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Comparative Efficacy of Aloe vera and Benzydamine Mouthwashes on Radiation-induced Oral Mucositis: A Triple-blind, Randomised, Controlled Clinical Trial

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Purpose: To compare the efficacy of an Aloe vera mouthwash with a benzydamine mouthwash in the alleviation of radiation-induced mucositis in head and neck cancer patients using a triple-blind, randomised controlled trial.

Materials and Methods: Twenty-six eligible head and neck cancer patients who were to receive conventional radiation therapy at the radiation oncology department were randomised to receive an Aloe vera mouthwash or a benzydamine mouthwash. Mucositis severity was assessed during the course of radiation therapy using the WHO grading system.

Results: At baseline, there was no difference in the distribution of mucositis severity between the two groups. The mean interval between radiation therapy and onset of mucositis was similar for both groups (Aloe vera 15.69 ± 7.77 days, benzydamine 15.85 ± 12.96 days). The mean interval between the start of radiation therapy and the maximum severity of mucositis were was also similar in both the Aloe vera and benzydamine groups (Aloe vera 23.38 ± 10.75 days, benzydamine 23.54 ± 15.45 days). Mean changes of mucositis severity over time in both groups were statistically similar and the effect of both treatments did not change signficantly with time (p = 0.09).

Conclusion: Aloe vera mouthwash was as beneficial as benzydamine mouthwash in alleviating the severity of radiation-induced mucositis and showed no side effects. The Aloe vera mouthwash could be an alternative agent in the treatment of radiation-induced mucositis in patients with head and neck cancers.

Key words: Aloe vera, benzydamine, radiation-induced oral mucositis

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Head and neck cancers include all carcinomas arising from the muco-squamous epithelium of lips, oral and nasal cavity, pharynx, larynx and middle ear. Head and neck cancers are the third most common type of cancer, involving 7% of all 22.4 million people diagnosed with cancer (except non-melanotic skin cancer) worldwide.[28]

Such tumours are often curable. Surgery, radiation therapy (RT) and chemotherapy are used individually or in combination with each other.[33] Radiation therapy is used alone or with other intervention measures, especially chemotherapy, as the definitive treatment of head and neck cancers.

Oral mucositis is a frequent complication of RT in the head and neck region and is characterised by pain, odynodysphagia, dysgeusia, malnutrition, dehydration and increased risk of infection in immunocompromised patients.[4,11,13,19,22,27,30,35,36,41,42,44] Usually, mucositis appears two weeks after patients begin RT and causes pain and difficulties in eating, drinking and speaking, weight loss and worsening of the general condition.[31] The incidence of mucositis is reported to be 80% of all cases treated by RT, with or without chemotherapy.[42] The outbreak of these complications depends on irradiated region, dosage, radiation protocol and combination with chemotherapy.[38]

In more than half of the patients with mucositis, the severity of the condition is so high that parenteral analgesic, interruption of RT or hospitalisation may be necessary. There is evidence indicating that the interruption of RT and the prevention of the delivery of the total planned dose of RT have a negative impact on the survival rate.[9]

Currently no generally approved treatment or prophylaxis protocol for radiation-induced oral mucositis (RIOM) exists.[3] Direct cytoprotectants such as sucralfate and antiprostaglandins,[34] antioxidants,[21,25] non-steroidal agents,[10,18] low level laser therapy,[24] immunosuppressive drugs[5] and indirect cytoprotectants such as haematopoietic growth factors and antimicrobial agents[3] have been suggested for the management of this complication. The adverse effects of each of these treatments cannot be neglected.

Aloe barbadensis miller, known as Aloe vera, is a plant with various biologically effective properties such as wound healing, antimicrobial and antifungal activities, hypoglycaemic (antidiabetic), antitumour, anti-inflammatory and immunoregulatory effects.[14,15] Aloe vera has been used for the treatment of various diseases, such as lichen planus,[16,20] aphthous stomatitis[12] and psoriasis[29] with no significant side effects. Recent studies with different results have attempted to evaluate the efficacy of Aloe vera in the prevention and treatment of radiation-induced mucositis in the oral cavity.[26,45] Benzydamine hydrochloride, a non-steroidal drug, has also shown topical anti-inflammatory, analgesic, anaesthetic and antimicrobial effects and is used to attenuate inflammatory conditions like RIOM or chemotherapy-induced oral mucositis (CIOM).[10,18] A burning sensation of mouth is reported to be the major side effect of benzydamine HCl mouthwash.[1,37,43]

Due to the antiinflammatory, bactericidal and wound healing effects of Aloe vera, the present study was conducted to evaluate and compare the treatment efficacy of Aloe vera mouthwash and benzydamine HCl mouthwash on RIOM.

MATERIALS AND METHODS

The present study was designed as a triple-blind randomised and controlled interventional, quality of life clinical trial. The patients diagnosed with head and neck cancer were at least 18 years of age and were referred to the Radiation Oncology Department of the Cancer Institute, Tehran University of Medical Sciences, from December 2011 to November 2012. The patients had received a total external-beam RT dose of at least 50 Gy in standard fractions where the oral cavity had been exposed to RT. To be included in the study, the Karnovsky performance status had to be more than 70%. The exclusion criteria were a history of RT within the past year, food allergy, hypersensitivity to benzydamine, other NSAIDs, or Aloe vera; patients who had an existing lesion in the oral cavity (e.g. active infection or ulcer) before staring RT, or those who were unwilling to participate. All participants provided written informed consent, and the protocol satisfied the local ethics committee requirements. The project was registered in the Iranian Registry of Clinical Trials (Registration ID: IRCT2012072410377N1)

The randomisation was performed using balanced block randomisation. The allocation was blinded to the physician, the patients and the personnel involved in the study. After randomisation, the patients were divided into two groups: Aloe vera mouthwash as the intervention group and benzydamine mouthwash as the control group.

The study medications were 1. Aloe vera mouthwash containing pure Aloe vera gel (Barij Aloe vera

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Table 1 WHO system of mucositis grading					
Grade	**0**	**1**	**2**	**3**	**4**
WHO	None	Soreness ± erythema	Erythema, ulcers, patient can swallow solid food	Ulcers with extensive erythema, patient cannot swallow solid food	Mucositis to the extent that alimentation is not possible

syrup, Barij Essence Pharmaceutical Co; Kashan, Iran), 0.0009% Brilliant Blue dye and 0.0006% tartrazine yellow dye and 2. 0.15% benzydamine mouthwash. Both were identical in colour and bottle. Subjects were given written instructions to rinse with 5 ml of the solution and not eat or drink for the subsequent 30 min, 3 times a day from the first day of RT to the end of the treatment. The patients were visited once prior to RT, then once a week during 6 weeks of RT and one week of follow-up (total of 8 visits); the grade of RIOM was recorded according to the WHO grading system (Table 1). Burning sensation of the mouth and dysphagia of solid food or liquids were recorded based on the patient reports and erythema and ulcers were observed clinically.

Statistical analysis

Efficacy analysis was based on the Intention to Treat (ITT). Demographic and qualitative information of the patients was presented using descriptive statistics and compared using the chi-square test. The quantitative data were reported as means and standard deviations and compared using the t-test. The intensity of mucositis was compared between groups using the Mann-Whitney U-test ($p < 0.05$). The GEE test (Generalised Estimating Equations) with correlation matrix AR (1) (AutoRegressive model) and an ordinal logistic model were performed to evaluate differences between mucositis grade changes during the 2-month treatment period. Data analysis was performed with SPSS for Windows (SPSS; Chicago, IL, USA).

RESULTS

Twenty-six patients were randomly allocated into two groups, with 13 per group. Demographics and patient characteristics for the treated population are summarised in Table 2. The age of the patients was between 26 and 80 years, with a mean of 57.35 years (SD ± 6 years).

All RT was done by megavoltage cobalt-60 machines and standard fractionation (2 Gy each fraction, five fractions a week). The mean total dose of RT was 65.54 Gy (50–70 Gy) in the Aloe vera and 66.15 Gy (54–70 Gy) in the benzydamine group. No patient reported any major adverse effect or withdrew from the study. Two patients (15.4%) in the Aloe vera group experienced nausea ($p = 0.48$).

The distribution of WHO mucositis grades between the treated groups is presented in Fig 1. No grade 4 was identified in these groups. No statistically significant differences in mucositis grade were found between the two mouthwashes ($p = 0.35$).

The mean time between the start of RT and onset of early signs of mucositis was 15.6 days in the Aloe vera group and 15.8 days in the benzydamine group. The mean duration between beginning of RT and maximum mucositis grade occurrence was 23.3 days in the Aloe vera group and 23.5 days in benzydamine group, but these differences were not statistically significant ($p = 0.97$ and $p = 0.98$, respectively) (Table 3).

The mean changes of mucositis grade in both groups are depicted in Fig 2. The effect of both treatments on the intensity of mucositis did not change or differ notably as time passed. There was no significant difference between Aloe vera and benzydamine groups in terms of mucositis grade changes over time ($p = 0.09$).

DISCUSSION

Oral mucositis is a major complication of RT of the head and neck region.[4,11,13,19,22,27,30,35,36,41,42,44] It causes pain and problems in eating, drinking and speech, weight loss and worsening of the general condition,[31] which might lead to interruption of RT. The latter could affect the survival rate of the patient.[10]

Several agents and medications have been used in the prevention, treatment or alleviation of this condition,[9] but there is no generally accepted prophylaxis or treatment available for this type of mucositis.

Aloe vera is a plant with 75 main active components, such as vitamins, minerals, polysaccha-

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Table 2 Demographic and patient characteristics of the treated population (N = 26)

Parameter		Aloe vera n=13	Benzydamine n=13	Sum
Gender	Male (n, %)	8 (61.5)	12 (92.3)	20 (76.9)
	Female (n,%)	5 (38.5)	1 (7.7)	6(23.1)
Age	(Min/Max)	(26/79)	(27/80)	(26/80)
	Mean ± SD	55.38 ± 17.99	59.31 ± 15.03	57.35 ± 16.37
Histology	SCC (n, %)	11 (84.6)	12 (92.3)	23 (88.5)
	Mucoepidermoid carcinoma (n, %)	1 (7.7)	0	1 (3.8)
	Osteosarcoma (n, %)	1 (7.7)	1 (7.7)	2 (7.7)
	Others (n, %)	0	0	0
Primary tumour site	Lips (n, %)	3 (23)	1 (7.7)	4 (15.38)
	Tongue (n, %)	1 (7.7)	2 (15.4)	3 (11.53)
	Parotid (n, %)	1 (7.7)	0	1 (3.84)
	Mandible (n, %)	1 (7.7)	0	1 (3.84)
	Maxilla (n, %)	0	1 (7.7)	1 (3.84)
	Nasopharynx (n,%)	2 (15.4)	3 (23.1)	5 (19.23)
	Oropharynx (n,%)	1 (7.7)	0	1 (3.84)
	Hypopharynx (n,%)	2 (15.4)	0	2 (7.69)
	Larynx (n, %)	2 (15.4)	4 (30.8)	6 (23.07)
	Others (n, %)	0	2 (15.4)	2 (7.69)
Tumour stage	1 (n, %)	0	0	0
	2 (n, %)	0	0	0
	3 (n, %)	9 (69.2)	7 (53.8)	16 (61.5)
	4 (n, %)	4 (30.8)	6 (46.2)	10 (38.5)
Previous surgery (n, %)		2 (15.4)	3 (23.1)	5 (19.2)
Chemotherapy	Yes (n, %)	9 (69.2)	12 (92.3)	21 (80.8)
	No (n, %)	4 (30.8)	1 (7.7)	5 (19.2)
Disease duration by month (from diagnosis to start of RT)	range	1.11–5.6	0.92–7.6	0.92–7.6
	Mean ± SD	3.11 ± 1.50	2.94 ± 1.80	3.03 ± 1.60
RT dose (Gy)	Range	50–70	54–70	50–70
	Mean ± SD	65.54 ± 6.23	66.15 ± 5.63	65.85 ± 5.85

Table 3 Mucositis outcomes by using Aloe vera and benzydamine

Parameter		Aloe vera	Benzydamine
Interval from start of RT to mucositis onset by day	Min/Max	7/34	6/54
	mean ± SD	15.69 ± 7.77	15.85 ± 12.96
Interval from start of RT to maximum mucositis grade by day	Min/Max	13/14	6/54
	mean ± SD	23.38 ± 10.75	23.54 ± 15.45

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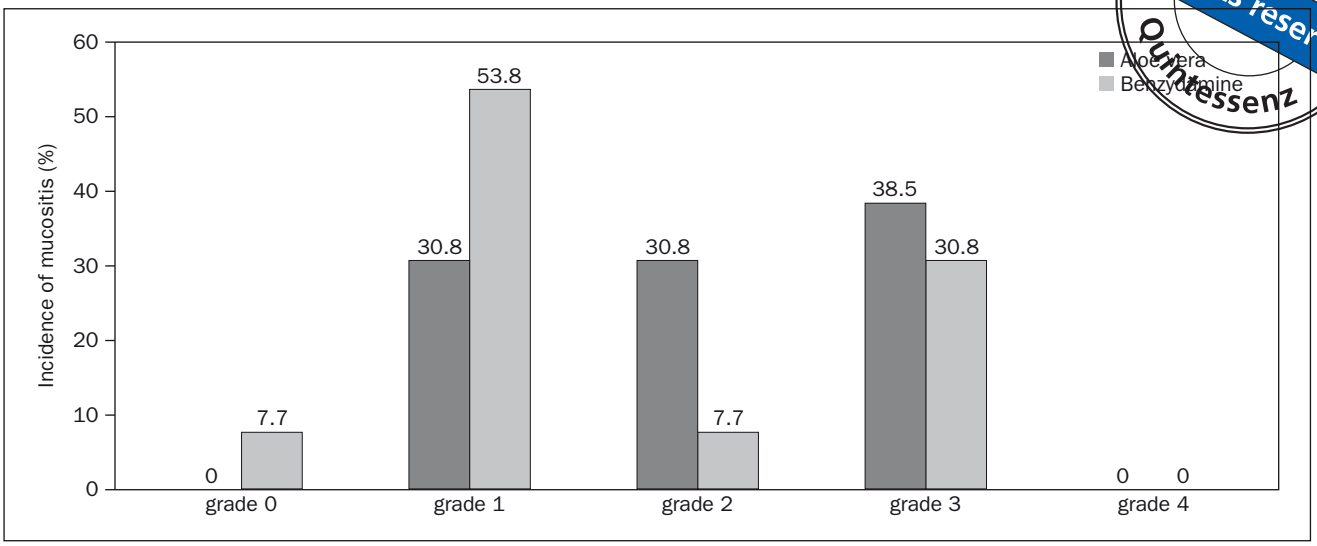


Fig 1 Distribution of mucositis by WHO grading in Aloe vera and benzydamine groups.

rides, lignin and saponins,[2,40] having miscellaneous biological effects such as wound healing, antimicrobial, anti-inflammatory and anti-tumour activity.[14,15] Several studies have evaluated the efficacy of Aloe vera in the treatment of various diseases, such as skin burns,[45] psoriasis,[29] radiation-induced dermatitis,[23] HIV infection,[26] lichen planus[16,20] and aphthous stomatitis.[12]

The efficacy of benzydamine hydrochloride – a non-steroidal anti-inflammatory agent with analgesic, anaesthetic and anti-microbial activity – in the treatment of oral mucositis induced by RT has been investigated in previous studies.[10,18]

Worthington et al[46,47] and Clarkson et al[7,8] published meta-analyses of interventions for preventing oral mucositis. Ten interventions showed some statistically significant evidence of benefits for either preventing or reducing the severity of mucositis compared to either a placebo or control group. One of these interventions was Aloe vera. Those authors concluded that the effectiveness of interventions utilised in prevention or reduction of the intensity of mucositis varies and implications for practice include consideration that advantages may be specific for certain treatments and cancer types.[7,8,46,47]

The present study shows that neither the Aloe vera nor the benzydamine mouthwash are capable of preventing mucositis, as all 13 patients in the intervention group and 12 patients in the control group (benzydamine) presented signs of mucositis. The current results also showed no statistically significant difference in mucositis grades between patients using Aloe vera or benzydamine mouthwashes. Both

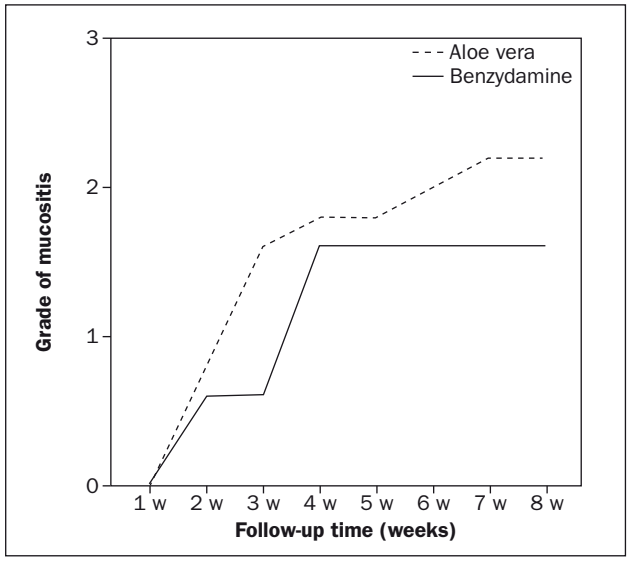


Fig 2 Mean changes of severity of mucositis in Aloe vera and benzydamine groups.

Aloe vera and benzydamine mouthwashes delayed the onset of mucositis and onset of maximum severity of mucositis in a similar way with no statistically significant difference between the mouthwashes.

Kazemian et al[18] investigated the prophylactic efficacy of benzydamine mouthwash against oral mucositis induced by radiation. They found benzydamine to be a safe, well-tolerated and effective treatment for mucositis which significantly reduced its incidence during RT. Kamian et al[17] also investigated benzydamine for the prophylaxis of radiation-induced oral mucositis in head and neck cancers. They also concluded that an oral rinse of benzyd-

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amine was effective, safe and well-tolerated in the prophylaxis of radiation-induced oral mucositis in head and neck tumours, as did Epstein et al.[10]

Choonhakarn et al[6] examined the efficacy of Aloe vera gel in the treatment of oral lichen planus. They concluded that Aloe vera gel is an effective and well-tolerated treatment for oral inflammatory ulcers such as lichen planus. In another study, Mansourian et al[20] compared the therapeutic effect of an Aloe vera mouthwash and triamcinolone acetonide 0.1% on oral lichen planus, concluding that Aloe vera mouthwash can be a good alternative to triamcinolone acetonide 0.1% mouthwash in the treatment of oral lichen planus lesions. This could also confirm the anti-inflammatory action of Aloe vera and justifies its use in patients with head and neck RT.

Puataweepong et al[32] conducted a placebo-controlled clinical trial assessing the efficacy of Aloe vera juice for oral mucositis induced by radiation, reporting that Aloe vera juice reduced the incidence of severe mucositis; however, it could not delay the onset of severe mucositis. All in all, Aloe vera is a good treatment for slowing down the progression of mucositis and alleviating mucositis. In contrast, Su et al[39] tested the use of Aloe vera for reduction of radiation-induced mucositis and reported it to be ineffective as a treatment for mucositis. However, they mentioned that the mean quality of life scores were greater – albeit statistically insignificantly so – in the Aloe vera group. These results might be due to a difference in the preparation of the solution used here, for which pure, fresh Aloe vera was produced by Barij Essence Pharmaceuticals, using a well-controlled technique of extraction.

It should be borne in mind that our patients had various types of head and neck cancer, which could have a negative effect on the results. For example, patients with laryngeal or nasopharyngeal cancer had dysphagia before the treatment started, thus possibly influencing the mucositis grading system. The relatively small number of patients is another limitation of the present study. It is suggested that in the future patients be categorised by their cancer type in order to yield more accurate results. A comparison of the effect of local Aloe vera application with ingested Aloe vera could be a subject of future studies.

CONCLUSION

Both Aloe vera and benzydamine may be prescribed for radiation-induced oral mucositis. As Aloe vera is less costly, more readily accepted by the patients as an antioxidant and herbal medication and has fewer side effects, it may be used as a good alternative for the treatment of oral mucositis in patients with head and neck RT.

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