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Research article

Effectiveness of topical application of aloe vera gel on radiation induced mucositis in patients receiving radiotherapy for head and neck malignancies

Rita Lakhani[1] and Pravina Mahadalkar[2]

[1]Fortis Institute of Nursing, Fortis Hospitals, Mulund, Mumbai, India
[2]Bharti Vidyapeeth, College of Nursing, Pune, Maharashtra, India

Abstract

Abstract: In recent years, the treatment of radiotherapy is commonly and concomitantly prescribed for patients with head and neck cancer. Radiotherapy is associated with high rates of mucotoxicity with no consensus/universal standard of its care. **Aim:** The objective of this study (part-publication) is to assess the effectiveness of topical application of aloe vera gel in the magnitude of increasing radiation-induced mucositis in malignant patients of head and neck. **Materials and Methods:** A triple-blind, control group design was adopted on 40 eligible respondents scheduled to receive conventional radiotherapy. The respondents were classified randomly between Group A and Group B; one among them being the experimental group using the drug aloe vera and the other group being the control group using base gel. Standardized tools were applied to assess the primary and secondary outcome of development of radiation induced mucositis. **Results:** Respondents in two groups were statistically identical in baseline characteristics (P>0.05). The radiation-induced mucositis grades were clinically less and not significant for Group A as compared to Group B (P>0.05). Further, by the end of treatment, two groups were statistically same in the maximal grade of toxicity (Z = 2.7, P>0.05), use of drugs, QOL scores, the percentage of weight loss and nutritional status. **Conclusion:** The researcher is blind to the allocation of the tubes but since, both the groups are same along various assessment parameters it can be safely concluded that aloe vera was not beneficial in reducing the magnitude of increasing radiation-induced mucositis. The Groups identity was revealed at the end of the main study; Group A was identified as the experimental group and Group B was the control group.

Key words: Aloe-vera, head and neck cancer, Radiation induced mucositis.

***Corresponding author: Prof. Rita Lakhani,** Principal, Fortis Institute of Nursing, Fortis Hospitals, Mulund, Mumbai, India. Email: rita.lakhani@fortishealthcare.com

1. Introduction

Head and neck malignancy (HNM) is a heterogeneous disease characterized by complex clinical and pathologic presentations. The treatment of HNM has undergone a gradual evolution over the past 3 decades, with an increased emphasis placed on organ preservation and multimodality management, including the use of radiotherapy (RT) and chemotherapy [1,3,4,10]. RT approach, however, is associated with increasing rates of mucotoxicity that have been well documented in the context of numerous clinical trials in light of the radiation oncology literature and Cochrane reviews containing no consensus or universal standard of care for the prevention or treatment of radiation-induced-mucositis (RIM) that occurs inevitably in all patients undergoing RT [2].The current management focuses more on palliative measures, such as pain management, nutritional support, and maintenance of good oral hygiene [6,8].

Studies have suggested that Aloe-vera can enhance wound healing by reducing vasoconstriction and platelet aggregation at the wound site, improving wound oxygenation, increasing collagen formation, inhibiting collagenase and metalloproteinase, and activating macrophages [5, 7]. Furthermore, it has antioxidant properties and eliminates production of free radicals.

Studies to-date has had different dimensions and only two clinical-studies have been undertaken so far and reviewed here. Su CK, et al., 2010 studied 50 patients using aloe-vera mouth wash produced “complete pain

remission" of mucositis but there was no significant difference in the incidence of severity of mucositis between the aloe vera and placebo group. Putipun Puataweeponga, et al., targeted 61 patients where patients consumed aloe vera oral juice; the incidence of severe mucositis was significantly lower in the aloe-vera group compared with the placebo group-53% vs. 87%, p=0.004.In the former study, the researcher used aloe vera as a mouth wash where its effect got limited over a few minutes and in the other research, the researcher used it in an oral form where it acted as a systemic agent than a local agent. Considering these factors and the uncertainties about the use of aloe-vera for the prevention of RIM, the researcher decided to examine the issue in a self-controlled clinical trial using local application gel of aloe-vera versus its base gel [7, 9]. Therefore, the present work is an attempt towards the use of an assessment of the effectiveness of topical application of aloe vera gel in radiation-induced mucositis.

Problem statement:

Effectiveness of topical application of aloe vera gel on radiation induced mucositis in patients receiving radiotherapy for head and neck malignancies

Objectives:

1. To compare the onset of occurrence of RIM in respondents receiving RT for HNM both in the experimental and the control group.
2. To compare the severity of RIM in the respondents during the progress of their therapeutic RT for HNM, both in the experimental and the control group
3. To associate selected demographic variables of the respondents receiving RT for HNM in the experimental group to the development of severity of RIM in them.

2. Material and methods

This study (part-presentation of the main study) is a single-institution, triple-blinded, (statistician blinded) pre-experimental, control group design carried out on patients treated with RT (1.8–2.0 Gy/fraction to total doses of 58–70 Gy, using conventional radiation techniques) on a six-MV-linear-accelerator between April'14 to March'15. Block randomization was done by computerized random number table using site and concomitant-chemo-radiotherapy (CCRT) as a matching variable. Among 40 respondents who met the inclusion criteria the respondents were classified randomly as Group A and Group B; one amongst them received the drug aloe vera and the other group received the base gel. The base gel had the same constituents as aloe vera gel but the aloe vera.

The informed-consent form was signed by the respondents after implementation of the patient information sheet and then block randomized. Further, eligible patients were required to have histological confirmed HNM undergoing RT, normal mucosa at baseline and Karnofsky-performance-status ≥ 70.Patients who had prior irradiation of the head and neck, history of allergy to Aloe-vera, underlying diabetes-mellitus, or immunosuppressant's and HIV-positive were excluded from this study.

In both the groups the researcher explained the patients to apply a thin layer of the gel three times daily beginning from the day of onset of RIM and continuing throughout the course of RT. They were explained not to consume anything for about 15 minutes. In the case of prescription of other oral applications, they were explained to first apply the gel and then the other medications can be taken with a 15-minute interval between the oral applications.

In this study, the researcher used the fresh stock of 10% Aloe-vera gel prepared under well-controlled laboratory checks and was stocked and stored in the cool atmosphere of the hospital. Both the tubes were identical except for the label as 1 and 2.

The tools used for the study were an Interview Schedule (biographic, tumor and medical related data, QOL and an Opinionnaire) and an Observational Tool (Karnofsky Performance Status, WHO scale for assessing RIM and weight assessment). The data collection plan is detailed in Table I. The following primary and secondary outcomes were considered in this review to assess severity of RIM:

1. Primary outcome:

a. WHO-Grading of the severity of RIM.
b. VAS-Oral pain scores.

2. Secondary outcome:

a. Need for analgesic, antifungal, anesthetic and antibiotic drugs; with its day of onset.
b. Any admission to the hospital arising due to toxicity of RIM
c. Nutritional support – insertion of RT
d. Interruption of RT due to its toxicity
e. Weight loss
f. Patient QOL: OMWQ-HN (Oral Mucositis Weekly Questionnaire– Head and Neck Cancer) and FACT-HN(Functional Assessment of Cancer Treatment–Head and Neck Questionnaire - Version 4)

Table I: Protocol and assessment schedule

Group	Intervention	Assessment: (primary & secondary outcome)
Group A- Tube 1 (Drug: Aloe Vera gel topical)	Application of gel tube 1 every day three times per day, 4-5 hourly, from the day of onset of RIM.	Assessment on day-1: • Biographic, Weight, KPS& health related data • OMWQ-HN& FACT–HN (version 4) & Pain assessment • WHO scale of grading mucositis **Weekly assessment:** • WHO scale of grading mucositis • OMWQ-HN (including pain assessment) **From the case sheet: during weekly visits:** • Onset of occurrence of RIM • **Need of:** the specified drugs, nutritional support (onset and duration), Interruption of RT (reason, onset, and number) **Assessment on last day of therapeutic RT:** • WHO scale of grading mucositis • Weight of the respondents • OMWQ-HN& pain assessment and FACT–HN
Group B- Tube 2 (Base gel topical application)	Application of gel tube 2 every day three times per day, 4-5 hourly, from the day of onset of RIM.	

3. Result

A total of 40 patients were recruited in this study; 20 respondents in Group A and 20 respondents in Group B. The respondents were comparable along most of the parameters as stated in Table II, III and IV except for the fact that there were more respondents with undifferentiated tumors and T4 tumors in Group A. All respondents reported good compliance with the gel tubes and no adverse reactions were reported by them. There were no toxicities that further developed of RIM, thus no patients required any nutritional support or got hospitalized. No participants dropped out from the study.

The onset of occurrence of RIM in Group B was earlier as compared to that in Group A (Figure 1). However, the difference in average onset of occurrence in RIM was not statistically significant as depicted in Table V.

Table-II: Respondents demographic characteristics

N=20,20

Demographic variable	Group A		Group B		p-value
	Freq	%	Freq	%	
Gender					
Male	17	85	16	80	0.34
Female	3	15	4	20	
Age					
< 40 years	4	20	4	20	0.74
41-50 years	8	40	8	40	
51-60 years	0	0	4	20	
> 60 years	8	40	4	20	
Educational status					
≤ 10^{th} standard	8	40	4	20	0.31
11^{th} standard – graduation	12	60	16	80	
History of smoking					
Never smoked/chewed tobacco	0	0	4	20	0.62
Ex-smoker/ chewed tobacco	20	100	16	80	
Pack-year history of smoking					
10 pack year	6	30	4	20	0.34
15 pack year	9	45	8	40	
20 pack year	5	25	4	20	
Duration of tobacco use					
18 years	0	0	4	20	0.38
19 years	8	40	4	20	
21 years	4	20	8	40	
22 years	4	20	0	0	

Demographic variable	Group A		Group B		
	Freq	%	Freq	%	
26 years	4	20	0	0	
NA	0	0	4	20	
Alcohol consumption					
Yes	16	80	12	60	0.41
No	4	20	8	40	
If yes, the consumption was:					
Daily	4	20	0	0	0.42
Weekly	8	40	0	0	
Occasionally	4	20	12	60	
If daily, since how many years					
10 years	4	20	0	0	
Previous surgery:					
Yes	16	80	16	80	00
No	4	20	4	20	

Table III: Tumor characteristics of the respondents

N=20, 20

Tumor characteristics	Group A		Group B		p-value
	Freq	%	Freq	%	
Primary tumor site					
Nasopharynx	0	0	4	20	0.43
Oral cavity	20	100	16	80	
Histology					
Squamous cell carcinoma	12	60	16	80	0.02
Undifferentiated/Poorly differentiated carcinoma	8	40	4	20	
Tumor staging					
TX	0	0	4	20	0.05
T1	0	0	4	20	
T2	4	20	8	40	
T3	4	20	4	20	
T4	12	60	0	0	
Nodal staging					
N0	8	40	4	20	0.71
N1	4	20	0	0	
N2	4	20	12	60	
N3	4	20	4	20	

Table IV: Treatment characteristics of the respondents

N=20, 20

Characteristics	Group A		Group B		p-value
	Freq	%	Freq	%	
Radiation therapy dose					
58 Gy	0	0	4	20	0.4
60 Gy	16	80	12	60	
70 Gy	4	20	4	20	
Total treatment time					
29 days	0	0	4	20	0.104
30 days	16	80	12	60	
35 days	4	20	4	20	
Concomitant chemotherapy					
No	8	40	4	20	0.829
Yes	12	60	16	80	
Analgesic requirement					
Yes	2	10	2	10	00
No	18	90	18	90	
When started					

Characteristics	Group A		Group B		P-Value
	Freq	%	Freq	%	
26th day	0	0	1	5	0.641
28th day	1	5	1	5	
29th day	1	5	0	0	
30th day	0	0	0	0	
31th day	0	0	0	0	
Antibiotic requirement					
Yes	20	100	20	100	
When started					
14 day	4	20	4	20	0.001
15 day	0	0	4	20	
17 day	4	20	8	40	
18 day	4	20	0	0	
19 day	0	0	4	20	
20th day	8	40	0	0	
Antifungal requirement					0.001
Yes	20	100	5	100	
When started					
14 day	4	20	4	20	
15 day	0	0	4	20	
17 day	4	20	8	40	
18 day	4	20	0	0	
19 day	0	0	4	20	
20th day	8	40	0	0	
Anesthetic requirement					
Yes	20	100	20	100	
When started					
14 day	4	20	4	20	0.001
15 day	0	0	4	20	
17 day	4	20	8	40	
18 day	4	20	0	0	
19 day	0	0	4	20	
20th day	8	40	0	0	
Mucositis development					
Yes	20	100	20	100	

Table V: Onset of occurrence of RIM in the two groups

Group	N	Mean	Std. Deviation	Std. Error Mean	T	df	p-value
A	20	17.8	2.5	1.1	0.99	8	0.176
B	20	16.4	1.9	.9			

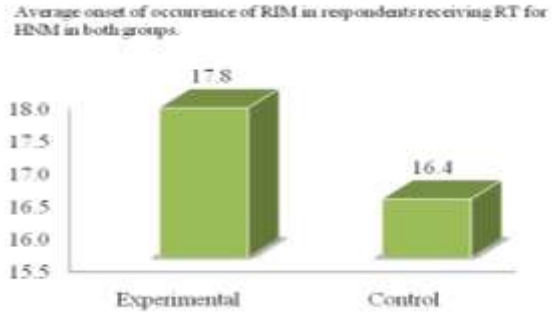

Figure 1: Average onset of occurrence of RIM in respondents of both the groups

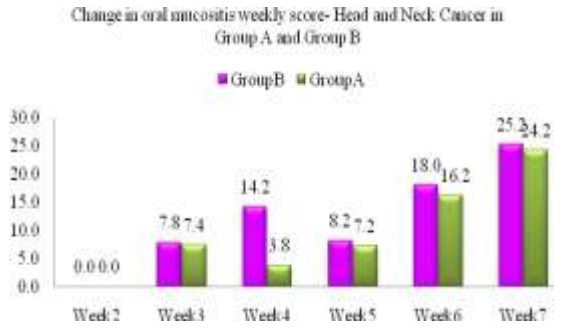

Figure 2: Change in OMWQ-HN scores of the respondents in both the groups

Finally, the respondents in the two groups had statistically the same outcomes along the variables as listed in primary and secondary outcome dimension to assess the severity of RIM:

Severity of RIM

Our study demonstrated that on the termination day of RT, RIM at different levels of severity was not significantly different between the two groups. (P=0.000).

Oral pain

On the termination day of RT our study showed that there was no significant difference in different grades of oral pain among the respondents of the two groups (P= 0.243).

Requirement of antibiotic

The respondents' mean onset day for the requirement of this drug was 30.8 day in Group A and 29.04 days in Group B and on the termination day of RT there was no significant difference in the incidence of use of this drug (P=0.83) among the respondents of both the groups.

Requirement of antifungal drug

The respondents mean onset day for the requirement of this drug was 17.8 days in Group A and 16.4 in Group B. and on the termination day of RT there was no significant difference in the incidence of use of this drug (P=0.78) among the respondents of both the groups.

Requirement of antacid and anesthetic drug

All the respondents were prescribed both these drugs on the day of onset of RIM. There was no significant difference observed in the respondents' mean day of onset for this drug and on the termination day of RT there was no significant difference in the incidence of use of this drug (P=0.176) among the respondents of both the groups.

Weight loss

On the termination day of RT, our study showed that there was no significant difference in weight loss among respondents in the experimental and control groups (P>0.05)

Quality of life (FACT-HN & OMWQ-HN)

The present study demonstrated that mean change in FACT-HN (Group A 45±5.4 and Group B 47.7±4.2; P=0.085) and OMWQ-HN (Group A 39.9±9.9 and Group B 41.2±16.5: P=0.76; P=0.085) in group A was clinically better than group B; however, the change was not significantly different.

4. Discussion

Oral mucositis remains the greatest challenge for a Radio-oncology team. It debilitates the patient causing a vicious cycle of RIM, reduced intake, weight loss accompanied by pain and affection of major oral functions.

The study results confirmed the risk of radiation toxicities due to RT in all the respondents. The two groups were not significantly different in biographical, tumor characteristics and treatment aspects, thus they were comparable. Sahebjamee et al showed that there was no difference in the distribution of mucositis severity between the groups [11].

The results of the study revealed a clinically favorable inclination towards Group A than the Group B, as the groups were clinically different along most of the outcome dimensions of the severity of RIM which includes above all, delayed progression of RIM and less oral pain during the course of RT. They also had reduced and delayed need of supportive drugs, reduced weight loss, as well as better scores on OMWQ-HN and FACT-HN. But both the groups were statistically same along all these objective dimensions. Su et al. demonstrated that aloe vera was less beneficial in radiation induced mucositis patients. Aloe vera was not effective in improving tolerance to head and neck radiotherapy, decreasing mucositis, and soreness. But the quality of life was improved in aloe vera patients [9].

Though the researcher was blind to the allocation of the gel tubes, the researcher did not find any statistical difference in the outcome parameters, thus the researcher concluded that there is no statistically significant benefit of adding aloe vera to the conventional oral care in the management of RIM. The group's identity was revealed by Bio green Healthcare at the end of the main study; Group A was designated as the experimental group and Group B as the control group.

The main limitations of this study are its small sample size and the fact that the researcher could not objectively evaluate the compliance to the application of gels by the respondents; though weekly gel tubes were given when the respondents returned the empty gel tube.

Conclusion

The study trial failed to find any statistically significant improvement in the RIM related outcomes from topical application of aloe vera. Thus, the addition of aloe vera did not improve tolerance to RT in HNM patients. Unless it proves otherwise, other approaches to the treatment of radiation-induced mucositis will be sorely needed.

The authors declare that they have no competing interests.

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