Efficacy of Benzydamine Hydrochloride, Chlorhexidine and Povidone Iodine in Treatment of Oral Mucositis among Patients Undergoing Radiotherapy in Head and Neck Malignancies

G Roopashri, K Jayanthi, R Guruprasad

1Senior Lecturer, Department of Oral Medicine and Radiology, MR Ambedkar Dental College and Hospital, Bengaluru Karnataka, India
2Professor and Head, Department of Oral Medicine and Radiology, Bangalore Institute of Dental Sciences, Bengaluru Karnataka, India
3Associate Professor, Department of Oral Medicine and Radiology, People’s Dental College and Research Institute, Bhopal Madhya Pradesh, India

Correspondence: G Roopashri, Senior Lecturer, Department of Oral Medicine and Radiology, MR Ambedkar Dental College and Hospital, Bengaluru, Karnataka, India, e-mail: roopadr@yahoo.co.in

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 is effective and delays the development of severe form of mucositis and appears more efficient in the management of radiation-induced mucositis.

Conclusions: 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: Oral mucositis, Benzydamine hydrochloride, Chlorhexidine, Povidone iodine.

INTRODUCTION

Oral mucositis is a major complication associated with radiotherapy (RT) administered to the head and neck area. Oral mucositis is associated with significant morbidity characterized by pain, odynodysphagia, dysgeusia, malnutrition, dehydration and also increases the risk for systemic infections in immuno-compromised patients. Oral mucositis can occur with cumulative radiotherapy doses as low as 1000 to 2000 cGy with therapy administered at a rate of 200 cGy per day. In greater 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 head and neck region. The present study was conducted to evaluate the efficacy of Benzydamine hydrochloride (0.15%), Chlorhexidine (0.2%) and Povidone iodine oral rinses in managing severity of radiation-induced mucositis.

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 radiotherapy.

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, Bengaluru, were selected.

Inclusion Criteria

1. Patients who were planned for radiotherapy with a daily dose of 220 cGy for a period of 6 weeks with a total dose of 6600 cGy 30 fractions.
2. Age group of the patients—30 to 70 years.

Exclusion Criteria

1. Patients suffering from mucositis due to other causes, like radiochemotherapy, bacterial / fungal infections of oropharynx.
2. Patients having atrophic mucosal changes, dryness of mouth before radiotherapy were not included.
3. Patients who received antibiotics and analgesics during the radiotherapy period were not considered.

Selected patients were divided into two groups:

- Study group
- Control group

The study group was further subdivided into group 1, group 2 and group 3. Each study group consisted of 25 patients and the control group also consisted of 25 patients, and they were given Benzydamine hydrochloride, Chlorhexidine, Povidone iodine and distilled water (placebo) respectively. These rinses were given after two weeks of radiotherapy 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 as well as the control groups were instructed to rinse the oral cavity with 15 ml of four respective rinses for at least 30 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 radiotherapy for about 6 weeks period.

Mucositis was recorded at the end of every week and graded as recommended by WHO.14
- 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 1 cm) 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
- 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 3rd week of radiotherapy, 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 radiotherapy. 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 3rd week.

At the end of 4th week of radiotherapy, there were differences in the grades of mucositis between the control 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 and 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 in group 1 was observed.

At the end of the 5th week of radiotherapy, the severity of mucositis had increased in patients of all the groups. The number of patients having grade 2 and grade 3 mucositis were more in 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.

### Table 1A: Comparison of grades of mucositis in control and the study groups in 5th week of radiotherapy

<table>
<thead>
<tr>
<th>Mucositis grade (5th week)</th>
<th>Control</th>
<th>Benzydamine HCl</th>
<th>Chlorhexidine</th>
<th>Povidone iodine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>16</td>
<td>14</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>(48.00%)</td>
<td>(64.00%)</td>
<td>(56.00%)</td>
<td>(64.00%)</td>
<td>(58.00%)</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>(36.00%)</td>
<td>(36.00%)</td>
<td>(32.00%)</td>
<td>(28.00%)</td>
<td>(33.00%)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>–</td>
<td>3</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(16.00%)</td>
<td></td>
<td>(12.00%)</td>
<td>(8.00%)</td>
<td>(9.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>23</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 1B: Comparison of grades of pain in control and the study groups in 5th week of radiotherapy

<table>
<thead>
<tr>
<th>Pain (5th Week)</th>
<th>Control</th>
<th>Benzydamine HCl</th>
<th>Chlorhexidine</th>
<th>Povidone iodine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>20</td>
<td>19</td>
<td>17</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>(64.00%)</td>
<td>(80.00%)</td>
<td>(76.00%)</td>
<td>(68.00%)</td>
<td>(72.00%)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>(16.00%)</td>
<td>(20.00%)</td>
<td>(20.00%)</td>
<td>(20.00%)</td>
<td>(19.00%)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>–</td>
<td>4</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(20.00%)</td>
<td></td>
<td>(4.00%)</td>
<td>(12.00%)</td>
<td>(9.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>
induced by therapeutic radiation and reported that there was little difference between the effectiveness of mouthwashes in controlling both mucositis and pain\textsuperscript{15} (Tables 1A and B).

It is important to observe that at the end of the 6th week of radiotherapy, the number of patients with grade 1 mucositis were more in all the study groups (44-68\%) as compared to the control group (28\%) (Figs 1 to 4). One patient in group 1 progressed to grade 3 mucositis, 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 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 radiotherapy to a single case of grade 3 mucositis by the end of the 6th week of radiotherapy (4\%). Patients from study group 2 and 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 radiotherapy 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, thereby appears more efficient in the management of radiation-induced mucositis (Tables 2A and B).

<table>
<thead>
<tr>
<th>Mucositis grade</th>
<th>Control</th>
<th>Benzydamine HCl</th>
<th>Chlorhexidine</th>
<th>Povidone iodine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6th week)</td>
<td>7 (28.00%)</td>
<td>17 (68.00%)</td>
<td>12 (48.00%)</td>
<td>11 (44.00%)</td>
<td>47 (47.00%)</td>
</tr>
<tr>
<td>2</td>
<td>10 (40.00%)</td>
<td>7 (38.00%)</td>
<td>8 (32.00%)</td>
<td>8 (32.00%)</td>
<td>33 (33.00%)</td>
</tr>
<tr>
<td>3</td>
<td>8 (32.00%)</td>
<td>1 (4.00%)</td>
<td>5 (20.00%)</td>
<td>5 (20.00%)</td>
<td>6 (33.00%)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain (6th week)</th>
<th>Control</th>
<th>Benzydamine HCl</th>
<th>Chlorhexidine</th>
<th>Povidone iodine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6th week)</td>
<td>10 (40.00%)</td>
<td>20 (80.00%)</td>
<td>19 (76.00%)</td>
<td>17 (68.00%)</td>
<td>66 (66.00%)</td>
</tr>
<tr>
<td>2</td>
<td>10 (40.00%)</td>
<td>5 (20.00%)</td>
<td>4 (16.00%)</td>
<td>5 (20.00%)</td>
<td>24 (24.00%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (20%)</td>
<td>2 (8.00%)</td>
<td>2 (12.00%)</td>
<td>3 (10.00%)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2A:** Comparison of grades of mucositis in control and the study groups in 6th week of radiotherapy

**Table 2B:** Comparison of grades of pain in control and the study groups in 6th week of radiotherapy

**Control Group [Distilled water (Placebo)]**

Figs 1A and B: Changes of mucositis in control group: (A) Mucositis in 5th week radiotherapy (B) Mucositis in 6th week of radiotherapy
Study Group 1 (Benzydamine Hydrochloride)

Figs 2A and B: Changes in mucositis in study group 1: (A) Mucositis in 5th week of radiotherapy (B) Mucositis in 6th week of radiotherapy

Study Group 2 (Chlorhexidine)

Figs 3A and B: Changes in mucositis in study group 2: (A) Mucositis in 5th week of radiotherapy (B) Mucositis in 6th week of radiotherapy

Study Group 3 (Povidone Iodine)

Figs 4A and B: Changes in mucositis in study group 3: (A) Mucositis in 5th week of radiotherapy (B) Mucositis in 6th week of radiotherapy
Mody RN and Talukdar S studied the efficacy of Benzydamine hydrochloride oral rinses in radiation mucositis and reported that Benzydamine hydrochloride mouth rinse helped in reducing the severity and the faster recovery of mucositis.\textsuperscript{16}

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

**CONCLUSIONS**

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 distil water (placebo), however, Benzydamine hydrochloride was more efficient and had better patients compliance.

From 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 treatment of radiation-induced oral mucositis.

**REFERENCES**