A RANDOMIZED CONTROLLED TRIAL ASSESSING THE EFFICACY OF HONEY PLUS ALOE VERA IN ALLEVIATING PAIN FROM RADIATION-INDUCED MUCOSITIS IN HEAD AND NECK CANCER PATIENTS

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ABSTRACT

OBJECTIVES: To assess the efficacy of Honey Plus Aloe Vera in Alleviating Pain from Radiation-Induced Mucositis in Head and Neck Cancer Patients.

MATERIALS AND METHODS: The proposed study was a randomized control trial, which was mainly conducted in collaboration with the *Radiation Oncology Department* at the Jinnah Postgraduate Centre (JPMC) in Karachi and the Pharmacology Department of the Basic Medical Sciences Institute. The study targeted patients that were referred to Radiation Oncology Department JPMC, Karachi for the management of HNC during July 2021 to December 2021. The Institutional Review Board (IRB) of the Basic Medical Science Institute, JPMC Karachi, approved the study. A randomized controlled trial on 80 subjects (40 in test group referred to as HA group and 40 in control group) was undertaken to study the analgesic effect of honey plus aloe vera in combination as better alternate of magic mouthwash in reduction occurrence and severity of pain in patients of HNC developing radiation-induced mucositis. The control group patients were advised to do gargles with magic mouthwash three times a day and test group patients gargled 20 ml honey plus aloe vera solution thrice a day during the entire course of radiation treatment. Patients were examined at baseline i.e. commencement of chemotherapy and/or radiotherapy (mentioned as 0 week) and then after every 15 days i.e., 2, 4 and 6 week to check the severity of the pain using Numeric Pain Intensity Scale and change in weight of patient. Using different statistical methods/tests for analysis of data, the results were analyzed. *p-value* < 0.05 was taken as significant.

RESULTS: The study revealed that on Pain Intensity Scale, 17 (42.5%) patients in Control Group were in extreme pain at week 6 against 6 (15%) in HA Group. The results were statistically significant (p value 0.040). The loss of weight was also remarkably lesser in HA Group than Control Group patients.

CONCLUSION: The study concluded that solution of honey plus aloe vera being a cheap, palatable, and natural medicament can be used for decreasing pain associated with radiation-induced mucositis in cancer patients as well as maintaining of the weight during treatment.

KEYWORDS: Cancer, Radiation, Honey, Aloe vera, Pain

INTRODUCTION

Head & Neck cancer especially oral cancer is one of the most challenging health issue faced by the mankind today due to cultural, ethnic factors and the addictive habits. Oral cancer ranks in top three of all cancer deaths in Pakistan[1]. The common oral complications occurred during treatment of such cancer include the oral mucositis. Oral mucositis is a severely painful condition characterized by erythema, edema and ulcerations of the oral mucosa. This complication occurs as a result of radiation therapy (RT) to the head and neck, chemotherapy, chemo radiotherapy, and hematopoietic stem cell transplantation (HSCT). Oral intake may be compromised due to pain, which in some cases may lead to the need for parenteral nutrition. In addition, the oral lesions affect the mucosa barrier thus causing local or systemic infection. In case of severe pain, the subsequent treatment may be delayed. Additionally, this affects patients' quality of life and worsening prognosis[2].

There are generic drugs and mouthwashes (usually referred to as Magic Mouthwash) available to treat oral mucositis and especially the pain but these commercially manufactured products are often expensive and have their adverse effects. Magic mouthwash has no fixed proportion or formula, but it usually contains at least three of the basic ingredients like Antihistamine or Anticholinergic agent, Anesthetic to relieve pain and uneasiness, Antacid to coat other ingredients in mouth, Antifungal to decrease growth of fungus, Corticosteroid to reduce inflammation, and Antibiotic to fight against bacteria[3].

Natural products are commonly and frequently used in poor class of society for treatment of pain due to OM as self-made remedies as an effort to ensure uninterrupted chemotherapy and/or radiotherapy. Honey plus aloe vera are two such natural products, which are used individually for such purpose. Honey has anti-bacterial and anti-fungal properties and has soothing effect. It is widely used as an effective remedy against oral health issues[4]. Aloe vera is a medicinal plant with antioxidant and antibacterial properties. Aloe vera benefits can include reducing dental plaque, accelerating wound healing, treat canker sores, reduces constipation, improve skin and prevent wrinkle, and it lowers blood sugar levels[5].

Radiation-induced mucositis and associated pain are the major and most important causes of morbidity and treatment gaps during the standard management. Pain imparts additional morbidity and economic burden to patients in the form of requiring parenteral analgesia, interruption of radiation therapy (RT) and/or hospitalization, parenteral or tube feeding, all of which have a negative impact on quality of life.

There are various drugs tried for prevention and treatment of pain, but none have achieved satisfactory level. Topical application of honey plus aloe vera to the oral cavity and pharynx results in reduction of pain to significantly low levels resulting in lesser analgesic use, treatment gaps and weight loss hence overall improving their compliance and tolerability toward radiation

schedule. This has helped in completing the radiation treatment protocol within stipulated time period, hence causing the maximum possible effect achieved by RT on the tumor[6].

Prophylaxis and management of radiation-induced mucositis by honey plus aloe vera has been studied in past in phase-II randomized controlled trials, and it has shown encouraging results[7]. This study attempts to evaluate the effect of honey plus aloe vera on pain due to radiation induced mucositis in our set up.

MATERIALS AND METHODS

Study design

This prospective, randomized open label controlled trial was undertaken in a tertiary care hospital "Radiation Oncology Department, Jinnah Post Graduate Medical Centre (JPMC) Karachi" setup to study the analgesic effect of honey plus aloe vera in locally advanced head and neck cancer (HNC) patients receiving the concomitant chemo radiation. An open label design was chosen because participants (patients) were necessarily aware of the treatment given and group assigned. The Institutional Review Board (IRB) of the Basic Medical Science Institute, JPMC, Karachi approved the study and informed consent was obtained from all participants.

Study population

Study population comprises of HNC patients attending Radiation Oncology Clinic from July 2021 to December 2021.

Sample size, enrolment, and study procedures

The study was designed and powered to detect the difference in reduction of pain score by using solution of honey plus aloe vera. Taking previous studies into consideration, the desired sample size comes out to be 40 in each arm. Keeping in view the drop outs and consent of the patients, patients were recruited for the study during first 4 months of the study.

Inclusion and exclusion criteria

The eligible patients included in study were 20-65 years of age, histologically proved patients of HNC and receiving 60-70 Gy radiation (5 days a week for 6 weeks). Those found not eligible or were suffering from any systemic disease were excluded.

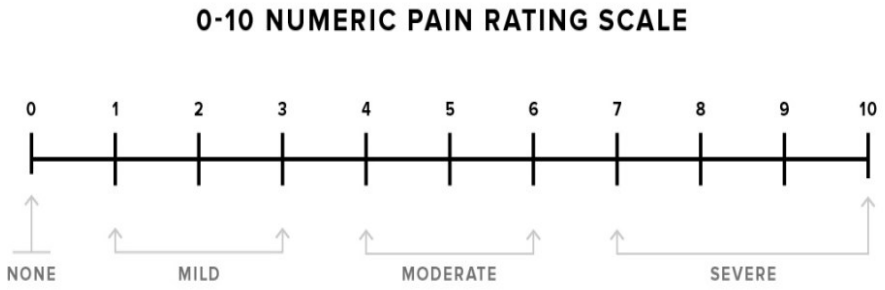
The solution of honey plus aloe vera was prepared as per guidelines regarding contents by the Hamdard University, Karachi. The solution prepared was sent to Pakistan Council of Scientific & Industrial Research Laboratories Complex, Karachi for its Acute Oral Toxicity Test and no signs of toxicity and mortality found during observation period. M/S Kausar Medicos, Karachi, prepared magic mouthwash. The standard recipe used in Radiation Oncology Department, JPMC

Karachi, which contains Nystatin, Xylocaine, Decadron, Gravinate, and Mucaine was followed during preparation of Magic Mouthwash.

With the commencement of radiotherapy, the patients in the HA Group were instructed to apply a 20 ml (two tablespoon) of a specially made honey plus aloe vera solution three times a day. Patients had to apply the solution 15 minutes before and 15 minutes after radiation therapy on treatment days, as well as before going to bed. This course of treatment was to be continued for the six weeks. The patients were instructed to hold the solution for three to five minutes before spitting it out. Patients in Control Group were suggested to use 5 ml (one teaspoon) of magic mouthwash three times a day at the same frequency as above. The patients of this group were also asked to hold the solution for 3-5 minutes and then spit out[8].

Assessment

Intensity of pain was evaluated using Numeric Pain Intensity Scale, whereas weight is recorded using digital weighing scale.



OBSERVATIONS AND RESULTS

The demographic distribution of data reveals that the study population comprises of 30 (75%) males and 10 (25%) females in HA Group whereas in Control Group, there were 32(80%) males and 8(20%) females. The mean age in HA Group is 49.88 ± 11.59 years while that in Control Group is 48.63 ± 10.19 years. The majority of patients in both groups were Urdu speaking (around 50%).

Variable	Group				Chi. Sq. Value	P-Value
	HA (n=40)		Control (n=40)			
	f	%	f	%		
Gender						
Male	30	75	32	80	0.2867	0.592
Female	10	25	8	20		

Variable	Group	n	Mean	SD	Total	t-value	p-value
Age (Years)	Control	40	48.630	10.19	80	0.512	0.610
	HA	40	49.880	11.59			

Majority of patients in both groups were found in habit of chewing pan or smoking or both. The data collected as far as Tumor site is concerned shows that there is an even distribution in both groups, majority of patients are suffering from tumor in Buccal mucosa region 35% in HA group and 37.5%in control group, followed by Alveolar mucosa region 25% in HA group and 20% in control group.

Habits	Group				Chi. Sq. Value	P-Value
	HA (n=40)		Control (n=40)			
	f	%	f	%		
Smoking	8	20	10	25	3.164	0.675
Pan	12	30	7	17.5		
Betelnut	5	12.5	4	10		
Naswar	2	5	1	2.5		
Gutka	3	7.5	6	15		
Smoking+Pan	10	25	12	30		

VARIABLE	Group				Chi.Sq.Value	P-Value
	HA (n=40)		Control (n=40)			
	f	%	f	%		
Tumorsite						
Lips	3	7.5	2	5	1.301	0.995
Buccal Mucosa	14	35	15	37.5		
Alveolar Mucosa	10	25	8	20		
Tongue	2	5	3	7.5		
Palate	5	12.5	4	10		
Floor of mouth	2	5	3	7.5		
Nasopharynx	1	2.5	2	5		
Oropharynx	2	5	2	5		
Larynx	1	2.5	1	2.5		

RESULTS OF NUMERIC PAIN INTENSITY SCALE:

Out of 80 patients, none was in pain at baseline in both arms of the present study. At week 2, mild pain started in the patients but all of them remained in mild category (pain scale 0 to 3). In Control Group, 21 (52.5%) patients were in clinically noticeable pain of scale 2 and 3, whereas in HA Group, 11 (27.5%) patients were noticed in scale 2 and 3. At week 4, the pain started to develop in moderate and extreme categories. In Control Group, 26 (65%) patients were in moderate category pain (pain scale 4 to 6) and 10 (25%) patients were in extreme category pain. In comparison, 30 (75%) patients of HA Group were in moderate category pain and 4(10%) in extreme category pain. The results were found statistically significant at week 2 with p value 0.043. At week 6, patients were found in extreme pain in Control Group with few of HA Group also developed extreme pain. In Control Group, 17 (42.5%) patients were in extreme pain at week 6 and in HA Group 6 (15%) patients were in extreme category. The results however were found to be statistically significant too at p value 0.040.

	Control Group				HA Group			
		Week 2	Week 4	Week 6		Week 2	Week 4	Week 6
MILD	Pain 0	8	0	0	Pain 0	12	0	0
	Pain 1	11	0	0	Pain 1	17	0	0
	Pain 2	14	1	0	Pain 2	8	2	0
	Pain 3	7	3	3	Pain 3	3	4	4
MODERATE	Pain 4	0	8	7	Pain 4	0	11	8
	Pain 5	0	4	5	Pain 5	0	9	12
	Pain 6	0	14	8	Pain 6	0	10	10
EXTREME	Pain 7	0	7	12	Pain 7	0	4	5
	Pain 8	0	3	2	Pain 8	0	0	1
	Pain 9	0	0	3	Pain 9	0	0	0
	Pain 10	0	0	0	Pain10	0	0	0

Follow-up duration	Group	n	Mean	S.D.	t-value	p-value
Week- 0 NPS	Control	40	0	0		
	HA		0	0		
Week -2 NPS	Control		1.5	1.0127	2.0961	0.0426
	HA		1.05	0.9044		
Week- 4 NPS	Control		5.5	1.5021	2.1225	0.0402
	HA		4.825	1.3376		
Week -6 NPS	Control		5.925	1.6546	2.2817	0.028
	HA		5.175	1.2586		

RESULTS OF CHANGE IN WEIGHT:

All 80 patients included in this study group were weighed at the baseline week 0 and the values were recorded. The change in weight was also calculated at regular intervals i.e., at week 2, 4

and 6. The data revealed that the mean weight in Control Group patients was 65.332 Kg at week 0 and in HA Group; the mean weight was 66.635 Kg.

Variable	Group	n	Mean	SD	Total	t-value	p-value
Weight (Kg)	Control	40	65.333	10.93	80	0.487	0.629
	HA	40	66.635	12.90			

At the end of treatment at week 6, mean weight of Control Group was recorded at 60.745 Kg and in HA Group, the patients lost comparatively lesser weight and mean weight remained 66.110 Kg. The results were found statistically significant at p value 0.043 (<0.05).

Follow-up Duration (Weeks)	Group	n	Mean	S.D.	t-value	p-value
Week-0 Weight (Kg)	Control	40	65.332	10.934	0.487	0.629
	HA		66.635	12.896		
Week-6 Weight (Kg)	Control		60.745	9.946	2.088	0.043
	HA		66.110	12.855		

DISCUSSION

The present study focused on the efficacy of honey plus aloe vera solution in the treatment of chemotherapy and radiotherapy induced pain and weight loss after the development of OM in HNC patients and its comparison with magic mouthwash, which is a standard treatment in such cases. Mucositis associated pain is the most disturbing symptom that affects their oral intake and tolerability to complete the RT schedule and reducing the local control and survival. Based on the evidence reported in this study, honey plus aloe vera solution has a positive effect regarding occurrence and severity of pain and weight loss caused due to OM.

In the current trial, honey plus aloe vera showed promising effects on pain intensity; after week 6 in the control group, 17 (37.5%) of patients were scoring 7 or higher on the Numeric Pain Scale, but only 6(15%) of patients using honey plus aloe vera experienced severe pain. As a result, the current study can be compared to and is consistent with the earlier study where effectiveness of topical application of honey was assessed for reduction in pain[9].

During another study, it was observed that aloe vera mouthwash produced complete pain remission of mucositis. During present study it was also noticed that honey plus aloe vera group patients experienced less intensity of pain as compared to control group[10].

The data of the present study revealed that the mean weight in Control Group and HA Group was 65.332 Kg and 66.635 Kg respectively at week 0. At the end of treatment at week 6, mean weight of Control Group was recorded at 60.745 Kg and in HA Group, the patients lost comparatively lesser weight and mean weight remained 66.110 Kg. The results were found statistically significant at p value 0.043 (<0.05). These results are in consistency with the meta-analysis conducted with 412 patients who were treated with honey for OM with positive impacts[11].

It is pertinent to mention that during the present study, neither any complication was reported in administration of honey plus aloe vera solution nor was any intolerance experienced from any patient.

CONCLUSION

Honey plus aloe vera is effective in reducing pain associated with radiation-induced mucositis. Being a cheap, palatable, and easily available product it can be used for decreasing mucositis associated pain in HNC patients receiving the concomitant chemo radiation.

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