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Exploring the role of "Glycerine plus Honey" in delaying chemoradiation induced oral mucositis in head and neck cancers

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Original Article

Abstract

Purpose: The purpose of this study was to assess the efficacy of adding "Glycerine plus Honey" to standard management protocol, in terms of time to delay in oral mucositis ≥ grade 2. **Methods**: Hundred patients of oral cavity and oropharangeal cancers, planned for concurrent chemoradiation (Dose: 60–66 Gy/30-33 fractions) were randomized 1:1 to receive either home-made remedy made of "Glycerine plus Honey" added to the standard management protocol to prevent mucositis versus standard treatment alone. CTCAE v 4 (Common toxicity criteria for adverse events) was used for assessing oral mucositis scores weekly. Chi square test was used to compare mucositis scores, weight loss, opioid use, ryles tube feeding, and unplanned treatment breaks in each cohort. Independent T-test was used to compare means to assess the effect of treatment in delaying mucositis ≥ grade 2. **Results:** Significantly higher number of patients developed grade ≥ 2 mucositis in control arm [n = 43 (86%)] compared to study arm [n = 30 (60%)] (p = 0.003). CTCAE scores favored Glycerine plus honey at week 4, and on last day of radiotherapy. Whereas, time to first occurrence of oral mucositis grade ≥ 2 was 23.17 (± 1.01) days for study arm [radiation dose 31.67 Gy (± 1.44)], it was 20.65 (± 0.8) days for control arm [radiation dose 28.14 Gy (± 1.16)] (p = 0.05). Study patients had lesser weight loss (2.76 kg) than control subjects (3.9 kg) with p = 0.008. There were significantly higher number of patients in control arm who required opioid analgesia, ryles tube insertion and had unplanned treatment breaks, compared to study arm. **Conclusion:** Glycerine plus honey demonstrated superiority in delaying oral mucositis, and the combination is safe and well tolerable.

Keywords: Mucositis, Glycerine, Honey, Head and neck cancer, Chemoradiation.

1. Introduction

The standard of care for head and neck cancers especially oropharyngeal cancers and inoperable oral cavity cancers, is concurrent chemoradiation.[1] Oral mucositis is the most common and irritating side effect of chemoradiation. At least 30-40% of the patients who take chemotherapy drugs, experience some degrees of mucositis which starts five to ten days after the initiation of the treatment regimen.[2] Not only does it adversely affects the quality of life, but also is associated with radiation treatment breaks and hospitalizations. A number of commercial agents have been marketed to prevent and treat oral mucositis, but these are expensive and have doubtful efficacy.[3] In developing countries like ours, where finances are the major issue, some home-made remedy can help the poor patients to deal with this chemoradiation induced side effect and continue their treatment without breaks. Glycerine and honey are the two such natural, cheap and easily available products. Glycerine has the hygroscopic property and honey is known for its natural healing and regenerative power,[4-7] the properties which can help combat the treatment related mucositis. In this randomized trial, the study patients were asked to apply the paste made by mixture of these two products orally, starting from the day of radiation till treatment completion, along with the standard management already being given in our institute, to prevent and treat oral mucositis. Whether this helps to delay the onset of mucositis or not, as compared to those patients who are

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managed by standard protocols only, was analyzed in the present study.

2. Methods and Materials

In this prospective double arm study, 100 patients were randomized by Simple randomization method, where patients were recruited in 1:1 ratio into study and control groups, based on even and odd numbers (Even number recruited into Study arm and Odd number into Control arm). All locally advanced (Stage III and IV), non metastatic, inoperable, biopsy proven cases of squamous cell carcinoma of oral cavity and oropharynx, with Karnofsky Performance Status ≥ 80, fit for concurrent chemotherapy and those who were willing to give informed consent were included in the study. The postoperative cases of head and neck cancers, and the cancers of larynx, hypopharynx, nasopharynx were excluded from the trial.

All the patients underwent standard clinical staging work up which included complete medical history and systemic physical examination including the oral cavity examination, full blood counts and biochemical profile, chest radiograph, biopsy from growth and contrast enhanced computed tomography of head and neck region.

2.1. Treatment Planning

The patients were treated by conventional radiotherapy, by two parallel opposed fields, for the dose of 60 – 66 Gy delivered in 30 – 33 fractions (spine shielding done after 40 Gy), to the primary tumor and the drainage area. They were given concurrent chemotherapy with Cisplatin (100 mg/m2) every three weeks, which is the standard protocol followed in our institute to treat such patients.

2.2. Intervention

The study group was asked to apply the thick viscid paste of glycerine plus honey in 1:1 ratio, post meals, with a target dosing frequency of three times per day beginning on the first day of radiation and continuing until the last day of radiation therapy. Patients were advised to refrain from eating or drinking for one hour post dosing. This was in addition to the standard treatment offered to the patients receiving radiation in our institute, to prevent mucositis. The control group was advised to have the standard treatment only i.e plenty of fluids (2-3 litres per day), combined anesthetic and antacid solution (containing Oxetacaine (10 mg), Aluminium hydroxide (291 mg),Magnesium (98 mg)] in the syrup form and gargles with analgesic tablets (containing acetylsalicylic acid). Patients were provided supportive therapy as needed including analgesics, antiemetics, antifungal therapy, hydration, or other treatment. Agents suggested to modify oral mucositis risk or course including amifostine, benzydamine, cevimeline, glutamine rinse, topical GM-CSF, interleukin-11, chlorhexidine, hydrogen peroxide, diphenhydramine, paliferim, pilocarpine, steroid rinses, and various oral rinse medical devices were excluded.

All patients were assessed weekly for oral mucositis scores using CTCAE v 4 (Common toxicity criteria for adverse events). Any treatment break, opiod use, emergency OPD visits or need for Ryles tube placement was checked. Also, patients were assessed for any change in weight at the end of the treatment.

2.3. Statistical Analysis

The statistical analysis was conducted using SPSS version 19. P value < 0.05 was considered statistically significant. An Independent T test was used to compare the means to assess the effect of treatment on the delay of mucositis ≥ grade 2. Chi square test was used to compare the numbers of patients in each cohort in comparisons of oral mucositis scores, weight loss, opioid use, frequency of ryles tube feeding, and unplanned breaks in treatment.

3. Results

3.1. Patient characteristics (Table 1)

100 patients were enrolled in the study and were equally distributed among the two treatment arms. There was no difference between study and control arms in terms of mean age, sex ratio and baseline weight. All the patients were locally advanced with majority having primary tumor origin from oropharynx, with base of tongue as the most common subsite. From the Table 1, it can be seen that number of patients of oral cavity tumors and oropharyngeal tumors, were not significantly different between the two arms. Therefore, the extent of oral mucosa irradiated though different in two sets of patients (i.e in oral cavity and oropharyngeal tumors) will not contribute to difference in number of patients with radiation mucositis among the two arms.

In both the treatment arms, majority of the patients were treated upto the dose of 60 Gy in 30 fractions over 6 weeks with concurrent 3-weekly chemotherapy. The p value is not significant among the two arms, suggesting that radiation dose and number of chemotherapy cycles received by patients, contributed equally as a co factor for radiation mucositis in both the arms.

3.2. Subjects with severe oral mucositis anytime during radiotherapy (Table 2)

Significantly higher number of patients developed Gd ≥ 2 mucositis in the control arm (n = 43 (86%) compared to the study arm (n = 30 (60%) (p = 0.003). However the difference between number of patients who developed Gd ≥ 3 mucositis anytime during radiotherapy could not reach statistical significance between the two arms (p = 0.07).

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Table 1: Patient profile

Characteristic	Study arm N = 50	Control arm N = 50	P
Age (years)			
Mean (SD)	50.82 (9.7)	49.36 (10.95)	0.48
Range	28 - 68	28 - 67	
Sex			
Male	47 (94%)	47 (94%)	0.66
Female	3 (6%)	3 (6%)	
Baseline weight (Kg)			
Mean (SD)	62.70 (11.90)	61.98 (9.76)	0.74
Range	32 – 89	40 - 80	
Site of primary tumour	14 (28%)	18 (36%)	0.26
Oral cavity	36 (72%)	32 (64%)	
Oropharynx			
Subsite of primary tumour			
Oral cavity			
Tongue	10	12	
Floor of mouth	1	2	
Retromolar trigone	1	-	
Hard palate	1	2	
Buccal mucosa	2	2	
Oropharynx			
Base of tongue	32	21	
Tonsil	3	9	
Soft palate	1	2	
AJCC Stage			
III	18 (36%)	25 (50%)	0.42
IVa	29 (58%)	22 (44%)	
IVb	3 (6%)	3 (6%)	
Radiation dose planned			
60 Gy	39 (78%)	42 (84%)	0.30
66 Gy	11 (22%)	8 (16%)	
Number of 3 - weekly chemotherapy cycles			
2	39 (78%)	42 (84%)	0.30
3	11 (22%)	8 (16%)	

Table 2: Subjects with severe oral mucositis anytime during radiotherapy among treatment groups

Characteristic	Study arm	Control arm	p[a]
Number of patients who developed Gd ≥ 2 mucositis anytime during radiotherapy	30 (60%)	43 (86%)	0.003
Number of patients who developed Gd ≥ 3 mucositis anytime during radiotherapy	10 (20%)	18 (36%)	0.07

[a] Chi square test

Table 3: Subjects with severe oral mucositis at Week 4, Day 1 and at the end of radiation therapy among treatment groups.

Characteristic	Study arm	Control arm	p[a]
Subjects with Gd ≥ 2 oral mucositis at week 4, day 1	20 (40%)	38 (76%)	0.001
Subjects with Gd ≥ 3 oral mucositis at week 4, day 1	2 (4%)	9 (18%)	0.03
Subjects with Gd ≥ 2 oral mucositis at end of radiotherapy	28 (56%)	43 (86%)	0.002
Subjects with Gd ≥ 3 oral mucositis at end of radiotherapy	1 (2%)	4 (8%)	0.36

[a] Chi square test

3.3. Subjects with severe oral mucositis at mid interval and at the end of radiotherapy among treatment groups (Table 3)

Assesssment of oral mucositis was performed at start of radiation week 4 and on last day of radiotherapy. CTCAE scores trended in favor of Glycerine plus honey at week 4, with mucositis (Gd ≥ 2) occurring in 20 (40%) patients only in study arm versus 38 (76%) in control arm with p = 0.001. Also, severe mucositis (Gd ≥ 3) occurred in 2 (4%) patients only in study arm versus 9 (18%) in the control arm, with p = 0.03. On the last day of radiotherapy, statistically significant benefit (P = 0.002) was seen in study arm for Gd ≥ 2 mucositis with frequency of 28 (56%) patients in study arm developing Gd ≥ 2 mucositis versus 43 (86%) patients in the control arm. The trend noted for severe mucositis Gd ≥ 3 was however not significantly different among the two arms (p = 0.36) on the last day of radiotherapy.

3.4. Delay in onset of Gd ⩾ 2 mucositis among the treatment groups (Table 4)

Glycerine plus honey appeared to delay the onset of significant oral mucositis Gd ≥ 2. Whereas, time to first occurrence of oral mucositis Gd ≥ 2 was 23.17 (± 1.01) Study patients had significantly lesser weight loss than control subjects (2.76 Kg loss versus 3.9 Kg loss) with p = 0.008.

days (approximately 3 weeks and 2 days) for study arm, it was 20.65 (± 0.8) days (approximately 2 weeks and 6 days) for control arm (p = 0.05). Similarly, the mean cumulative radiation dose at which patients developed Gd ≥ 2 mucositis was 31.67 Gy (± 1.44) among study arm versus 28.14 Gy (± 1.16) among the control arm (p = 0.06).

3.5. Change in body weight from baseline among the treatment groups (Table 5)

3.6. Comparison of Opioid use, ryles tube insertion, treatment breaks among the two treatment groups (Table 6)

There were significantly higher number of patients in the control arm who required opioid analgesia during treatment, required ryles tube insertion and had unplanned treatment breaks, compared to the study arm. However, there were no relevant differences with respect to number of days for which opioid analgesia was required and number of days of treatment break among the two treatment arms. All patients who had treatment breaks were restarted on treatment after gap correction.

Table 4: Delay in onset of Gd ≥ 2 mucositis in terms of time to first occurrence and dose of first occurrence of mucositis among the two treatment groups.

Characteristic	Study arm	Control arm	p[a]
Time to First Occurrence of Gd ≥ 2 mucositis (in days)			
Mean (SE)	23.17 (1.01)	20.65 (0.8)	0.05
Median (SD)	22 (5.54)	22 (5.24)	
Range	(15 – 36)	(15 – 36)	
Delay in Onset of Gd ≥ 2 mucositis			
in terms of radiotherapy dose (Gy)	31.67 (1.44)	28.14 (1.16)	0.06
Mean (SE)	30 (7.91)	30 (7.63)	
Median (SD)	20 - 50	20 – 50	
Range			

[a]Independent T test

Table 5: Change in body weight from baseline among the treatment groups.

Characteristic	Study arm	Control arm	p[a]
Baseline			
Mean (SD)	62.70 (11.90)	61.98 (9.76)	0.74
Median	60.50	62	
Range	32 - 89	40 – 80	
At the end of treatment			
Mean (SD)	58.88 (12.17)	57.98 (9.7)	0.39
Median	58	58	
Range	30 - 87	35 – 78	
Change in weight from baseline to the end of treatment			
Mean (SD)			
Median	- 2.76	- 3.9	0.008
Range	- 2.00	- 4.0	
	0 -7	2 - 11	

[a] Chi square test

Table 6: Comparison of Opioid use, ryles tube insertion, treatment breaks among the two treatment groups.

Characteristic	Study arm	Control arm	p[a]
Patients who received opioid analgesia			
N	15 (30%)	24 (48%)	0.07
Opioid analgesia (no. of days required)			
Mean (SD)	10.27 (4.48)	11.96 (6.46)	0.13
Range	7 - 21	5 – 21	
Patients who required ryles tube insertion			
N	9 (18 %)	19 (38 %)	0.04
Patients who had unplanned treatment breaks			
N	9 (18 %)	19 (38 %)	0.04
Number of days of treatment break			
Mean (SD)	8.67 (1.01)	7.37 (0.77)	0.33
Median	7 (3.04)	7 (3.37)	
Range	7- 14	3 – 14	

4. Discussion

Oral mucositis is one of the frequent complications of cancer treatment, and is experienced in some degrees by almost all head and neck cancer patients undergoing concurrent chemoradiation.[1,3] Undoubtedly, its effective therapy can substantially reduce the oral complications and the risk of oral and systemic infections.

Most of the medical devices available in market are costly, have doubtful efficacy, and also use chemicals that may have ill effect on the health. In a country like India, where finances are the major issue for majority of patients with head and neck cancer, some cheap, easily available and indigenous home-made remedy can deal with this chemoradiation induced side effect.

Glycerine is a sweet and colourless liquid, and is one such natural and cheap product, which due to its hygroscopic property has the ability to attract moisture from the air and hold it. When diluted to a concentration below 50%, it acts as a lubricant, emollient and demulcent. Also, glycerine and water act together to promote softness and flexibility and prevent drying out of mucosa.[4] Study by Mouly et al. showed that oxygenated glycerol triester lubricant oral spray was superior to saliva substitute Saliveze in improving xerostomia and oral tissue condition in older institutionalized patients.[8]

Another natural product is honey which contains more than 200 substances such as sugars, proteins, minerals, some vitamins, organic acids and antioxidants (phenolic compounds, enzymes, flavonoids, amino acids, carotenoid-like substances and other phytochemicals).[9] Honey by its antioxidants, can increase cytokine release and has antimicrobial effects. It reduces inflammation and edema, stimulates epithelialisation and tissue regeneration and thus improves granulation and debridement which in turn accelerates tissue repair and leads to wound healing. It is also known to stimulate salivary secretion by its sweetness. Raeessi *et al.* in a randomized controlled trial showed that combination of honey and coffee significantly decreased the oral mucositis scores compared to topical steroids in the treatment of chemoradiation induces oral mucosistis.[5]

Previously also, some studies have proved promising effects of honey on the cancer treatment induced oral mucositis.[6, 7]

Though, the above two products have been used either alone or in combination with some other products in literature, this is probably the first study where the two have been used in combination. Whether this combination helps to delay the onset of mucositis or not, as compared to those patients who are managed by standard protocols alone, was analyzed in this trial.

The study findings showed that there was a statistically significant reduction in the degree of oral mucositis in the course of radiotherapy with the use of honey and glycerine, compared to standard protocol. Overall, only 60% patients (30) in study arm compared to 86% (43) in control arm developed Gd ≥ 2 mucositis (p = 0.003). However the difference between number of patients who developed Gd ≥ 3 mucositis anytime during radiotherapy could not reach statistical significance between the two arms (p = 0.07). The result is in accordance with the study by Biswal *et al.*[10] and Maiti *et al.*,[11] who evaluated the effect of honey in management of radiation induced mucosits, in which only 18 - 20% patients in experimental group developed grade III or grade IV mucositis compared to 41 - 75% patients in control group.

On assessment of oral mucositis scores at start of radiation week 4, it was found that CTCAE scores trended in favor of Glycerine plus honey, with mucositis (Gd ≥ 2) occurring in 20 (40%) patients only in study arm versus 38 (76%) in control arm with p = 0.001. Also, severe mucositis (Gd ≥ 3) occurred in 2 (4%) patients only in study arm versus 9 (18%) in the control arm, with p = 0.03. Compared to this, on the last day of radiotherapy, total 28 (56%) patients in study arm had Gd ≥ 2 mucositis versus 43 (86%) patients in the control arm. This indicates 16% increase in number of patients who develop Gd ≥ 2 mucositis since week 4 till the last day, compared to only 10% increase in number of patients in control arm. This odd increase in oral mucositis scores in study arm can be explained by the fact that, 19 patients (38%) had unplanned treatment break in the control arm due to Gd ≥ 3 mucositis, compared to 9 patients only (19%) in the study arm. Thereby 38% patients in the control arm got adequate time for their oral mucositis grades to heal and resolve.

In addition, honey plus glycerine use was associated with other favorable outcomes compared to the control. Whereas the time to first occurrence of oral mucositis Gd ≥ 2 was 20.65 (± 0.8) days (approximately 2 weeks and 6 days) in control arm, similar frequency of oral mucositis was not seen in study group until 23.17 (± 1.01) days (approximately 3 weeks and 2 days). Also, the mean cumulative radiation dose at which patients developed Gd ≥ 2 mucositis was 31.67 Gy (± 1.44) among study arm versus 28.14 Gy (± 1.16) among the control arm (p = 0.06). Similar results were shown by Jayalekshmi et al in her study,[12] who found that the time to first occurrence of mucositis Gd ≥ 2 was 14 days (20 Gy) in control group and 21 days (30 Gy) in study group (patients who had topical application of honey), however the results could not achieve statistical significance in her study.

Besides this, the study patients had significantly lesser weight loss than control subjects (2.76 Kg loss versus 3.9 Kg loss) with p = 0.008. Biswal *et al.*[10] in his study also found that the compliance of honey-treated group of patients was better than controls. 55% patients treated with topical honey showed no change or a positive gain in body weight compared to 25% in the control arm (p =0.053), the majority of whom lost weight.

In our study, there were significantly higher number of patients in the control arm who required opioid analgesia during treatment, required ryles tube insertion and had unplanned treatment breaks, compared to the study arm. However, the number of days for which opioid analgesia was required and the number of days of treatment break were not statistically different among the two treatment arms.

A metaanalysis was conducted by Cho *et al.*[13] on the effects of honey on oral mucositis in patients with head and neck cancer. Nine studies comprising 476 patients were included in this meta-analysis. It was found that the incidence of moderate to severe mucositis and the mean mucositis grade during the first 3 weeks of therapy were significantly lower in the honey group than the control group. Additionally, the onset of mucositis was significantly later in the honey group than the control. Although there were no significant differences in the incidences of microbial colonization and pain experienced between the two groups, the incidence of weight loss was significantly lower in the honey group than control group.

Compared to honey, the use of glycerol for preventing mucositis has rarely been found in literature. In one of the study conducted by Srivastava *et al.*[14] in 69 patients of head and neck cancer, 48 patients were treated with the Orosol liquid solution (Filmogen glycerol containing procyanidin fraction of plant tannins) and 21 with glycerol as a spray. A statistically significant difference in mucositis healing was observed in the Orosol group compared to the glycerol group. The study thereby concluded that filmogen liquid glycerol applied as paste attracts hypotonic liquid for a much longer period of time, cleans the lesion, and helps promote recovery.

Apart from the patient compliance to the use of this homemade mixture, limited patient number was major limiting factor of this study. Further randomized trials with larger number of patients can better approve the

results of this study. And if approved, this can be a major turnover in the prevention and treatment of chemoradiation induced oral mucositis, as both glycerol and honey are cheap, easily available and indigenous remedies, free from any side effects. Besides this, Quality of life (QOL) assessment was not taken up in this study, as the focus of this research was to find out the efficacy of "glycerine and honey" in delaying chemoradiation induced mucositis. However, QOL assessment could also have contributed in demonstrating superiority of "glycerine and honey" in such patients, who are otherwise treated by standard protocols to prevent chemoradiation induced mucositis.

5. Conclusion

This study represents the first report on the combination of glycerol and honey for preventing and delaying oral mucositis. The study results support the addition of glycerol and honey to the standard management protocol used for the management of oral mucositis in patients of head and neck cancers being treated with concurrent chemoradiation. The product is cheaper compared to currently practiced/recommended agents for oral mucositis. Moreover, both the products did not produce any side effects and were well tolerated by most of the patients.

Conflict of Interest

The authors declare no conflicts of interest in the preparation of the manuscript or during the study. No financial grants were obtained during the study period.

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