Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: A drug trail

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Abstract

Background and Objectives: Oral mucositis is a common and debilitating complication of radiotherapy, which is associated with significant morbidity. It is therefore extremely important that mucositis be prevented, or at least treated to reduce its severity and sequelae. The objective of the study was to manage oral mucositis induced by radiotherapy and to reduce pain by using Benzydamine hydrochloride (0.15%), Chlorhexidine (0.2%), and Povidone iodine (5%). **Results:** Benzydamine hydrochloride was observed to be effective and delayed the development of severe form of mucositis and appears more efficient in the management of radiation-induced mucositis. **Conclusion:** Benzydamine hydrochloride (0.15%) is safe, well tolerated, helps not just in delaying the progression of mucositis but also reduces the intensity of pain.

Keywords: Benzydamine hydrochloride, chlorhexidine, oral mucositis, povidone iodine

Introduction

Oral mucositis is a major complication associated with radiotherapy (RT) administered to the head and neck area. It is associated with significant morbidity characterized by pain, odynodysphagia, dysgeusia, malnutrition, dehydration, and also increases the risk for systemic infections in immunocompromised patients.[1-12] Oral mucositis can occur with cumulative RT doses as low as 1000–2000 cGy with therapy administered at a rate of 200 cGy per day.[10] In more than half of patients with mucositis, the condition is of such severities that requires parental analgesia, interruption of RT, and hospitalization. This is of marked concern, as a strong clinical and radiobiologic evidence that protraction of overall treatment time has an adverse influence on the radiocurability of certain human tumors, particularly squamous cell carcinoma of the head and neck region.[13] The present study was conducted to evaluate the efficacy of Benzydamine hydrochloride (0.15%), Chlorhexidine (0.2%), Povidone iodine oral rinses in managing the severity of radiation-induced mucositis.

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Aims and objectives

To compare and study the efficiency of Benzydamine hydrochloride (0.15%), Povidone iodine (5%), and Chlorhexidine (0.2%) used in the management of oral mucositis and pain induced by RT.

Materials and Methods

A total number of 100 patients undergoing RT (Cobalt external beam therapy) for head and neck malignancies at the Radiotherapy Department, Kidwai Memorial Institute of Oncology, Bangalore were selected.

Patient selection

Patients were selected based on the following criteria. (i) Patients who were planned for RT with a daily dose of 220CGy for a period of six weeks, with a total dose of 6600CGy 30 fractions, and (ii) Age group of the patients between 30 and 70 years. We excluded patients falling under the following criteria. (i) Patients suffering from mucositis due to other causes like radiochemotherapy, Bacterial /fungal infections of oropharynx, (ii) Patients having atrophic mucosal changes, dryness of mouth before RT were not included, and (iii) Patients who received antibiotics and analgesics during the RT period were not considered.

Selected patients were divided into study and control groups. The study groups were further subdivided into group 1, group 2, and group 3. Each study group consisted of twenty

five patients and the control group also consisted of twenty five patients; the three study group and the control group were given Benzydamine hydrochloride, Chlorhexidine, Povidone iodine, and distilled water (Placebo), respectively. These rinses were given after two weeks of RT at the onset of oral mucositis.

Methodology

After explaining about the study to the patients, an informed consent was obtained and a detailed case history with relevant clinical finding were recorded.

Patients in the study groups as well as the control group were instructed to rinse the oral cavity with 15 ml of their respective rinses for at least thirty seconds, four times a day at 6 hours interval. The mouth rinsing regimen was performed under professional supervision. The samples of mouth rinses, were given to the patients without dilution for one week use, at a time, for convenience. The patients were also provided measuring cups to measure the quantity of oral rinses. All the patients were examined at the end of every week during the RT for about six weeks period.

Mucositis was recorded at the end of every week and graded as recommended by WHO.[14]

The criteria is as follows:

- Grade 0: No changes.
- Grade 1: Soreness / (+) erythema.
- Grade 2: Erythema (++), Ulcer, can eat food. (Erythema with ulcers less than 1 cm)
- Grade 3: Ulcer (+++), (erythema with ulcers more than 1cms) require liquid food.
- Grade 4: Ulcer with hemorrhage and necrosis, alimentation not possible.

Pain was recorded at the end of every week and graded as recommended by Lindquist/Hickey scale.[14] Scale indicated: 0 - no pain, 1 - Slight burning (mild), 2 - Oral pain but able to eat (moderate), 3 - Severe pain and unable to eat (severe)

Results and Discussion

It was observed that at the end of the third week of RT, there were more patients with absent/no mucositis (32%–44%) in the study groups, as compared to the control group (16%). However, mucositis was present in mild forms in control group as well as in the study groups. Hence, it appears that Benzydamine hydrochloride (0.15%), Povidone iodine (5%), and Chlorhexidine (0.2%) did not delay the progression of mucositis, and thus, did not control the cascade of inflammatory events associated with RT. Mild pain had developed in more number of patients in control group (84%) as compared to the study groups (52%–68%). At the same period, more number of patients developed grade 1 mucositis in all the groups. No statistically significant difference was found between the control and the study groups at the end of third week [Tables 1a, b].

At the end of fourth week of RT, there were differences in the grades of mucositis between the control group and the study groups. Patients from all the groups had mucositis. Patients from the control group were seen to progress towards severity, when compared to study groups, in which most of patients had either grade 0 or grade 1 mucositis. However, there were no patients from group 1 and group 2 who had grade 3 mucositis. Most of the patients in the control group and in the study groups were complaining of varying degrees of pain. Patients with severe pain were more in the control group (16%) when compared to the study group (0%–4%). Resolution of pain from severe to moderate was observed in group 1 [Tables 2a, b].

At the end of the fifth week of RT, the severity of mucositis had increased in patients of all the groups. The numbers of patients having grade 2 and grade 3 mucositis were more in the control group (16%–36%), whereas more patients had grade 1 mucositis in the study groups (56%–68%). It is important to observe that none of the patients from Group 1 had progressed to grade 3 mucositis. Patients with severe pain were more in the control group (20%) than in the study groups (4%–12%). None of patients from group 1 complained of severe pain, however, a single patient from group 2 complained of severe pain. The intensity of pain was comparable to the progression of mucositis. As mucositis escalated, the pain also increased in intensity accordingly. Hence, it appears that with the increase in severity of mucositis, Benzydamine hydrochloride (0.15%) helped in reducing the intensity of pain. Although there was no statistically significant difference seen among the study groups, it is also important to note that there were little differences between group 1 and group 2 in controlling pain and mucositis. These findings are similar to the study conducted by Samaranayake *et al* who compared the effects of Chlorhexidine and Benzydamine mouth washes on mucositis induced by therapeutic radiation and reported that there was little difference between the effectiveness of mouthwashes in controlling both mucositis and pain [Tables 3a, b].[15]

It is important to observe that at the end of the sixth week of RT, the number of patients with grade 1 mucositis were more in all the study groups (44%–68%) as compared to the control group (28%). One patient in Group 1 progressed to grade 3 mucositis, and simultaneously there was resolution of mucositis from grade 2 to grade 1 in another patient. Patients with moderate and severe pain were more in number in the control group and patients with mild pain were more in the study groups. Although a single patient from Group 1 had grade 3 mucositis, the patient complained of moderate pain; this might be attributed to the anti-inflammatory and anesthetic property of the oral rinse. Thus it appears that

Table 1a: Comparison of grades of mucositis in control and the study group in third week of radiotherapy

Mucositis grade-week 3	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
0	4 (16)	11 (44)	8 (32)	9 (36)	32 (32)
1	20 (80)	14 (56)	17 (68)	15 (60)	67 (66)
2	1 (4)			1 (4)	2 (2)
Total	25	25	25	25	100

Pearson Chi-Square -.241

Table 1b: Comparison of grades of pain in control and the study group in third week of radiotherapy

Pain week 3	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
0	4 (16)	11 (44)	8 (32)	10 (40)	33 (33)
1	21 (84)	13 (52)	17 (68)	14 (56)	65 (65)
2		1 (4)		1 (4)	2 (2)
Total	25	25	25	25	100

Pearson Chi-Square-.248

Table 2a: Comparison of grades of mucositis in control and the study group in fourth week of radiotherapy

Mucositis grade-week 4	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
1	16 (64)	20 (80)	20 (80)	20 (80)	76 (76)
2	7 (28)	5 (20)	5 (20)	4 (16)	21 (21)
3	2 (8)			1 (4)	3 (3)
Total	25	25	25	25	100

Pearson Chi-Square - 545

Table 2b: Comparison of grades of mucositis in control and the study group in fourth week of radiotherapy

Pain week 4	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
0			1 (4)		1 (1)
1	17 (68)	21 (84)	19 (76)	18 (72)	75 (77)
2	4 (16)	4 (16)	5 (20)	6 (24)	19 (21)
3	4 (16)			1 (4)	5 (1)
Total	25	25	25	25	100

Pearson Chi-Square-.661

Table 3a: Comparison of grades of mucositis in control and the study group in fifth week of radiotherapy

Mucositis grade-week 5	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
1	12 (48)	16 (64)	14 (56)	16 (64)	58 (58)
2	9 (36)	9 (36)	8 (32)	7 (28)	33 (33)
3	4 (16)		3 (12)	2 (8)	9 (9)
Total	25 (100)	25 (100)	25 (100)	25 (100)	100 (100)

Pearson Chi- Square-.546

Table 3b: Comparison of grades of pain in control and the study group in fifth week of radiotherapy

Pain week 5	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
1	16 (64)	20 (80)	19 (76)	17 (68)	72 (72)
2	4 (16)	5 (20)	5 (20)	5 (20)	19 (19)
3	5 (20)		1 (4)	3 (12)	9 (9)
Total	25 (100)	25 (100)	25 (100)	25 (100)	100 (100)

Pearson Chi-Square-.747

Table 4a: Comparison of grades of mucositis in control and the study group in fifth week of radiotherapy

Mucositis grade-week 6	Control (%)	Benzydamine HCl (%)	Chlorhexidine (%)	Povidone iodine (%)	Total (%)
1	7 (28)	17 (68)	12 (48)	11 (44)	47 (47)
2	10 (40)	7 (38)	8 (32)	8 (32)	33 (33)
3	8 (32)	1 (4)	5 (20)	6 (24)	20 (20)
Total	25	25	25	25	100

Pearson Chi-Square-.121

Table 4b: Comparison of Grades of pain in control and the study group in fifth week of radiotherapy

Pain week 6	Control	Benzydamine HCl	Chlorhexidine	Povidone iodine	Total
1	10 (40)	20 (80)	19 (76)	17 (68)	66 (66)
2	10 (40)	5 (20)	4 (16)	5 (20)	24 (24)
3	5 (20)		2 (8)	3 (12)	10 (10)
Total	25	25	25	25	100

Pearson Chi-Square-.078

Benzydamine hydrochloride is very effective in controlling pain and mucositis.

In the present study, though there was no significant difference in the number of patients having mucositis in both the control and the study groups, there was a difference in the severity of mucositis. Benzydamine hydrochloride (0.15%) oral rinse reduced the intensity and duration of oral mucositis during RT to a single case of grade 3 mucositis by the end of the sixth week of RT (4%). Patients from study group 2 and study group 3 were found to have grade 3 mucositis (20%–24%), similar to that of control group (32%). It was also observed that as the period of RT progressed, intensity of pain increased in the control group, which was followed by Group 3 and Group 2, whereas none of them had complained of severe pain in Group 1. Hence, Benzydamine hydrochloride is found be effective in delaying the progression of severity of mucositis and pain, and thereby appears more efficient in the management of radiation-induced mucositis. [Tables 4a, b]

Mody R.N and Talukdar S studied the efficacy of Benzydamine hydrochloride oral rinses in radiation mucositis and reported that its mouth rinse helped in reducing the severity and the faster recovery of mucositis.[16]

These findings are similar to that of earlier studies of Epstein J.B. *et al* who found Benzydamine hydrochloride rinse to be effective in accelerating resolution of mucositis and pain.[13] Kim *et al* also observed that Benzydamine hydrochloride used as a rinse/gargle provided a significant and clinically meaningful alleviation of oropharyngeal mucositis.[17]

Conclusion

Oral mucositis is a common and important side effect of many cancer therapies. It is therefore essential that dentists have an understanding of cancer therapy and a sound working knowledge of the prevention and management options for the oral sequelae of cancer treatment. All the oral rinses helped in controlling pain and mucositis when compared with distilled water (Placebo), however Benzydamine hydrochloride was more efficient and had better patients compliance.

Based on the results of this study, we conclude that the use of Benzydamine hydrochloride (0.15%) helps not just in delaying the progression of mucositis but also reduces the intensity of pain, and hence it is more efficient in the management of radiation-induced mucositis. However, long term follow-up studies with larger sample size would further help to assess the significance of these drugs in the treatment of radiation-induced oral mucositis.

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