

Investigating the effect of Aloe vera on the prevention and treatment of radiotherapy-induced oral mucositis in patients with head-and-neck cancer

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Background: Oral mucositis is one of the main complications of radiotherapy (RT) while treating head-and-neck cancers and can affect the patients' treatment process and life. Therefore, this study evaluated the effect of Aloe vera on the prevention and treatment of radiotherapy-induced oral mucositis (RIOM) in patients with head-and-neck cancer. **Materials and Methods:** This was a double-blind clinical trial performed in 2019 on 75 patients with head-and-neck cancer. Patients were randomly assigned to two groups receiving gargles of 5 cc Aloe vera and the same dose of placebo mouthwash three times a day, respectively. Then, the incidence and severity of RIOM were evaluated and compared between the two groups over 6 weeks of RT. **Results:** There was no significant difference between the two groups in terms of the severity of RIOM from the 1st to 3rd weeks of RT ($P > 0.05$). However, the severity of RIOM in the 4th, 5th, and 6th weeks of RT was significantly lower in the Aloe vera group compared with the placebo group ($P < 0.05$). **Conclusion:** According to the results of the present study, the long-term use of Aloe vera mouthwash can reduce the severity of RIOM.

Key words: Aloe vera, head-and-neck cancer, oral mucositis, radiotherapy

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INTRODUCTION

Nowadays, cancer has been recognized as one of the most significant problems in the medical field. Changes in lifestyle and dietary habits as well as a decrease in physical activity are among the factors increasing the rate of cancer over recent decades^[1] such that the number of new cases was expected to increase to 17 million in 2020.^[2] In this regard, various treatment methods, including chemotherapy and radiotherapy (RT) as common and effective ones,^[3] have been proposed for controlling and treating cancers.

RT alone or combined with chemotherapy causes the destruction of cancer cells by the mechanism of

interfering with cell division and reducing the half-life of cells.^[4] However, RT can lead to the inflammation of the oral mucositis.^[3,5] Accordingly, the incidence of radiotherapy-induced oral mucositis (RIOM) has been reported to be about 30%–60%, while the incidence of oral mucositis in chemotherapy and RT is 40%–75% and 90%, respectively.^[6,7] This complication can manifest as painful lesions with swallowing disorder and can lead to the termination of RT due to the severity of these lesions.^[3,5,8] Regarding the treatment, pain reduction, or prevention of this complication, numerous studies have been conducted and reported the effect of supportive care, the effect of medicines such as steroidal and nonsteroidal anti-inflammatories, local anesthetics, food supplements, antibiotics (polymyxin, tobramycin, and

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amphotericin), cryotherapy, granulocyte colony-stimulating factor, intravenous glutamine supplementation, keratinocyte growth factor, laser, and benzydamine mouthwash,^[9-15] or the effect of herbal and traditional treatments such as baking soda, thyme, curcumin, cloves, beeswax, Aloe vera, and other plants on the pain reduction and severity of oral mucositis.^[16-22] However, no definitive and accepted prevention or treatment methods have been reported for this type of mucositis.

Aloe vera is one of the medicinal plants that has attracted the attention of researchers in recent years. Aloe vera gel originates from its central cells and plays an important role in healing skin diseases and lesions.^[23] Thus far, the effect of this substance has been reported on skin diseases such as psoriasis and lichen planus due to its anti-inflammatory properties.^[24] Furthermore, this substance has proved to be useful for healing head-and-neck radiotherapy-induced lesions and mucositis,^[11,25] while some other studies have reported its insignificant effect on reducing and improving RIOM.^[26,27]

It seems that the restorative and anti-inflammatory properties of Aloe vera can play a crucial role in the prevention and treatment of mucositis. Therefore, this study aimed at investigating the effect of Aloe vera on the prevention and treatment of RIOM in head-and-neck cancer considering the uncertainty in research findings and the nonevaluation of the Iranian race and native Iranian Aloe vera.

MATERIALS AND METHODS

This double-blinded clinical trial was conducted in 2019 in Seyed al-Shohada affiliated to Isfahan University of Medical Sciences, after approval of the Research Committee of Isfahan University of Medical Sciences, signing the written informed consent for entering the study by patients, and the confirmation of the Ethics committee (Ethics code: IR.MUI.MED.REC.1399.973, Iranian Registry of Clinical Trials [IRCT] code: IRCT20201203049585N1).

The study population included all patients with head-and-neck cancer with an indication for head-and-neck RT with a dose of at least 50 Gy with a standard daily dose administered to the oral mucosa and oropharynx.

Based on the sample size formula, at the confidence level of 95%, the test power of 80%, and considering the standardized effect size related to the mucositis score between the two Aloe vera and placebo groups from previous studies^[28] equal to 0.7 and the same size in both groups, the number of 40 patients in each group was determined.

The inclusion criteria for the study comprised patients with head-and-neck cancer, an indication for head-and-neck RT, the age of at least 18 years, no history of previous RT, no previous RT- and chemotherapy-induced mucositis, no evidence of distant metastasis, the Karnofsky Performance Status score ≥ 70 , no chronic use of nonsteroidal anti-inflammatory drugs, steroid, or other analgesics, lack of pregnancy, RT dose of at least 50 Gy, and satisfaction to participate in the study. In addition, the patients were excluded from the study in case of unwillingness to cooperate, death, or incidence of serious complications during the treatment.

Eighty patients were included in the study using the nonprobability sampling method and were divided into two groups by random allocation software. At the beginning of the study, the patients' basic and clinical information such as age, sex, tumor location, disease stage, smoking, history of surgery, chemotherapy, and RT dose and fraction were recorded.

It should be noted that all patients underwent 3D conformal treatment as well as nutritional and dental evaluations before the treatment.

The patients were advised to gargle 5 cc of the received solution for 2 min three times a day from the start till the end of the RT treatment, which took an average of 6 weeks for each patient. On the 1st day of the treatment, each patient was instructed on how to use the mouthwash. Every 2 weeks, an empty bottle of mouthwash was replaced by a new one, according to the suggested dosage.

To comply with the conditions of blinding, two solutions containing Aloe vera and placebo with an identical bottle, volume, and color were prepared by a single pharmacist (at the Faculty of Pharmacy of Isfahan University of Medical Sciences) and labeled A and B before the start of the intervention. In this way, the patient and the interventionist had no knowledge of the type of intervention in each group.

The Aloe vera solution contained pure Aloe vera gel plus 0.2% methylparaben and 0.02% propylparaben as preservatives. The placebo solution was similar to the Aloe vera solution in terms of taste, fluidity, and ingredients, and only ordinary water was used instead of the Aloe vera extract.

In both groups, the treatment including diphenhydramine, antacid, and nystatin was prescribed after the occurrence of second- or higher-grade mucositis.

The study subjects were visited and examined weekly. The severity of mucositis was determined and recorded based on the Radiation Therapy Oncology Group criteria including grades 0–4 [Table 1].^[29]

Finally, the collected data were entered into the Statistical Package for Social Sciences (SPSS) (version 22; SPSS Inc., Chicago, IL, USA) software (version 26). The data were presented as means ± standard deviation, median (minimum–maximum), or frequency (percentage). Independent *t*- and Mann–Whitney *U*-tests were used to compare the mean or median of quantitative variables between two groups. Friedman’s test was used to compare the median changes of mucositis grade overtime during the intervention in each of the two groups. Furthermore, to compare the frequency distribution of qualitative variables between the two groups, the Chi-square test was used. The level of <0.05 was considered significant in all analyses.

RESULTS

In this study, out of 40 patients in the Aloe vera group, two cases due to noncompliance with the correct use of mouthwash and one case due to nonreferral in subsequent follow-ups were excluded. Out of 40 patients in the placebo group, one case due to noncompliance with the correct use of mouthwash and one case due to nonreferral in subsequent follow-ups were excluded. Therefore, two groups of Aloe vera and placebo groups were analyzed with 37 and 38 patients, respectively [Figure 1].

There were no significant differences between the two groups in terms of age, sex, smoking, previous surgery, tumor location, cancer grade, chemotherapy, RT dose, and chemotherapy fraction ($P > 0.05$) [Table 2].

The evaluation of RIOM revealed that there was no significant difference between the two groups from the 1st to 3rd weeks of RT in terms of the severity of mucositis ($P > 0.05$). However, in the 4th, 5th, and 6th weeks of RT, the severity of mucositis in the Aloe vera group was significantly lower than its severity in the placebo group ($P < 0.05$) [Table 3 and Figure 2].

It should be noted that in none of the two groups, RIOM grade was not significantly different between patients with and without chemotherapy ($P > 0.05$) [Table 4].

In addition, the third-grade RIOM in the 4th, 5th, and 6th weeks with values of 0%, 5.4%, and 5.4%, respectively, was significantly lower in the Aloe vera group compared with the placebo group with values of 23.7%, 26.3%, and 28.9%, respectively [Figure 3].

DISCUSSION

The results of the present study revealed that the use of Aloe vera mouthwash in the first 3 weeks of treatment did not have a significant effect on the reduction of the incidence or severity of RIOM in patients with head-and-neck

cancer. However, the intensity of RIOM in the Aloe vera group was significantly lower than that of the placebo group in the second 3 weeks of treatment. The frequency of third-grade RIOM in the 4th, 5th, and 6th weeks was significantly lower in the Aloe Vera group compared with the placebo group.

In this regard, the results of Kazemian *et al.*'s study showed that in both benzydamine and placebo groups, the intensity

Table 1: Severity of mucositis based on the radiation therapy oncology group

Grade	Severity of mucositis
Grade 0	Unchanged mucus
Grade 1	Simple inflammation of the mucosa, sometimes with brief pain that did not require painkillers
Grade 2	Punctate mucositis with probable serous secretions accompanied by a simple inflammation and mild pain that required painkillers
Grade 3	Continuous and diffuse mucositis with fibrin secretions accompanied by severe pain that required painkillers
Grade 4	Wound and bleeding or necrosis

Table 2: Patient’s demographic and clinical characteristics in the two groups

Characteristics	Aloe vera (n=37), n (%)	Placebo (n=38), n (%)	P
Sex			
Male	22 (59.5)	28 (73.7)	0.226
Female	15 (40.5)	10 (26.3)	
Age (year)			
<50	17 (45.9)	17 (44.7)	0.916
≥50	20 (54.1)	21 (55.3)	
Smoking	10 (27.0)	8 (21.1)	0.369
Tumor location			
Tongue	10 (27.0)	4 (10.5)	0.443
Larynx	14 (37.8)	13 (34.2)	
Nasopharynx	5 (13.5)	8 (21.1)	
Parotid	1 (2.7)	4 (10.5)	
Mandible	1 (2.7)	2 (5.3)	
Hypopharynx	1 (2.7)	2 (5.3)	
Maxilla	0	1 (2.6)	
Other	5 (13.5)	4 (10.5)	
T-classification			
T1	9 (24.3)	7 (18.4)	0.580
T2	13 (35.1)	10 (26.3)	
T3	12 (32.4)	15 (39.5)	
T4	3 (8.1)	6 (15.8)	
N-classification			
0	21 (56.8)	27 (71.1)	0.344
1	8 (21.6)	4 (10.5)	
2	8 (21.6)	7 (18.4)	
Previous surgery	6 (16.2)	12 (31.6)	0.112
Chemotherapy	30 (81.1)	18 (47.4)	0.068
Dose of RT (Gy)	65.24±4.59	63.29±5.07	0.085
Fraction	31.59±1.44	31.19±2.45	0.396

RT= Radiation therapy

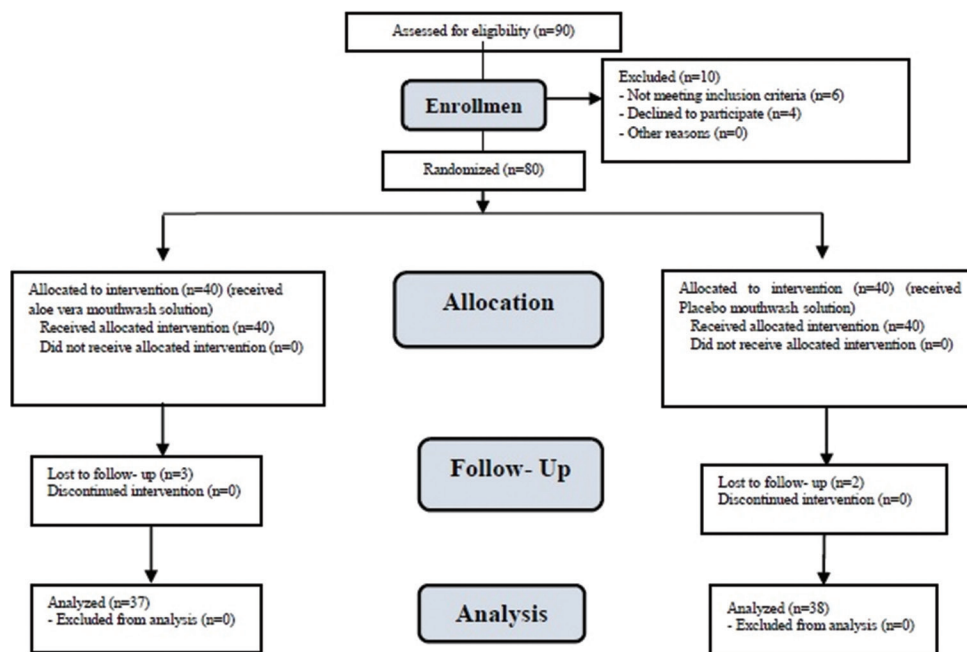


Figure 1: Consort flowchart of patients

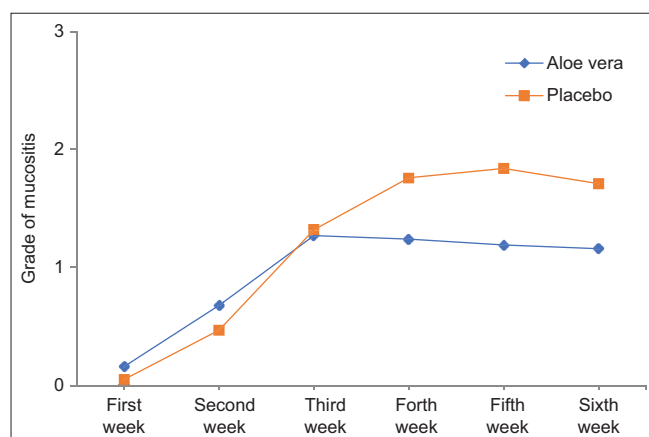


Figure 2: The mean of radiotherapy-induced oral mucositis between the two groups in the studied follow-ups

of mucositis increased to grade 2 up to the 4th week of treatment. In the benzydamine group, the grade of mucositis was without change to the end of therapy; however, in the placebo group, it raised to grade 3 ($P < 0.001$). The median interval to observation of grade ≥ 2 mucositis was 24 days in the placebo group and 28 days in the benzydamine group ($P = 0.12$). They said that benzydamine oral rinse can be effective, safe, and well tolerated for prophylactic treatment of radiation-induced oral mucositis in head-and-neck tumors.^[10]

Sahebamee *et al.*'s study showed that the average interval between the start of RT till the incidence of the maximum grade of mucositis severity and the decrease in its severity over time was not significantly different between the Aloe vera and benzydamine groups. Indeed, they stated

Table 3: Comparison of radiotherapy-induced oral mucositis grade between the two groups up to 6 weeks

RIOM	Aloe vera (n=37)	Placebo (n=38)	P ^a
1 st week	0 (0-2)	0 (0-1)	0.224
2 nd week	0 (0-3)	0 (0-2)	0.261
3 rd week	1 (0-2)	1 (0-2)	0.784
4 th week	1 (0-2)	2 (0-3)	0.004
5 th week	1 (0-3)	2 (0-3)	0.003
6 th week	1 (0-3)	2 (0-3)	0.018
P ^b	<0.001	<0.001	

^aThe significance level obtained from the Mann-Whitney *U*-test to compare the median of mucositis grade between two groups in each of the follow-up times, ^bThe significance level obtained from Friedman's test to compare the change trend of mucositis grade overtime during the intervention in each of the two groups. Data are shown as median (minimum-maximum). RIOM=Radiotherapy-induced oral mucositis

that Aloe vera could have the same effect without any complications as that of the routine treatments (the use of benzydamine) on postponing the incidence of RIOM or reducing its severity.^[11] Although our study did not evaluate the delay in the incidence of this complication, the long-term effectiveness of this plant was examined in both studies. Aloe vera has 75 key active constituents, including polysaccharides, saponins, minerals, vitamins, and lignin, and enjoys miscellaneous biological effects such as anti-tumor, anti-inflammatory, wound healing, and antimicrobial activity.^[30-32]

Numerous studies have examined the possible role of Aloe vera in the treatment of a good number of diseases such as lichen planus,^[32,33] radiation-induced dermatitis,^[34] psoriasis,^[35] HIV infection,^[36] aphthous stomatitis,^[37] and skin burns.^[38] Some studies have evaluated the effectiveness of Aloe vera gel in the treatment of oral lichen planus and

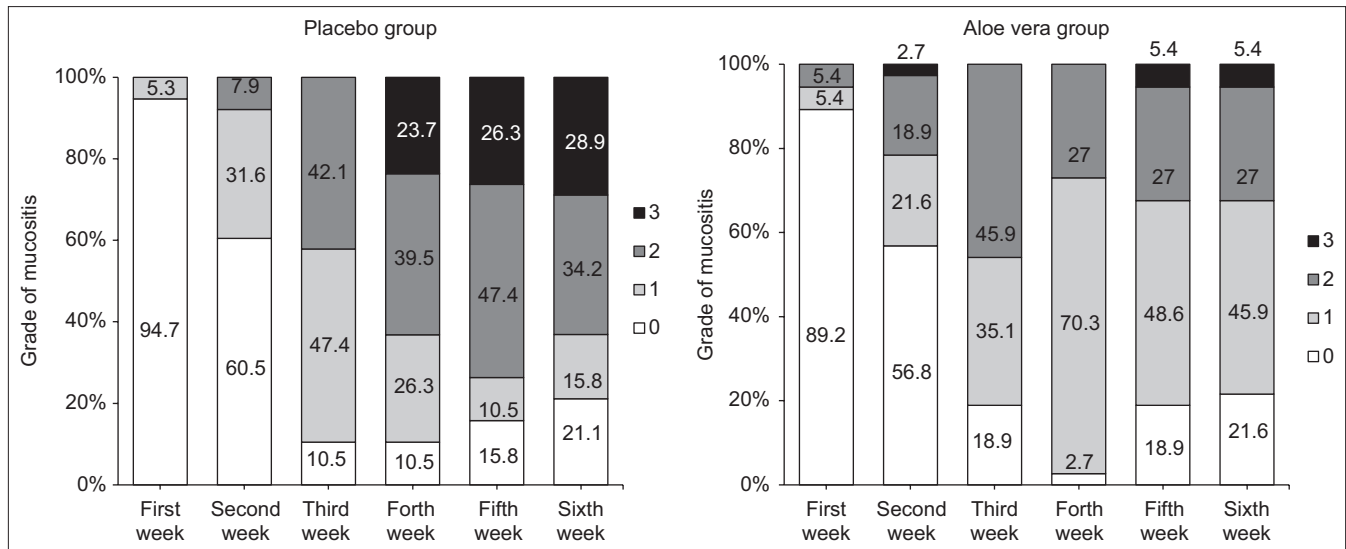


Figure 3: Frequency distribution of radiotherapy-induced oral mucositis grade between two groups in the studied follow-ups

Table 4: Comparison of radiotherapy-induced oral mucositis grade between two with and without chemotherapy in each group up to 6 weeks

RIOM	With chemotherapy	Without chemotherapy	P
1 st week			
Aloe vera (n=37)	0 (0-1)	0 (0-2)	0.064
Placebo (n=38)	0 (0-1)	0	0.133
2 nd week			
Aloe vera (n=37)	0 (0-3)	1 (0-2)	0.554
Placebo (n=38)	0.5 (0-2)	0	0.219
3 rd week			
Aloe vera (n=37)	1.5 (0-2)	1 (0-2)	0.116
Placebo (n=38)	1 (0-2)	2 (0-2)	0.191
4 th week			
Aloe vera (n=37)	1 (1-2)	0 (0-2)	0.275
Placebo (n=38)	2 (0-3)	2 (0-3)	0.352
5 th week			
Aloe vera (n=37)	1 (0-2)	2 (0-3)	0.16
Placebo (n=38)	2 (0-3)	2 (0-3)	0.181
6 th week			
Aloe vera (n=37)	1 (0-3)	2 (0-3)	0.947
Placebo (n=38)	2 (0-3)	2 (0-3)	0.091

Data are shown as median (minimum–maximum). RIOM=Radiotherapy-induced oral mucositis

indicated that this gel can be an effective and portable treatment for inflammatory oral ulcers like lichen planus.^[24] In addition, another study has reported the Aloe vera gel as a suitable alternative to triamcinolone acetonide 0.1% in the treatment of lichen planus.^[32] Therefore, these results can confirm the anti-inflammatory effect of Aloe vera and justify its administration in patients with head-and-neck cancer undergoing RT. The results of Puatawepong *et al.*'s controlled clinical trial examining the effectiveness of Aloe vera juice on RIOM also indicated that Aloe vera juice reduced the incidence of severe mucositis, as a result

of which its juice was suggested as a good treatment for decreasing the progress of mucositis and relieving mucositis.^[39]

In contrast, Su *et al.* did not consider the administration of oral Aloe vera to be very effective in reducing RIOM and only stated a minor improvement in patients' quality of life.^[26] Furthermore, the results of three other large-scale trials conducted on breast cancer patients showed that Aloe vera had no effect on the prevention of radiation dermatitis.^[27,40,41] The findings of Marucci *et al.*'s study also indicated that although the use of Aloe vera could have some beneficial effects like shortening the healing time of the mucosa, it was ineffective in preventing third-grade acute mucositis.^[42]

Conceivably, the reason for the difference in the results of the studies can be justified by considering the differences in the preparation of the used solution and its quality and purity. The stage of cancer, the duration of concurrent RT or chemotherapy, and the dose of RT are the confounding factors that affect the effectiveness of the treatment. However, all these factors were controlled in our study, and the two groups did not have any significant differences in terms of these factors. In addition to the mentioned point as one of the strengths of the present study, the researchers ensured that patients with laryngeal or nasopharyngeal cancer did not suffer from dysphagia before starting the intervention as it might probably have an effect on the severity of mucositis. However, the small number of samples and the lack of comparison made between various types of head-and-neck cancers can be regarded as the limitations of this study. It is suggested to compare topical and oral use of Aloe vera in future studies since the way of its administration may also affect its effectiveness.

CONCLUSION

According to the results of the present study, the long-term use of Aloe vera mouthwash (from the 4th to 6th weeks of RT) can reduce the severity of RIOM progression. Therefore, it seems that this medicinal plant without any complications can be used as an oral wound healer in patients with head-and-neck cancer.

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Conflicts of interest

There are no conflicts of interest.

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