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Comparative Evaluation of Sucralfate and Honey in Oral Mucositis amongst Patients of Head and Neck Cancers Receiving Radiotherapy and Concurrent Chemotherapy

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I. INTRODUCTION

Head and neck cancer (HNC) is a term used to describe malignant tumours originating in the upper aerodigestive tract, including the oral cavity, larynx, pharynx and nasopharynx. Majority (90%) of cancers are squamous cell carcinomas arising from epithelial mucus membrane.[1] HNCs are among the ten most frequent cancers and are the sixth most common cancers worldwide. They constitute five percent of all cancers accounting for more than 550,000 cases annually.[2,3] Incidence rate is more than twice as high in males and is showing an increase in most parts of the world.[2,4]

Radiotherapy for HNC is typically given in daily fractions of 180cGy (centi-Gray) to 200cGy, five days a week to a total dose of 6000cGy to 7000cGy. However radiotherapy causes DNA damage to cells of surrounding critical structures, resulting in acute side effects such as skin reactions, oral mucositis (OM) and xerostomia which can severely affect a patient's nutritional status and quality of life (QOL). Concurrent chemo-radiotherapy is often used to improve loco-regional control, organ preservation and overall survival in patients with advanced disease but at the expense of increased toxicity (fibrosis and dysphagia leading to feeding tube dependency).[13-16]

Oral mucositis (OM) is a general term referring to inflammatory reactions and erosive, ulcerative lesions in the mouth and oropharynx due to damage to basal epithelial cells. Incidence of OM varies depending on modality of treatment used i.e, type, dose, intensity and schedule of radiotherapy, and chemotherapy regimen used.

Clinically OM develops within 10-14 days after start of radiotherapy, beginning at 15Gy, becomes full blown at 30Gy and may persist till 2-3 weeks after stopping treatment. Severe OM is associated with pain, erythema, ulcers and sores on oral mucosa (including gums, mouth or tongue), burning sensation in mouth, loss of taste, sensitivity to hot, cold or spicy food, difficulty in swallowing and talking owing to dryness of mouth and presence of ulcers, leading to impaired intake. This negatively impacts the patient's QOL (Quality of Life) and often results in malnutrition, weight loss and depression.[20-22]

Treatments have historically been aimed at the palliation of symptoms associated with OM such as pain and dysphagia, and treatment of secondary complications such as infection, weight loss and malnutrition. Currently there is no standard treatment for OM in head and neck patients worldwide and there is a lack of clinical data to direct patient care and management of OM is therefore limited to symptom control including pain relief and maintenance of good oral hygiene.[23]

Sucralfate is a complex of sucrosulfate and aluminum hydroxide. It has mucosal protectant effect and its role has been thoroughly evaluated for the prevention of mucositis. Significant pain relief and resolution of mucositis occurs with it. This agent stimulates the production of prostaglandin E2, resulting in increased mucosal blood flow, higher mitotic activity and migration of epithelial cells. Prostaglandin E2 possesses cytoprotective activity. It also prevents the colonization of microorganisms on the mucous membrane.[25,26]

Natural honey has been shown to be an effective agent in managing radiation induced oral mucositis. It is a simple, potent and inexpensive agent, which is easily available, and it can be an affordable therapeutic agent in managing radiation mucositis in developing countries like India for the management of this morbidity.[28]Honey is mainly composed of sugars (70-80%) such as fructose, sucrose, glucose, etc., a low level of water, proteins, hydrogen peroxide, and gluconic acid. Honey can prevent infection by forming a physical protective barrier which stops tissue oxygenation by sealing damaged tissue from air and allows a moist healing environment for new cells to grow. It also possesses additional anti-inflammatory, antimicrobial and wound healing properties.[28,29]

Aims and Objectives

1. To compare the time to onset of oral mucositis in patients receiving sucralfate or honey.
2. To determine the relative efficacy of sucralfate and honey in the total mean Oral Mucositis Assessment Scale score.
3. To determine the effect of honey on weight of patient receiving radiotherapy and concurrent chemotherapy for head and neck cancers.

II. MATERIAL AND METHODS

The protocol for study was submitted to the Institutional Ethics Committee (IEC) and approval was sought. After getting approval from concerned authorities, 60 subjects were included in the present study.

Materials used:

Drugs to be investigated:

Sucralfate 15ml of 10% suspension, 10mg/100ml four times a day for total duration 7 weeks.

Honey pure and natural, 20 ml given 15 min before and 15 min after radiotherapy along with weekly concurrent chemotherapy and 6 hours later, (three times a day) for 7 weeks .

At the time of recruitment, all the patients were screened for the presence of any exclusion criteria. Initial evaluation was started with a thorough medical history, a general physical and detailed ear, nose and throat examination which was recorded on the prescribed proforma.

1. Complete medical history was obtained and recorded on a prescribed proforma from all the patients. Complete general physical examination and detailed ear, nose and throat examination of patient was done.

2. Patients meeting inclusion criteria recruited in the study were divided into two study groups A and B.

- **Group A:** Patients received sucralfate 15ml of 10% suspension, 10mg/100ml four times a day for 7 weeks duration.
- **Group B:** Patients received honey pure and natural, 20 ml given 15 min before and 15 min after radiotherapy with concurrent weekly chemotherapy and 6 hours later, three times a day for 7 weeks duration.

3. Patients were subjected to a general health status assessment on the basis of Karnofsky scale and assessed for body weight, hematological profile and grade of oral mucositis on the basis of OMAS scale.

4. Patients were advised:-

- Regarding basic oral hygiene.
- To maintain adequate fluid and water intake for adequate hydration.
- Regarding maintenance of adequate food intake, avoiding hard, spices, hot and salty food.
- To avoid acidic fruits like orange, grapes and lemon, while encouraging intake of banana, melon, mango along with bland, soft and pureed food.
- To have food items with high protein content like eggs and pulses etc.

5. Patients compliance was ensured and monitored for any additional medication intake, other significant events or difficulties and report any adverse event during the study period.

6. After 7 days of commencement of radiotherapy with concurrent chemotherapy, patients were followed up and assessed for body weight and OMAS score. Similar assessment of patient was done weekly up to end of 7 weeks or till completion of radiotherapy and concurrent chemotherapy.

7. During the course of radiotherapy whenever patient's OMAS grade became equal to or more than grade 2, then patient were put on additional rescue therapy.

Assessment and Scoring Methodology:

The Karnofsky Performance Scale Index is used to quantify patients on the basis of general well-being and activities of daily life. Based on this score, patients can be classified according to their functional impairment. Therefore, it can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. This score is useful in following patient's course of illness. Karnofsky score ranges from 100 to 0. 100 point means complete healthy status and 0 is death. Lower values of score means poor prognosis.

Oral Mucositis Scoring with Oral Mucositis Assessment Scale (OMAS):

Oral Mucositis Assessment Scale was designed by Sonis et al. (1999). It is a valid, reliable and easy to use scale which separates the objective from the functional measurements and can be used by people with minimal training in large scale multi-site clinical trials. The objective measurement divides the mouth into 9 different anatomical areas and gives each a score from zero to three for ulceration and zero to two for erythema. Degree of ulceration and redness in the mouth are primary indicators of OM while oral pain, difficulty in swallowing, and the ability to eat are taken as secondary indicators. A single score is not produced from this scale, rather a score for ulceration and redness based on different locations in the mouth are used.[37]

Statistical analysis: Analysis was based on data obtained from patients who have completed 7 weeks of study phase. Data generated from study was tabulated with respect to all the parameters at specific intervals. The results were expressed as mean±SD of each variable. Comparison was done by appropriate statistical (student t-test) tests and significance was expressed as 'p' value of < 0.05 for each parameter.

III. OBSERVATIONS

Distribution Based On Anatomical Site

ANATOMICAL SITE	Number of patients		TOTAL	P value
	GROUP A Sucralfate	GROUP B Honey		
Oral cavity	15(50%)	15(50%)	30(50%)	0.913(NS)
Nose and paranasal sinus	2(6.67%)	1(3.33%)	3(5%)	
Pharynx	6(20%)	7(2.33%)	13(21.67%)	
Larynx	6(20%)	5(16.7%)	11(18.33%)	
Salivary glands	1(3.33%)	1(3.33%)	2(3.33%)	
Misc	0(0.00%)	1(3.33%)	1(1.67%)	
TOTAL	30(100%)	30(100%)	60(100%)	

Out of total 60 patients, 30(50%) of cancers arise from oral cavity, 13(21.67%) from pharynx, 11(18.67%) from larynx, 3(5%) from nose and paranasal sinuses and 2(3.33%) from salivary glands and 1(1.67%) from miscellaneous sites:

Intra-Group Comparison of Omas Score

TIME	GROUP A Sucralfate N=30	GROUP B Honey N=30
	Mean Rank	Mean Rank
Day 0	1.28	1.60
Week 1	3.05	2.78
Week 2	4.53	4.37
Week 3	5.62	5.52
Week 4	6.12	6.37
Week 5	6.70	6.35
Week 6	5.48	5.47
Week 7	3.22	3.55
P Value	<0.001**	

Based on non-parametric Friedman test.

For group A, Chi square value=123.684, df=7 and p value <0.001(0.000)

For group B, Chi square value=114.829, df=7 and p value <0.001(0.000)

For group A on sucralfate and group B on honey, the mean rank values were:

Day 0: Mean rank OMAS score values for group A and B were 1.28 and 1.60 respectively.

Week 1: Mean rank OMAS score values increased for group A and B were 3.05 and 2.78 respectively.

Week 2: Further increase in Mean rank OMAS score values for group A and B seen was 4.53 and 4.37 respectively.

Week 3: Mean rank OMAS score values for group A and B were raised to 5.62 and 5.52 respectively.

Week 4: Mean rank OMAS score values increased in group A and B to 6.12 and 6.37 respectively.

Week 5: Again mean rank OMAS score values increased in group A and B to 6.70 and 6.35 respectively.

Week 6: Mean rank OMAS score values for group A and B were reduced to 5.48 and 5.47 respectively.

Week 7: Mean rank OMAS score values for group A and B were 3.22 and 3.55 respectively.

The difference throughout the duration of treatment was highly significant with p value of <0.001 among each group.

Comparison for Time To Onset In Weeks

GROUP	N	Mean ±SD	Mean difference	T value	P value
A-Sucralfate	30	1.23±0.504	0.567	2.637	0.011*
B-Honey	30	1.80±1.064			

The mean values for time to onset in weeks for group A and B was 1.23±0.504 and 1.80±1.064 respectively. P value was 0.011* which was statistically significant.

Comparison of Weight between Group-A and Group-B

Weight	Group-A (Sucralfate) N=30	Group-B (Honey) N=30			
	Mean±SD	Mean±SD	Mean difference	T value	P value
Day 0	55.87±11.581	56.53±10.197	0.667	0.237	0.814 (NS)
week 1	53.87±11.881	54.63±10.230	0.767	0.268	0.790(NS)
At week 2	52.53±11.752	52.90±10.600	0.367	0.127	0.899(NS)
At week 3	50.73±11.626	51.57±10.278	0.833	0.294	0.770(NS)
At week 4	49.08±11.445	49.75±10.602	0.667	0.234	0.816(NS)
At week5	47.15±11.050	49.33±10.762	2.186	0.776	0.441(NS)
At week 6	45.27±10.837	48.10±10.545	2.833	1.026	0.309(NS)
At week 7	46.87±10.628	50.50±10.484	3.633	1.333	0.188(NS)

NS means P value >0.05; not significant.

For group A on sucralfate and group B on honey, the mean values for weight were:

Day 0: Mean values for group A and B were 55.87±11.581 and 56.53±10.197 respectively. The difference was statistically not significant with p value of 0.814.

Week 1: Mean values for group A and B were 53.87±11.881 and 54.63±10.230 respectively. The difference was statistically not significant with p value of 0.790.

Week 2: Mean values for group A and B were 52.53±11.752 and 52.90±10.600 respectively. The difference was statistically not significant with p value of 0.899.

Week 3: Mean values for group A and B were 50.73±11.626 and 51.57±10.278 respectively. The difference was statistically not significant with p value of 0.770.

Week 4: Mean values for group A and B were 49.08±11.445 and 49.75±10.602 respectively. The difference was statistically not significant with p value of 0.816.

Week 5: Mean values for group A and B were 47.15±11.050 and 49.33±10.762 respectively. The difference was not statistically significant with p value of 0.441.

Week 6: Mean values for group A and B were 45.27±10.837 and 48.10±10.545 respectively. The difference was not significant with p value of 0.309.

Week 7: Mean values for group A and B were 46.87±10.628 and 50.50±10.484 respectively. The difference was statistically not significant with p value of 0.188.

A. Assessment From Baseline

Change in Weight from Baseline in Group a (Sucralfate)

TIME	Mean±SD	Change from baseline	P value
At Day 0	55.87±11.581	**9.000±1.894**	**0.000****
At week 7	46.87±10.628		

**P value < 0.001 highly significant.

In group A on sucralfate, the mean weight was 55.87±11.581 on day 0, which reduced to 47.87±10.628 at end of week 7. The difference in the values on day 0 and at end of week 7 was highly significant when compared to baseline value of day 1 ($p < 0.001$).

Change in Weight from Baseline in Group B (Honey)

TIME	Mean±SD	Change from baseline	P value
At Day 0	56.53±10.197	6.03±1.47	0.00**
At week 7	50.50±10.484		

**P value < 0.001 highly significant.

In group B on honey, the mean weight was 56.53±10.197 on day 0, which reduced to 50.50±10.484 at end of week 7. The difference in the values on day 0 and at end of week 7 was 6.03±1.47 which was highly significant when compared to baseline value of day 1 ($p < 0.001$).

IV. DISCUSSION

Oral mucositis (OM) occurs as a result of cytotoxic cancer treatments such as radiotherapy and chemotherapy. The present study was conducted among sixty patients with the aim to compare the effect of sucralfate and honey on oral mucositis in patients receiving radiotherapy and concurrent chemotherapy for head and neck cancers. Patients with Karnofsky score >70% were selected for study.[38]Comparison of both Group A and B demonstrated that mean time to onset in Group A (sucralfate) and B (honey) was 1.23 and 1.80 weeks respectively. A significant delay in onset of mucositis was seen in Group B (honey) as compared to Group A (sucralfate) ($p< 0.05$). This was concordant with previous placebo controlled study done on HNC patients showing delay in time to onset of OM.[39]

In 2010, another single-blinded, randomized, controlled study showed significantly lower proportion of patients with intolerable OM in honey group (p=0.000). Distinct mucosal protective benefit limited the severity of OM and improving the QOL of patients.[219] In 2012, another study on 55 patients of HNCs evaluated the effect of 20 ml pure natural honey three times a day on radiation-induced mucositis at weekly follow ups using the WHO grading system showed a significant reduction in the symptomatic grades 3 and 4 mucositis in honey-treated patients compared to controls i.e., 18% versus 41% for grade 3 and 4% versus 22% for grade 4 mucositis was seen.[41]

Another randomized study on forty patients diagnosed with HNC showed that prophylactic use of pure and natural honey was effective in reducing chemo-radiotherapy induced mucositis.[47]

This was in agreement with a meta-analysis done in 2012 based on three randomised trials involving 120 patients which found that overall relative risk of developing mucositis was almost 80% lower (risk ratio, 0.19; 95% CI, 0.098 - 0.371) in the honey treatment group than in the control group.[48]

No relation was seen between time to onset and severity of mucositis.

Mean weight were also comparable at baseline at day 0 in both the Group A (sucralfate) and B (honey). Although loss of weight was observed every week till week 6 after which slight recovery was seen in both the groups at week 7 but it did not reach to significant levels throughout the treatment($p>0.05$). Comparison of change in weight from baseline at day 0 till week 7 between both Group A and B showed highly significant mean weight loss of 9.0 kg and 6.03 kg in sucralfate and honey group respectively. ($p<0.001$). Therefore honey is more effective in decreasing weight loss. This was in accordance with two studies done in past as follows.

In 2008 another randomized single blind study reported mean weight loss of 1±0.35 (0 to 7 kg) compared to the control group where mean weight loss was 6.3±0.53 (2 to 11 kg). ($p<0.001$)[46]

In a study carried out in 2012 seventy-one per cent of patients treated with topical honey showed no change or a positive gain in body weight. Also 22% patients in the control Group showed no weight loss as well, although none showed weight gain, demonstrating that natural honey is effective in managing RT induced OM.[50-54]

V. SUMMARY AND CONCLUSION

A significant delay in onset of mucositis was seen in Group B (honey) as compared to Group A (sucralfate) ($p< 0.05$). In Group A, onset of mucositis was earlier and more severe as compared to Group B. Median value for OMAS was higher in Group A (sucralfate) as compared to Group B (honey) throughout follow up but reached a significant level only in first and second week ($p<0.05$). This suggested that more patients in Group A had higher OMAS values i.e.; more severe mucositis. Thus treatment with honey not only delayed the onset of mucositis compared to sucralfate, it also kept OMAS at lower value hence reducing the severity of oral mucositis.

Highly significant weight loss occurred in both Group A (sucralfate) and Group B (honey). Although no significant difference in weight was seen between Group A and B however, the mean weight loss was more in sucralfate group compared to honey. Therefore honey is more effective in decreasing weight loss as compared to sucralfate.

Limitation of this study

Although HNCs mainly present in fifth to sixth decade of life, exclusion of patients age>65years might have lead to selection bias. Due to small sample size, results could not be extrapolated to larger population. Larger multi-centric trials are needed to establish the efficacy of honey. Both patients and investigator could not be blinded. Poor compliance in some cases might be source of bias.

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