the study group (table 4) and reduced the severity in the remaining 15% of cases. And the results in (table 7) showed a decrease in

the duration of OM, with a maximum duration of 10 days observed in the control group compared to 7 days in the study group.

These results were in agreement with a study conducted by Alkhouli et al. 2021, who found that AV 70% solution was better at lowering the severity of OM compared to the sodium bicarbonate group in the 2nd, 3rd, 4th, and 7th weeks.[36]

The results of the current study were also consistent with a clinical trial conducted by Mansouri et al. 2016, which showed that AV solution is effective in decreasing stomatitis intensity and pain when used topically in lymphoma and leukemia patients while our results clarified that it can prevent OM in addition to lowering duration and severity of it. This may be justified that it was used in gel form that kept in adherence of the oral mucosa for longer time.[37]

A study by Vogel et al. 2018, in agreement with us demonstrated that patients who used AV gel experienced a significant reduction in the incidence (prevention) and severity of OM compared to those receiving standard care.[38]

In contrast, Su et al. 2004, showed that the use of AV at the start of radiotherapy did not improve either mucositis or the quality of life of the patients compared to a placebo. This could be attributed to the fact that radiation-induced mucositis is characterized by the exposure of basement membrane after the erosion of the mucosal layer. Healing this type of injury may rely on regeneration and repopulation of basement membrane collagens rather than inhibiting the mediators of inflammation. This may explain why AV, did not make a notable difference.[39]

The current study was the first study that threw the light on the efficacy of AV in prevention and treatment of CIOM in a group of Egyptian children suffering from ALL; however one significant limitation was the small sample size, which may restrict the generalizability of our findings. While the results are promising, a larger sample would enhance the statistical power and provide more robust evidence regarding the effectiveness of AV gel in preventing and treating OM.

Conclusion

Within the limitations of the current study the following conclusions could be drawn:

1. Topical application of 70% AV in the form of gel can significantly prevent the appearance of oral mucositis.
2. AV can significantly decrease the duration and severity of oral mucositis .

Therefore, AV gel application before chemotherapy could be a promising and valuable choice for the prevention and treatment of CIOM.

Conflict of Interest

The authors that they have no affiliations with or involvement in any organization or entity with any financial or non financial interest in the subject matter discussed in the manuscript

Availability of data and materials

All data generated or analyzed during this study are included in this published article .

Ethics approval

Ethical approval was granted from the research ethical committee at faculty of Dentistry, Ain shams university (FDASU-REC) in feb. 2021 (EecIM 022203. informed consent was taken from participants .

Competing interests

The authors declare that they have no competing interests.

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