Efficacy of Aloe Vera gel topical application on Radiation Induced Mucositis in Head and Neck Malignancy: A Double-blind, Randomised Clinical trial in Mumbai, India

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***INTRODUCTION*:**

One word that is even more daunting than the death itself and eats up a person from the inside is cancer.

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. RT approach, however, is associated with increasing rates of muco-toxicity 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. The current management focuses more on palliative measures, such as pain management, nutritional support, and maintenance of good oral hygiene.

***NEED AND SIGNIFICANCE*:**

Studies have suggested that Aloe-vera can enhance wound healing by reducing vasoconstriction and platelet aggregation at the wound site, improving wound oxygenation, scavenging free radicals, increasing collagen formation, inhibiting collagenase and metalloproteinase, and activating macrophages. [(1-4)] 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 as specified in review of literature. In one 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 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.

***PROBLEM STATEMENT*:**

"A randomized double blind clinical trial to assess the effectiveness of topical application of Aloe-Vera gel versus base-gel on radiation-induced mucositis in patients receiving radiation therapy for Head and Neck Malignancy in a selected hospital in Mumbai, India"

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 magnitude of increasing development of 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.

CONCEPTUAL FRAMEWORK:

Using the Systems Theory, the professional nurse aims to know the effectiveness of the intervention of topical application of aloe vera gel on RIM.

The theory has three componenets:

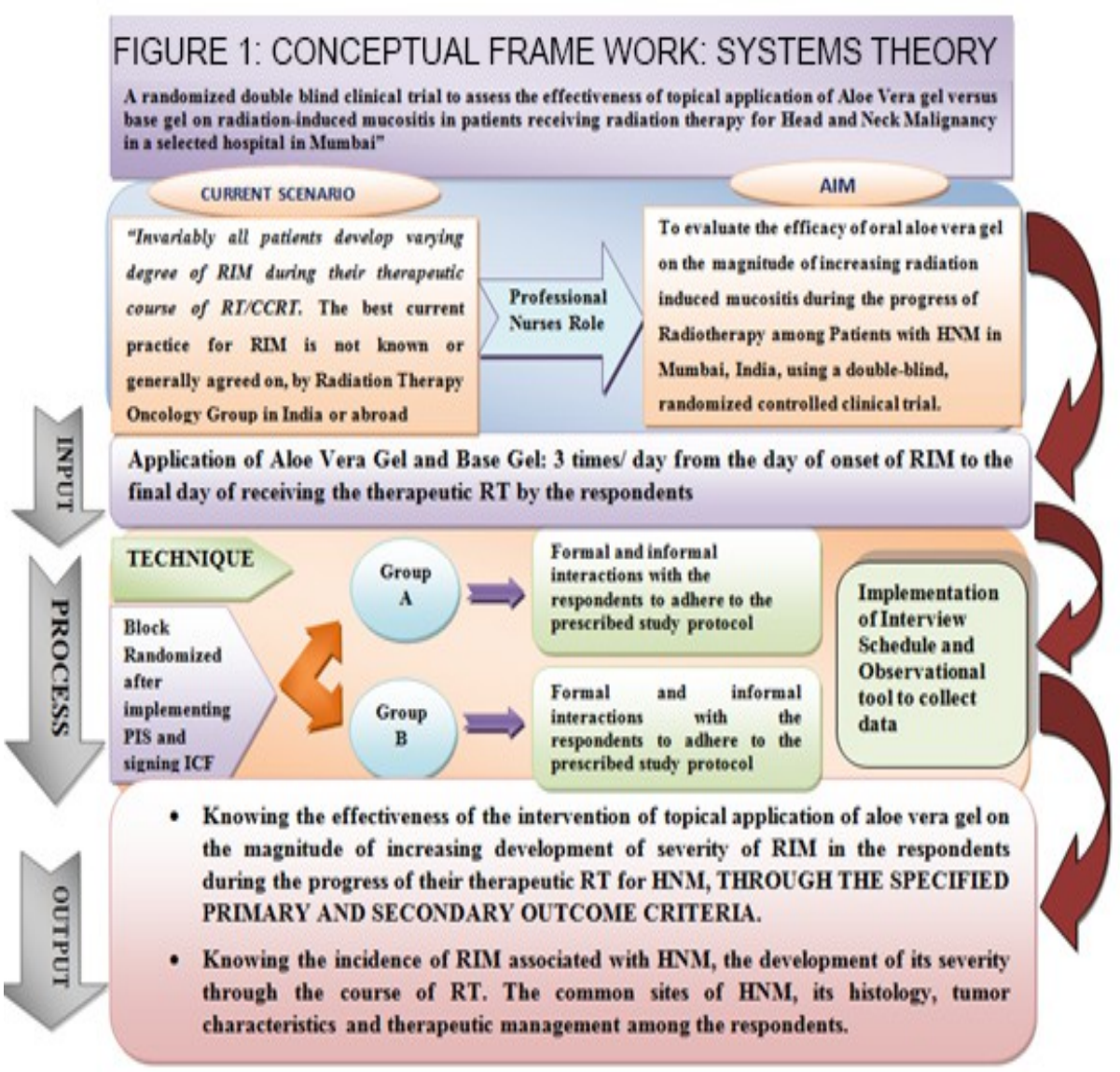
Input: refers to the topical application of aloe vera gel or base gel on RIM by the respondents in the experimental and the control group, respectively.

Process: refers to the double-blinded implementation of the following steps with an aim to collect data regarding the effectiveness of aloe vera:

a) Implementing the Patient Information Sheet (PIS) in the two groups and gaining consent on the Informed Consent Form (ICF)
b) Block randomization of the respondents in the two groups; that is, Group A and Group B;
c) Giving of the tubes 1 and 2 to the respondents in the two respective groups, that is, A and B on development of RIM, for self-application during the course of RT.

Output: refers to:

a) Knowing the effectiveness of the intervention of topical application of aloe vera gel on the magnitude of increasing development of severity of RIM in the respondents during the progress of their therapeutic RT for HNM. (as specified in the conceptual definition of effectiveness)
b) Knowing the incidence of RIM associated with HNM, the development of its severity through the course of RT, the common site of HNM and its histology among the respondents.



REVIEW OF LITERATURE:

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.

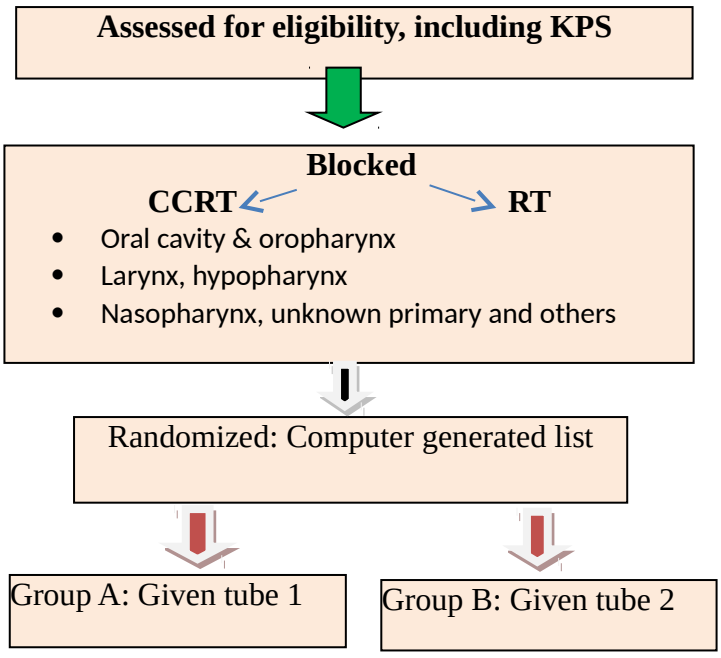
MATERIAL AND METHOD

This was an evaluative, single-institution, double-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 September'14 to September'15.

Block randomization was done by computerized random number table using site and concomitant-chemo-radiotherapy (CCRT) as a matching variable. Among 110 respondents who met the inclusion criteria, 10 patients were lost, 100 patients completed the trial; 51 in Group A and 49 in Group B. Informed-Consent-Form was signed by the respondents after implementation of Patient-Information-Sheet and then block randomized. Eligible patients were required to have histologically confirmed HNM undergoing RT, normal mucosa at baseline and Karnofsky-performance-status ≥ 70. The patients who had prior irradiation of the head and neck, history of allergy to Aloe-vera, underlying diabetes-mellitus, on immunosuppressant's and HIV-positive were excluded from this study.

The treating physicians otherwise treated the study patients no differently than the other HNM patients receiving RT. 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 case of prescription of other oral applications, they were explained to first apply the gel and then the other medications with a 15 minute interval between the oral applications. In this study, the researcher used 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 A and B.

Figure-2: Flowchart of enrollment of respondents in the study



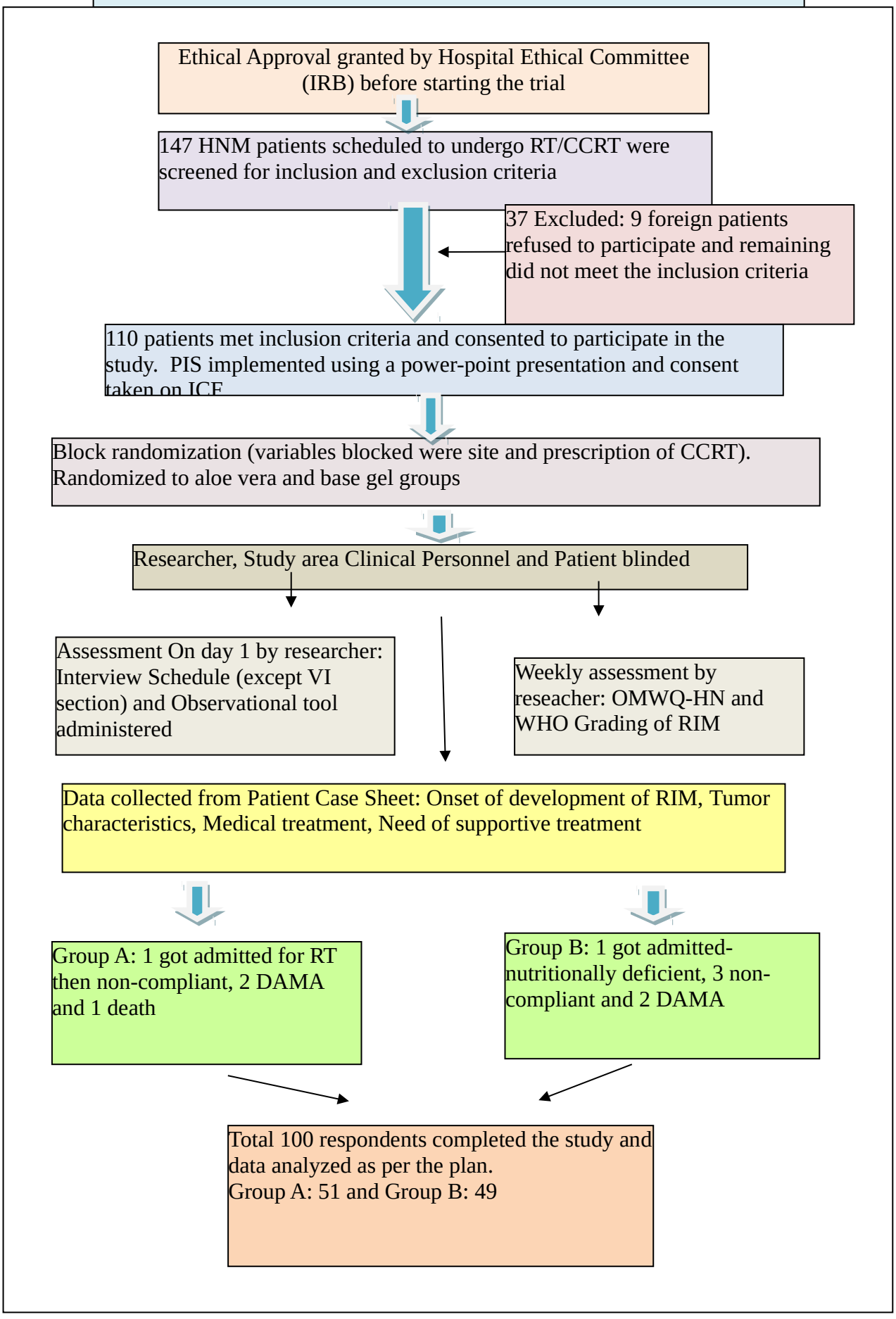
The tools used for the study were:

- Interview Schedule
- Observational Tool

The following primary and secondary outcomes were considered in this review to assess **Severity of RIM:**

1. **Primary Outcome: (weekly assessment)**
    a. WHO-Grading of severity of RIM
    b. VAS-Oral pain scores
2. **Secondary Outcome**:
    a. Need for analgesic, antifungal, anaesthetic and antibiotic drugs; with its day of onset
    b. Any admission to the hospital
    c. Nutritional support
    d. Interruption of RT
    e. Weight loss (1^{st}-day and final-day)
    f. Patient QOL: OMWQ-HN and FACT-HN (1^{st}-day & final-day)

Figure 7: Flow of respondents during the study



RESULTS

Patient demographic data:

Table-I: Respondents Characteristics and Tumor & Treatment Characteristics

N=51, 49

Characteristics	Experimental group		Control group		p-value
	Freq	%	Freq	%	
Gender					
Male	44	86.3%	41	83.7%	0.784
Female	7	13.7%	8	16.3%	
Age					
< 40 years	6	11.8%	4	8.2%	0.753
41-50 years	12	23.5%	16	32.7%	
51-60 years	16	31.4%	15	30.6%	
> 60 years	17	33.3%	14	28.6%	
Educational status					
≤ 10th standard	35	68.6%	36	73.5%	0.349
11th standard – graduation	15	29.4%	11	22.4%	
Post-graduation	0	0%	2	4.1%	
Professional courses	1	2.0%	0	0.0%	
History of smoking					
Never smoked	0	0%	1	2.0%	0.033
Present smoker	0	0.0%	0	0.0%	
Occasional smoker	2	3.9%	7	13.7%	
Ex-smoker	17	33.3%	9	17.6%	
Pack-year history of smoking/smoked					
Up to 10 pack years	6	11.8%	8	15.7%	0.603
11-20 pack years	10	19.6%	9	17.6%	
21-30 pack years	3	5.9%	0	0.0%	
History of tobacco chewing					1.000
Never chewed tobacco	0	0.0%	0	0.0%	
Occasional tobacco chewer	1	2.0%	0	0.0%	
Present tobacco chewer	0	0.0%	0	0.0%	
Ex-tobacco chewer	31	60.8%	32	62.7%	
Years of tobacco chewing					
11-20 years	15	29.4%	18	35.3%	0.687
21-30 years	12	23.5%	8	15.7%	
31-40 years	4	7.8%	4	7.8%	
41-50 years	1	2.0%	2	3.9%	
Karnofsky Performance Status					
70	11	21.6%	11	22.4%	1.000

80	40	78.4%	38	77.6%	

Contd. Table-I

N=51, 49

Characteristics	**Experimental group**		**Control group**		**p-value**
	Freq	**%**	**Freq**	**%**	
Primary tumor site					
Oral cavity	37	72.5%	37	75.5%	0.792
Larynx	6	11.8%	6	12.2%	
Nasal cavity/paranasal sinus	7	13.7%	6	12.2%	
Unknown primary	1	2.0%	0	0.0%	
Histology					
Squamous cell carcinoma (well & moderately differentiated	46	90.2%	48	98.0%	0.104
Adeno-carcinoma (Moderately differentiated)	2	3.9%	0	0.0%	
Undifferentiated/Poorly differentiated carcinoma SSC	0	0.0%	1	2.0%	
Any other	3	5.9%	0	0.0%	
Tumor staging					
TX	1	2.0%	1	2.0%	0.829
T1	5	9.8%	9	18.4%	
T2	23	45.1%	20	40.8%	
T3	9	17.6%	9	18.4%	
T4	13	25.5%	10	20.4%	
Nodal staging					
N0	18	35.3%	17	34.7%	0.365
N1	25	49.0%	19	38.8%	
N2	8	15.7%	13	26.5%	
Metastasis					
Mo	51	100%	49	100%	
Radiation therapy dose					
58 Gy	8	15.7%	8	16.3%	0.909
60 Gy	27	52.9%	24	49.0%	
62/62.5 Gy	2	3.9%	5	10.2%	
64 Gy	1	2.0%	1	2.0%	
66 Gy	11	21.6%	9	18.4%	
70 Gy	2	3.9%	2	4.1%	
Total period of RT					
36-40 (5.1-5.7 weeks)	5	9.8%	5	10.2%	
41-45 (5.8-6.4 weeks)	29	56.9%	28	57.1%	
46-50 (6.5-7.1 weeks)	13	25.5%	14	28.6%	
51-55 (7.2-7.8 weeks)	4	7.8%	2	4.1%	
Concomitant Chemotherapy					0.695
No	25	49.0%	26	53.1%	
Yes	26	51.0%	23	46.9%	
Previous surgery: Yes	40	78.4%	36	73.5%	0.642
No	11	21.6%	13	26.5%	

The baseline characteristics of patients, nature of tumours, and treatments are summarized in Table 1. These characteristics did not differ significantly between the two groups

Table-1I: Comparison of Onset of occurrence of RIM

N=51, 49

Group	N	Mean	SD	z	df	p-value
Experimental	51	17.5	2.1	1.70	98	0.043
Control	49	16.8	2.0			

The occurrence of onset of RIM in the experimental group is significantly later as compared to the control group since the difference is statistically significant (P<0.05).

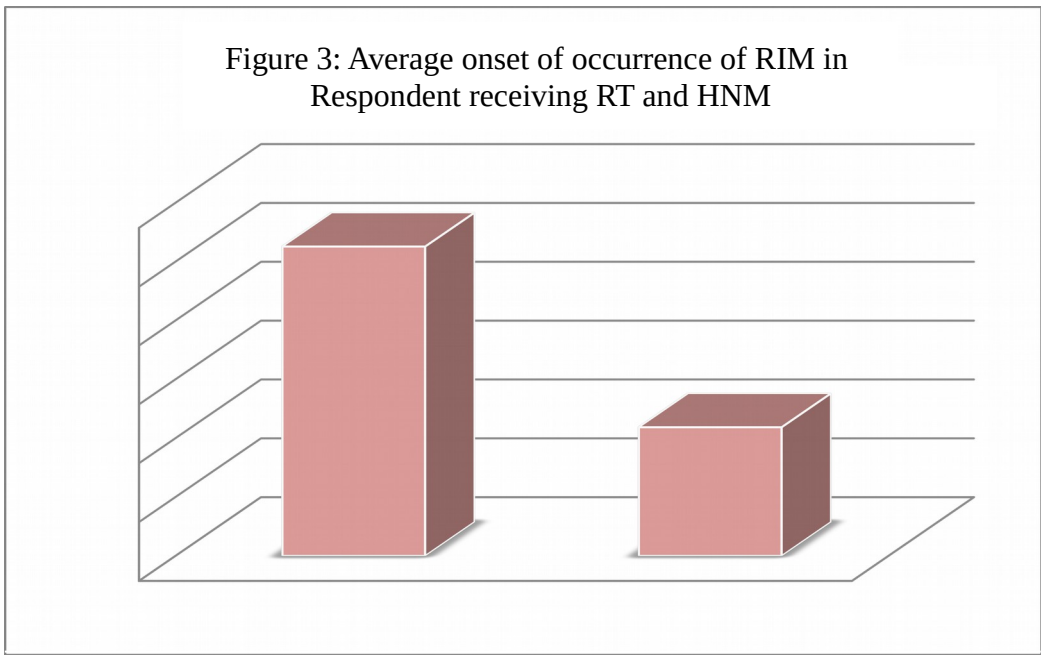
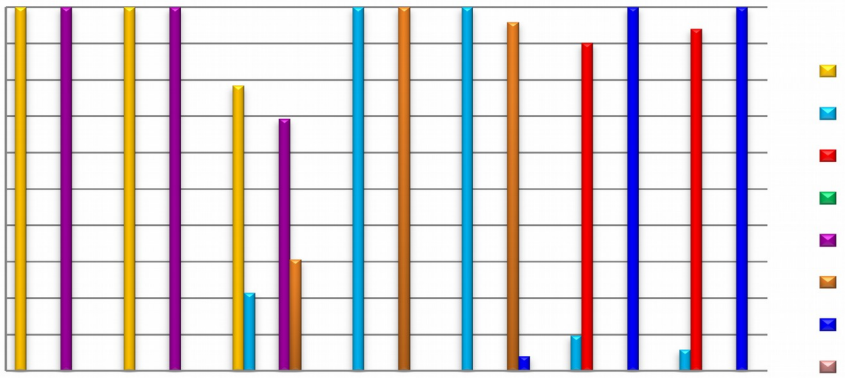


Table II: Comparison of assessment of severity of RIM using the primary and secondary criteria

Variable		Experimental		Control		p-value
		Freq	%	Freq	%	
Primary Criteria						
RIM grades (Last day of RT)	0	0	0.0%	0	0.0%	
	1	4	7.8%	0	0.0%	
	2	33	64.7%	10	20.4%	0.000
	3	14	27.5%	38	77.6%	
	4	0	0.0%	1	2.0%	
Oral pain	Mild	3	5.9%	0	0.0%	
	Moderate	48	94.1%	49	100.0 %	0.243
	Severe	0	0.0%	0	0.0%	
Secondary Criteria						
Admission to the hospital	Yes	1	2.0%	3	6.1%	0.675
	No	50	98.0%	46	93.9%	
Analgesic requirement	No	51	100%	49	100.0 %	-
Day Antifungal started	Mean	31.5		29.4		0.000
	SD	2.35		1.7		
Day Anesthetic & Antacid started	Mean	17.45		16.83		0.043
	SD	2.05		1.95		
Day Antibiotic started	Mean	30.8		29.04		0.000
	SD	1.86		1.36		
Nutritional support	Yes	1	2.0%	3	6.1%	0.675
	No	50	98.0%	46	93.9%	
Interruption of RT		0	0.0%	0	0.0%	-
Weight loss During RT (Upto)	4 kg	48	94.1%	27	55.1%	0.000
	4-6 kg	3	5.9%	20	40.8%	
	6-8 kg	0	0.0%	2	4.1%	
Quality of life (OMWQ)	Mean	43.0		47.7		0.000
	SD	4.4		3.2		
Quality of life (FACT-HN)	Mean	31.9		41.2		0.001
	SD	9.9		16.5		

Figure 4: Oral Pain In Experimental And Control Group



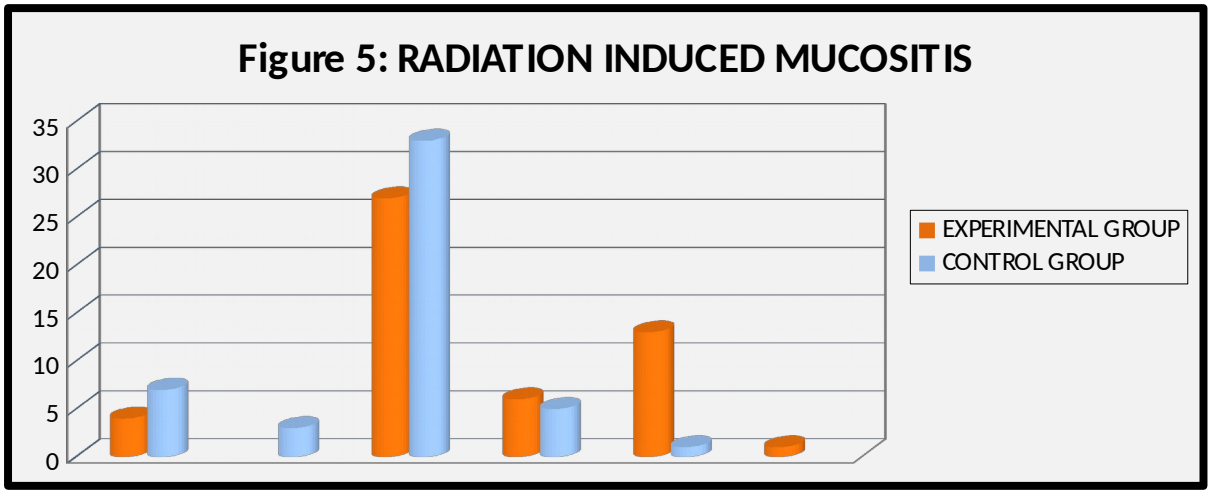


Figure 6: Average Weight Loss in Experimental And Control Group

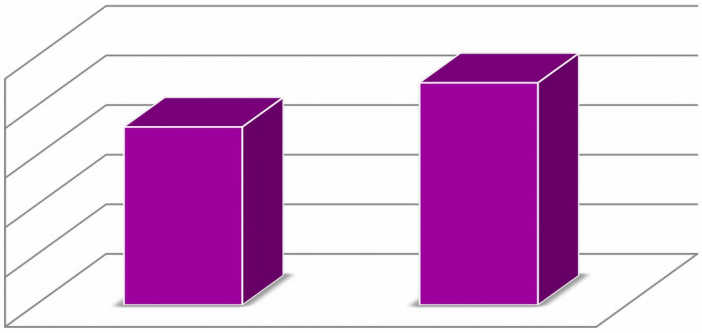
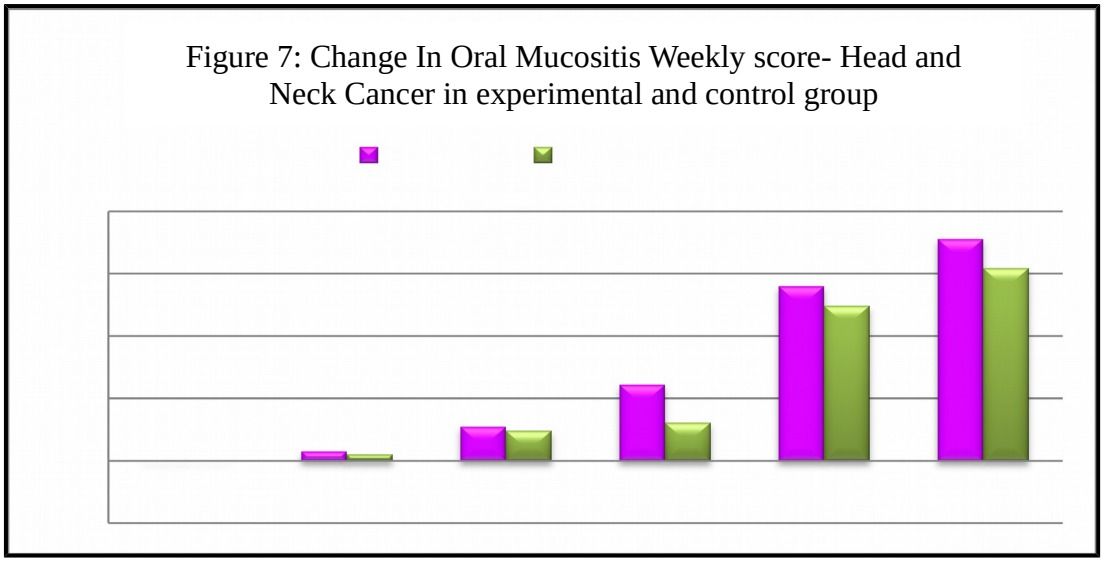


Figure 7: Change In Oral Mucositis Weekly score- Head and Neck Cancer in experimental and control group



The results of the study revealed a favorable inclination towards the experimental group than the control group, as the groups were statistically ($P<0.05$) 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 statistically ($P<0.05$) reduced and delayed need of supportive drugs, reduced weight loss, reduced need of RT-feedings; as well as better scores on OMWQ-HN and FACT-HN. The need for hospitalization and nutritional support was same in the two groups ($P>0.05$).

The two groups were not significantly different in biographical, tumor characteristics and treatment aspects, which imply that the groups were similar at the baseline for comparison. At the onset time to RIM, there was a significant difference between the two groups, that is the experimental group developed RIM later than the control group, but there was statistically significant difference in the outcome criteria; the experimental group had lower mean severity scores than the control group. Significantly lower mean severity scores of RIM supported the notion that aloe-vera has healing potentials[1-4] and thus had superior preventive and relief effect on this symptom compared to base gel application.

CONCLUSION:

Aloe-vera gel was safe, well tolerated and effective in delaying the intensity of progressive RIM during the course of the respondents' therapeutic-RT.

IMPLICATIONS

Aloe-vera is readily accessible and of relatively low cost and must be considered as a good alternative agent for treating RIM during RT.

RECOMMENDATIONS

Aloe-vera should be included in the management of RIM during the course of the respondents therapeutic- RT in patients with HNM.

The authors claim no conflict of interest.

REFERENCES:

1. Puataweepong P, Dhanachai M, et al. The efficacy of oral Aloe-vera juice for RIM in HNM patients:a double-blind-study. Asian Biomed 2009;3:375-382. www.advbiores.net/article.asp?issn=2277-9175;year=2015.
2. Su CK, Mehta V, et al. Phase-II double-blind randomized-study comparing oral Aloe-vera versus placebo to prevent radiation-related-mucositis in patients with HNM.Int.J.Radiat.Oncol.Biol.Phys.2010;60:171-177. *www.ncbi.nlm.nih.gov/pubmed/15337553*
3. Ahmadi A. Potential prevention-Review: Aloe-vera-mouthwash may reduce radiation-induced-oral-mucositis in HNM patients. Chinese-Journal-of-Integrative-Medicine,2012,Volume:18,Page635. http://link.springer.com/article/10.1007%2Fs11655-012-1183.
4. Takiar R, Nadayil D, Nandkumar A, Asian Pac J Cancer Prev. 2010.11(4):1045-9. Projection of number of cancer cases in India (2010-2020) by Cancer Groups. Available from: http:/www.ncbi.nlm.gov/pubmed/21133622
5. Ferlay J. Soerjomatram I. Ervik M. dikshit R. et al.GLOBOCAN 2012 v1.0. Cancer Incidence and mortality worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer 2013. Available from: http://globocan.iarc.fr/Default.aspx
6. Ramesh C. Department of Epidemiology and Biostatistic. Kidwai memorial Institute of Oncology. Available from: http://www.kidwai.kar.nic.in/statistics.htm

7. Kulkarni MR. (2013). Head and Neck Cancer burden in India, Jaypee Journals: 4/1:29-35. Available from: DOI : 10.5005/jp-journals-10001-1132 | FREE
8. Boyle P, Sullivan R, Zielinski C and Brawley OW. (Eds). State of Oncology 2013. iPRI, Lyon, France (2013). Available from: http://www.i-pri.org/oncology2013/
9. Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, et al. (2012) Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. CA Cancer J Clin 62: 400–422. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22972543
10. Epstein, J.B. and M.M. Schubert, Oropharyngeal mucositis in cancer therapy. Review of pathogenesis, diagnosis, and management. Oncology (Williston Park), 2003. 17(12): p. 1767-79; discussion 1779-82, 1791-2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14723014
11. Lalla RV, Sonis ST, Peterson DE. Management of Oral Mucositis in Patients with Cancer. Dental clinics of North America. 2008; 52(1):61-viii. Available from: doi:10.1016/j.cden.2007.10.002.Am, 2008. 52(1): p. 61-77, viii.
12. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, et al. (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiation therapy with or without chemotherapy: a systematic literature review. Radiother Oncol 66: 253-62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12742264.
13. Aishan S, Miaskowski C, Dodd, M J, Stotts, NA, MacPhail. Mechanisms for Radiation-Induced Oral Mucositis and the Consequences. Cancer Nurs. 2003;26(3) Available from:http://www.medscape.com/viewarticle/456818_8
14. Davies AN, Epstein JB (2010) Oral complications of Cancer and its Management. 1st edition. Oxford, UK: Oxford University Press. pp. 35-42.
15. Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, et al. (2010) Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 8: CD001973. Available from: www.ncbi.nlm.nih.gov/pubmed/20687070
16. Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, et al. (2011) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 4: CD000978. Available from: www.ncbi.nlm.nih.gov/pubmed/21491378.

17. Lalla RV (2013) The MASCC/ISOO Mucositis Guidelines Update: introduction to the first set of articles. Support Care Cancer 21: 301–302 Available from: www.ncbi.nlm.nih.gov › NCBI › Literature › PubMed Central (PMC) List.
18. National Cancer Institute. Radiation therapy for cancer. (2010)
19. Bhide SA, Gulliford S, Fowler J, Rosenfelder N, Newbold K, Harrington KJ, Nutting CM. Characteristics of response of oral and pharyngeal mucosa in patients receiving chemo-IMRT for head and neck cancer using hypofractionated accelerated radiotherapy. Radiother Oncol 2010; 97(1): 86-91. Available from: www.ncbi.nlm.nih.gov/pubmed/20826031
20. Baujat B, Bourhis J, Blanchard P, Overgaard J, Ang KK, Saunders M, Le Maître A, Bernier J, Horiot JC, Maillard E, Pajak TF, Poulsen MG, Bourredjem A, wet al ; MARCH Collaborative Group. Hyperfractionated or accelerated radiotherapy for head and neck cancer. Cochrane Database Syst Rev 2010; (12):CD002026.
21. Saadeh, C.E., Chemotherapy- and radiotherapy-induced oral mucositis: review of preventive strategies and treatment. Pharmacotherapy, 2005. 25(4): p. 540-54. Available from: www.ncbi.nlm.nih.gov/pubmed?db=pubmed&cmd=link...uid...
22. Weissman DE, Janjan N, Byhardt RW. Assessment of pain during head and neck irradiation. J Pain Symptom Manage. 1989; 4(2):90–95. Available from: http://jncimono.oxfordjournals.org/content/2001/29/37.full.pdf.
23. Elting LS, Cooksley CD, Chambers MS, Garden AS (2007) Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 68: 1110–1120. Available from: http://www.redjournal.org/article/S0360-3016%2807%2900247-7/abstract.
24. Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, Bhasker S, Tatsuzaki H, Grau C. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. Lancet Oncol 2010; 11(6): 553-560. Available from: www.ncbi.nlm.nih.gov/pubmed/20382075
25. Rosenthal DI (2007) Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes. J Support Oncol 5(9 Suppl 4)23–31 Available from: http://jco.ascopubs.org/content/29/20/2815.
26. Lambertz CK, Gruell J, Robenstein V, Mueller-Funaiole V, Cummings K, et al. (2010) NO SToPS: Reducing treatment breaks during chemoradiation for head and neck cancer. Clin J Oncol Nurs 14: 585–593 Available from: www.ncbi.nlm.nih.gov/pubmed/20880816

27. Parulekar W1, Mackenzie R, Bjarnason G, Jordan RC. Scoring oral mucositis. Oral Oncol. 1998 Jan;34(1):63-71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9659522
28. Gussgard AM, Jokstad A, Wood R, Hope AJ, Tenenbaum H (2015) Symptoms Reported by Head and Neck Cancer Patients during Radiotherapy and Association with Mucosal Ulceration Site and Size: An Observational Study. PLoS ONE 10(6): e0129001. doi:10.1371/journal.pone.0129001
29. López-Castaño F, Oñate-Sánchez RE, Roldán-Chicano R, Cabrerizo-Merino MC. Measurement of secondary mucositis to oncohematologic treatment by means of different scale. Review. Med Oral Patol Oral Cir Bucal. 2005 Nov-Dec;10(5):412-21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16264
30. Browman GP, Levine MN, Hodson DI, Sathya J, Russell R, Skingley P, Cripps C, Eapen L, Girard A. The Head and Neck Radiotherapy Questionnaire: a morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. J Clin Oncol 1993; 11(5): 863-872. Available from: ww.ncbi.nlm.nih.gov/pubmed/8487051
31. Grundmann O. Aloe vera gel research review- an overview of its clinical and proposed mechanism of action. Natural medicine journal. 2012.Vol4 (9). Available from: http://naturalmedicinejournal.com/journal/2012-0.
32. Mansourian A, Momen-Heravi F, Saheb-Jamee M, Esfehani M, Khalilzadeh O, Momen-Beitollahi J. Comparison of Aloe vera mouthwash with triamcinolone acetonide 0.1% on oral lichen planus: a randomized double-blinded clinical trial. Am J Med Sci 2011 ;342 :447-451. Available from: www.ncbi.nlm.nih.gov/pubmed?cmd=Link&LinkName=pubmed...