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RESEARCH ARTICLE

Effect of application of honey on oral mucositis : Randomized Clinical trial

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Abstract

Back Ground and objective: The main stream of management of head and neck cancer is by radiotherapy and surgery. During radiation therapy in head and neck cancers oral cavity is directly exposed to high dose radiation which will lead to several side effects, oral mucositis being the most distressing one. This study intended to assess the effect of application of honey on oral mucositis. **Material and Methods:** The research design used in this study was Randomized Control Trial with single blinding method in radiotherapy unit of Regional Cancer Centre (RCC), JIPMER. The study population included total of 28 patients Participants in experimental group were given 15 ml natural honey for applying on oral mucosa and in control group 15ml plain water were given. Assessment of oral mucosa was done after every 5 doses of radiation therapy using RTOG scale and severity of oral mucositis was assessed. **Results**: There was a statistically significant difference in degree of oral mucositis between the experimental and control group in week 4, 5 and 6.($p<0.01$). During the whole course of study, 9(64.28%) participants in control group developed grade III oral mucositis while only one participant (7.14%) in experimental group developed grade III oral mucositis.. **Conclusion**: The study concluded that natural honey was effective for oral mucositis among patients receiving external beam radiation therapy for head and neck cancers.

INTRODUCTION

Chemotherapy and radiotherapy are extensively used for treatment of cancer for cure, control and palliation. During radiation therapy oral cavity is directly exposed to high dose radiation which will lead to several side effects, oral mucositis being the most distressing one. Chemotherapy and radiotherapy preferentially act on rapidly dividing cells which may include tumor cells as well as basal cells of mucosal lining.[1-2] Due to this effect it slows down the formation of new cells instead of damaged tissue for repair. Thus the time for repair is prolonged. Radiation therapy causes direct exposure of tissues of oral cavity, salivary glands and bones to ionizing radiation causing direct damage to them. The type of cancer and the modality used for treatment affects the occurrence and severity of oral mucositis. Brown et al[3] reported that 400,000 people develop oral complications from cancer therapy each year. Epstein et al[4] found that 30%–75% of chemotherapy patients experienced oral mucositis while 100% of patients receiving head and neck radiotherapy (of doses greater than 5,000 cGy) and 90% of patients receiving stem cell transplants develop oral mucositis. Trotti et al[5] studied over 6000 people with SCCHN who received

radiotherapy with or without chemotherapy and found out that 80% of cases developed OM with 39% having grade 3 & 4 OM.

Poorly managed oral mucositis frequently lead to unplanned treatment interruptions. Thus the total time for treatment is thus prolonged. When the treatment time is prolonged, the probability of control of tumor growth by particular therapy is reduced. Moreover the total cost of treatment increases when the total duration of treatment is prolonged. Various agents were used on experimental basis to reduce oral mucositis but a single efficacious agent has not yet been identified.[6-7] In current practice there is no standard care for oral mucositis. Common oral gargling agents used by physicians include chlorhexidine mouth washes. Chlorhexidine mouthwashes itself will cause severe pain while gargling due to irritation caused by it. Narcotic analgesics are prescribed to control pain. If the clients develop grade 3 mucositis further, the radiotherapy will be stopped and restarted once the mucositis subsides.

Honey has been traditionally used as an anti-inflammatory as well as wound healing agent. Honey is highly concentrated and hence bacteria cannot survive in. It is also well tolerated by patients and is cheap, easily available, non pharmacological measures with almost no side effects. Honey if proven effective can be an easily available cheap measure of preventing oral mucositis which patient themselves can apply. A good preventing agent for oral mucositis can be a great good thing towards the clients suffering from the most distressing effects of cancer. Although a few studies were conducted abroad to assess the effect of honey in oral mucositis there are very little studies conducted in India. Hence this study undertaken with the objective of to assess the effect of application of honey in prevention of oral mucositis among subjects undergoing external beam radiation therapy for head and neck cancers

Material and Methods:

Randomized Control Trial with single blinding method was conducted in radiotherapy unit of Regional Cancer Centre (RCC), of a tertiary care center. The study consisted of 14 subjects in each group with recently diagnosed squamous cell carcinoma of head and neck and planned to receive external beam radiation therapy (EBRT) using cobalt 60 machine alone or EBRT and concomitant chemotherapy with Inj. Cisplatin. All subjects received EBRT 200cGy per day once daily for 5 days a week, upto a total of 32 fractions, i.e. 6 – 7 weeks duration.

Sample size was calculated to be 34 with 80% power and α- 5% with an expected 45% difference in severity of mucositis based on previous study conducted by Beena K et al.[60] Estimated sample size was 17 subjects in each group. But since adequate subjects fulfilling criteria was not available during the study period, the investigator did an interim analysis with 52.5% difference observed at end of 6th week. The modified sample size was 14 in each group. **Inclusion criteria** included, patients newly diagnosed with squamous cell carcinoma of head and neck, age and general condition fit to receive radiation therapy and those who were willing to participate in study**. Exclusion criteria** was patients with pre-existing oral illness**,** recurrent or residual cancer patients, patients receiving corticosteroids**,** immune compromised client, patients who has known history of allergy to honey**,** patients with diabetes mellitus and patients receiving treatment other than standard protocol (i.e. with cisplatin) **Sampling:** Simple random sampling by using sealed envelope was used to allocate the subjects into experimental and control group. **Instruments:** Subject data sheet had a set of questions that was oriented to the demographic and clinical data of subjects. Oral mucositis assessment was done with RTOG (Radiation Therapy Oncology Group) scale. The RTOG scale is a standardized tool developed by radiation therapy oncology group for assessing the severity of oral mucositis. **Data collection procedure:** Data collection was started after getting ethical committee permission & permission from hospital authority. Informed consent was taken from study participants. Subject data sheet was filled by investigator. A pre assessment of oral mucosa was done to identify any pre-existing oral illness and to assess the level of oral hygiene. Participants in both groups were given three similar bottles each having 15ml of a solution in it. The solution provided to experimental group subjects contained 15ml of natural honey while control group subjects received 15ml of water. All subjects were asked to rinse mouth and slowly swallow the given solution thrice daily ie. 15mts before receiving radiation, 15 minutes after receiving radiation and 6 hours after the radiation therapy. The oral mucosa was assessed after every 5th dose to identify the development of mucositis and to find out its severity (using RTOG scale)**. Ethical considerations:**Research proposal was approved Institute Ethical Committee and Permission from hospital authority was obtained. Informed consent was taken from study participants. Assurance was given to the subjects that anonymity and confidentiality will be maintained.

Data analysis: The distribution of background variables was expressed as frequencies and percentage. The scores of various domains were expressed as mean with standard deviation. The homogeneity of group was confirmed using

chi- square. Distribution of mucositis score was expressed using frequency and percentage. Comparison of scoring of mucositis was done using Mann Whitney U test

Results:

- The mean age of participants in control group and experimental group was 52.28±14.04yrs and 59.71±10.34 respectively. BMI distribution of the study participants revealed that 50% of subjects in control group were underweight but 64.28% of subjects in experimental group had normal BMI. But the difference in BMI between the groups was not statistically significant. 42.86% of participants in control group and 50% of participants in experimental group were smokers at the time of diagnosis of disease. 50% of participants in control group and 64.29% of participants in experimental group were alcoholic at the time of diagnosis of disease and 64.29% of participants in both control and experimental group were chewers at the time of diagnosis of disease. But all participants stopped habits of smoking, alcoholism or tobacco chewing after diagnosis of disease. (Table 1)
- Frequency distribution of subjects according to location of tumor shows that seven participants in control group and six participants in experimental group had tumor of tongue. Three participants in control group and one participant in experimental group had tumor of buccal mucosa. In control group one participant each had tumor of soft palate, supraglottis, glottis & floor of mouth each. In experimental group two participants each had tumor of soft palate and supraglottis and one participant each had tumor of left lower alveolus, secondary lymph node and oropharynx.(figure 1)
- Distribution of participants according to stage of tumor shows that 71.43% of participants in experimental group and 64.28% of participants in control group had stage 4 tumor, 21.42% of participants each in both group had stage 3 tumor, 14.28% of participants in control group and 7.14% of participants in experimental group had stage 2 tumor & none of the participants who participated in the study had stage 1 tumor. (figure 2)
- Distribution of participants in experimental and control group according to treatment plan shows that 12 participants in the control group got external beam radiation therapy with concurrent chemotherapy using Inj. Cisplatin. In experimental group only 6 participants received concurrent chemotherapy with Inj. Cisplatin. Other participants in both groups received only external beam radiation therapy. (Table 2)
- There was a statistically significant reduction in the degree of oral mucositis especially in week four ($p<0.05$), Five and six ($p<0.01$). In control group eight (61.54%) subjects developed grade III oral mucositis. In experimental group only one (9.09%) subject developed grade III oral mucosits.

Table 1: Frequency and percentage distribution of background variables

N = 28

Variable	Control group f (%)	Experimental group f (%)	Chi square value
Age			$X^2 = 0.144$
<60	8(57.14)	7(50)	df = 1
>60	6(42.86)	7(50)	p = 0.70
BMI			
<18.5	7(50)	5(35.72)	X^2 =0.583
18.5 – 24.9	7(50)	9(64.28)	df = 1
			p = 0.492
H/osmoking			
yes	6(42.86)	7(50)	$X^2 = 0.144$
no	8(57.14)	7(50)	df = 1
			p = 0.705
H/o alcoholism			
yes	7(50)	9(64.29)	$X^2 = 0.583$
no	7(50)	5(35.71)	df = 1
			p = 0.445

H/o chewing			
yes	9(64.29)	9(64.29)	X^2 =0.000
no	5(35.71)	5(35.71)	df = 1
			p = 1.000

Table 2. Distribution of subjects according to treatment plan

N = 28

Treatment plan	Control group f (%)	Experimental group f (%)	Chi square value
RT only	2(14.29)	8(57.14)	X^2 = 5.6**
RT + Inj. Cisplatin	12(85.71)	6(42.86)	df = 1
			p = 0.048

*p<0.05, ** p<0.01, ***p<0.001

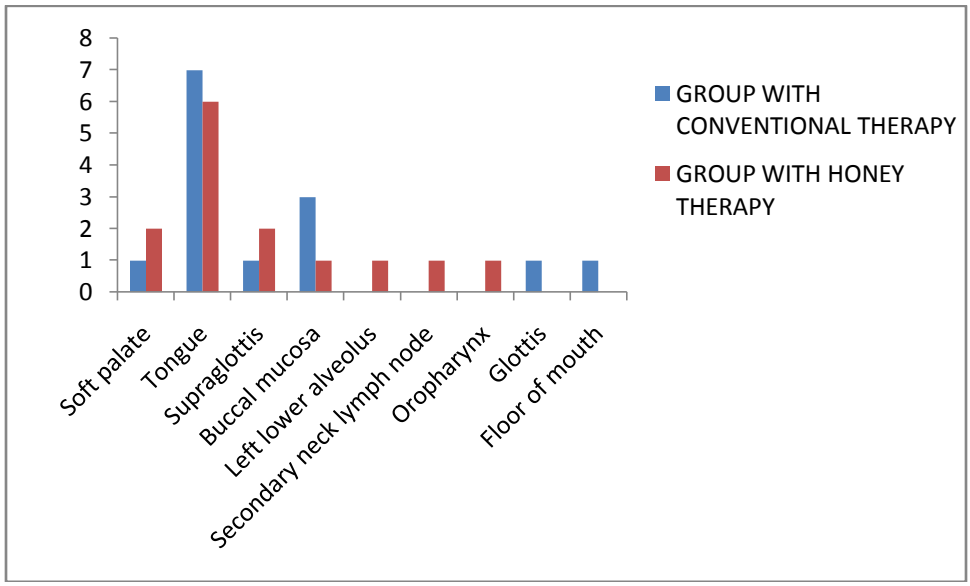

Figure 1. Frequency distribution of subjects according to location of tumor

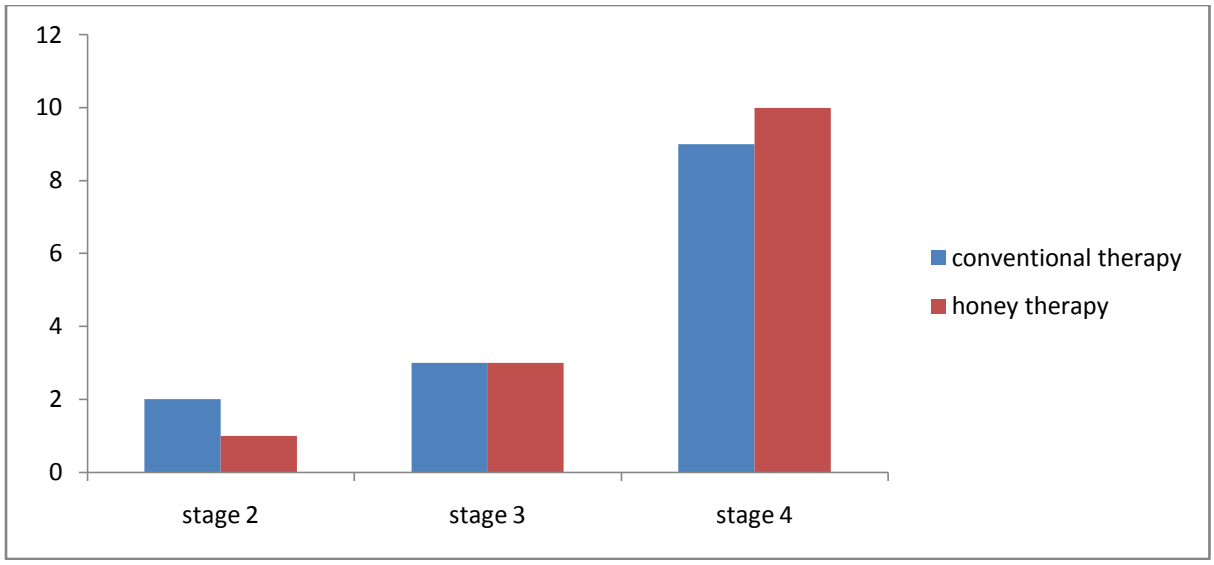

Figure 2. Distribution of subjects according to stage of tumor

Table 3. Distribution of severity of oral mucositis in each week

Time	Grade of mucositis	Control group		Experimental group		U value
		f	%	f	%	
Week 1	0	13	92.86	14	100	p= 0.769
	I	1	7.14	0	0	
	II	0	0	0	0	
	III	0	0	0	0	
	IV	0	0	0	0	
Week 2	0	3	21.43	4	30.7	p = 0.220
	I	6	42.86	8	7	
	II	5	35.71	1	61.5	
	III	0	0	0	4	
	IV	0	0	0	7.69	
Week 3	0	0	0	0	0	p = 0.118
	I	4	28.57	8	66.6	
	II	8	57.14	3	25	
	III	2	14.29	1	8.33	
	IV	0	0	0	0	
Week 4	0	0	0	0	0	p = 0.008
	I	1	7.69	4	36.3	
	II	4	30.77	6	54.5	
	III	8	61.54	1	9.09	

	IV	0	0	0	0	
Week 5	0	0	0	0	0	p =0.004
	I	0	0	5	45.4	
	II	4	50	6	54.5	
	III	4	50	0	0	
	IV	0	0	0	0	
Week 6	0	0	0	0	0	
	I	0	0	6	60	p= 0.003
	II	4	57.14	4	40	
	III	3	42.86	0	0	
	IV	0	0	0	0	

Discussion:

This study findings showed that there was a statistically significant reduction in the degree of oral mucositis particularly in week four ($p<0.05$), five and six ($p<0.01$). Grade III mucositis that was developed in the single subject of experimental group was found to be resolved to grade II oral mucositis by 5th week without using any other drugs.

In the first week of treatment, 7.14% of participants in control group developed grade I mucositis while no mucositis was developed in any participants in the experimental group. End of second week, 42.86% of participants in control group and 61.54% of participants in experimental group remained with grade I mucositis. 33.33% of participants in control group developed grade II oral mucositis compared to 7.69% in experimental group at end of second week. (Table 3)

By 3rd week all patients in both group developed oral mucosits. 14.29% participants in control group developed grade III mucositis in control group while only 8.33% of participants in experimental group developed grade III mucositis by the same time. 66.67% of participants in experimental group still had grade I mucositis while only 28.57% of participants in control group continued to have grade I oral mucositis by end of 3rd week. (Table 3)

By the end of 4th week 61.54% of participants in control group developed grade III oral mucositis compared to 9.09% in experimental group. 50% of participants in control group developed grade III mucositis by the end of 5th week. In experimental group none of the patients had grade III oral mucositis by 5th week. Grade III mucositis which was developed in only one participant in the experimental group itself was found to be reduced by the end of 5th week without using any other treatment. By the end of 6th week 42.86% of participants in control group had grade III oral mucositis while 60% of participants in experimental group still had only grade I oral mucositis ($p<0.01$). (Table 3)

Similar study conducted by Biswal et al to evaluate effect of application of honey in management of radiation induced mucosits, 20% of participants in experimental group developed grade III or grade IV mucositis compared to 75% of participants in control group.[8-9]

Yet another study by Rashad[10] on use of honey to prevent radio chemotherapy induced oral mucositis, none of the patients in the experimental group developed grade IV mucositis. Three patients in experimental group developed grade III mucositis. But 13 patients in control group developed grade III or grade IV mucosits. In this study only one subject in study arm developed grade III oral mucositis while 8 subjects in control group developed grade III mucositis. In control group therapeutic treatment interruptions was made in five patients to prevent progression into grade IV mucositis but no therapeutic interruption was reported in experimental group. None in the experimental group developed grade 4 OM.

A single blinded experimental study conducted by Motallabnejad et al[11] to evaluate the effect of honey on irrradiation mucositis found out that there were significant reduction in the degree of oral mucositis in experimental group compared with control group. In current study also there was a delay in onset of oral mucositis as well as a reduction in severity of mucositis in experimental group. 35.71% subjects in control group developed grade II oral mucositis by end of second week itself but only 7.69% subjects in experimental group had grade II oral mucositis by the same time. Majority of subjects in experimental group (54.54%) developed only grade II oral mucositis. Only one subject developed grade III OM compared to 8 subjects in control group. 60% of subjects in experimental group remained in grade I oral mucositis even at the end of 6th week while in control group all the subjects developed grade II or grade III oral mucositis at the end of 6th week.

In present study 21.42% of patients in control arm were hospitalized due to severe mucositis. In experimental group none of the patients were hospitalized due to severe mucositis. Therapeutic treatment interruptions was reported in 5 subjects in control group severe oral mucositis while none in experimental group had treatment interruptions. A study conducted by Trotti et al[5] also reported hospitalization 16% of patients who received radiotherapy due to severe mucositis. Unplanned break in treatment protocol was also reported in 11% of patients in the same study

Conclusion

The study concluded that natural honey was effective for oral mucositis among patients receiving external beam radiation therapy for head and neck cancers. Honey is cheaper compared to currently practiced/ recommended agents for oral mucositis. More over honey does not have any side effects and is better tolerated by most of the patients.

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