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*Original Research Article*

# Role of Benzydamine in Radiation-Induced Oral Mucositis in Head and Neck Cancer Patients

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## ABSTRACT

**Background:** Benzydamine is a local acting non-steroidal and anti-inflammatory drug which is used in the treatment of oral mucositis. Majority of the patients of head and neck cancer receiving radiotherapy develop mucositis due to poor oral hygiene, dehydration, and malnutrition. During treatment patients develop major complications and stop radiotherapy. Therefore we have to use Benzydamine to prevent mucositis and for completion of treatment.

**Objectives:** The objective of the study was to observe the effect of Benzydamine in radiation induced oral mucositis.

**Materials and Methods:** We have enrolled 80 patients in our study which is divided into two arms; study arm and control arm by random sampling, each arm consisting of 40 patients selected from July to December 2015. The study arm patients used Benzydamine and control arm patients used Povidone-iodine rinses from the beginning of radiotherapy which was delivered to the tumor as 180-200 cGy per fraction for 6-7 weeks. The total dosage given varied from 60 to 66 Gy. Mucositis was recorded and graded by RTOG criteria. All the patients were examined at the end of every two week, from third week onwards during the radiotherapy and after one month of radiotherapy.

**Results:** After one month of radiotherapy only 4 patients (10.3%) in the study arm were found to have grade-II mucositis, compared to that of 6 patients in the control arm (15.7%) while 24 patients (61.5%) in the study arm had grade-0 mucositis compared to 17 patients (44.8%) in the control arm. One patient lost for follow-up in study arm while two patients lost for follow-up in control arm.

**Conclusion:** We conclude that the Benzydamine is effective in the prophylaxis and treatment of radiation-induced oral mucositis.

**Keywords:** Benzydamine, Head and neck cancer, Radiation induced oral mucositis.

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## INTRODUCTION

Head and neck cancer is the most common malignancy in the Indian subcontinent, incidence being more than 25% of all malignancies. The treatment modalities are radiotherapy, surgery, or chemotherapy while radiotherapy is established to be the standard modality in the treatment.[1]

Radiation induced oral mucositis is a most common complication occurring in about 40% of patients. It is common and often debilitating complication for which there is no preventive or predictable therapy currently available.[2] It is characterized by pain, dysphagia, malnutrition, and dehydration. In severe mucositis radiation therapy may be stopped. Protraction of overall treatment time has adverse influences on the curability of tumors.[3]

Radiation mucositis is aggravated by Bacterial colonization in the oral cavity. Smoking, tobacco chewing and poor oral hygiene can contribute to pre-existing mucositis.[4] Its severity is directly related to the type of radiation and to the total dosage, fractionation, and duration of treatment. It can occur with cumulative RT doses as low as 16-20 Gy with dose rate of 200 cGy per day.[5] It is recognized as an epithelial and sub epithelial injury that develops in five phases as Initiation, Primary damage response, Signal amplification, Ulceration and Healing.[6] Its prophylaxis is still limited to reduction of its severity by reducing pain and discomfort, oral hygiene, and elimination of microbes involved in development of mucositis.[7]

An ideal oral rinse should be nontoxic, anti-microbial, promoting healing of lesions, and with an acceptable taste. Benzydamine is a local acting non-steroidal, analgesic, anti-microbial and anti-inflammatory drug which is used in the treatment of oral mucositis. Povidone-iodine also appears to be beneficial in controlling radiation-induced oral mucositis.[8-10]

In our study we have evaluated the effect of Benzydamine oral rinses in radiation-induced oral mucositis with compare to Povidone-iodine.

## OBJECTIVES

The objective of the study is to evaluate the effect of Benzydamine used in the prophylaxis and treatment of radiation-induced oral mucositis.

**ELIGIBILITY CRITERIA**

- Age should be above 18 years.
- Patients with histopathology report confirming squamous cell carcinoma.
- Patients planned for radiotherapy with a total dose of 60-66 Gy.
- ECOG status 0-2.
- Patients not requiring concurrent chemotherapy.
- No history of previous radiotherapy/chemotherapy.
- No other local/systemic diseases.

## MATERIALS AND METHODS

This was randomized prospective comparative study. We have enrolled 80 patients in our study and divided into two arms; study arm and control arm, by random sampling, each arm consist of 40 patients, selected from July to December 2015.

Informed consent was taken from all the patients, followed by proper history taking with complete clinical examination. Conventional fractionated radiation was delivered to the tumor volume at a dose rate of 180-200 cGy per fraction, with five fractions per week to a total period of 6-7 weeks. The total dosage given varied from 60 to 66 Gy.

All of the Patients in the study were advised to use the 0.15% Benzydamine hydrochloride mouthwash in study arm and 2% Povidone-iodine in control arm for at least five minutes, three times a day. These rinses were given from the beginning of radiotherapy.

The radiation therapy oncology group (RTOG) has developed the acute radiation morbidity scoring criteria for the evaluation of radiotherapy treatment. The RTOG grading is reliant on a clinician's ability to judge the anatomical change associated with oral mucositis (size and characteristics of ulcers).[11] In this study mucositis was graded as recommended by RTOG scoring criteria as follows.

| Grade | Description |
|---|---|
| **Grade-0 (none)** | No change over baseline |
| **Grade-I (mild)** | Irritation, may experience slight pain, not requiring analgesics |
| **Grade-II (moderate)** | Patchy mucositis that may produce inflammatory serosanguinous discharge, may experience moderate pain requiring analgesia |
| **Grade-III (severe)** | Confluent fibrinous mucositis, may include severe pain requiring narcotics |
| **Grade-IV (life threatening)** | Ulceration, hemorrhage or necrosis |

All the patients were examined at the end of every two week from third week onwards during the radiotherapy for about seven weeks and after one month of radiotherapy. The primary endpoint of the study was one month after the completion of radiotherapy. The observations are statistically analyzed with SPSS version 11 software.

## RESULTS

The study was started in July 2015 and completed in December 2015, and almost all patients received radiotherapy as planned.

At the end of the third week of radiotherapy it was observed that, only 18 patients (45%) in the study arm had grade-I mucositis, while 24 patients (60%) from the control arm develop grade-I and grade-II mucositis. None of the patients in study arm had grade-II mucositis, while 2 patients (5%) developed grade-II mucositis in control arm. No statistically significant difference was found between the control and the study arms at the end of third week.

After fifth week, the 24 patients in the study arm had grade-I mucositis (60%) and 16 patients had grade-II mucositis (40%) whereas 14 patients in the control arm had grade-II (35%) and 3 had grade-III mucositis (7.5%). None of the patients in the study arm had grade-III mucositis even at the end of fifth week. There was no statistically significant difference seen among the arms.

At the end of the seventh week of radiotherapy, 14 patients in the study arm had grade-I mucositis (35%) as compared to the 13 patients the control arm (32.5%). Grade-II mucositis was seen in 57.5% patients in the study arm and 40% patients in the control arm. Grade-III mucositis was seen in 3 patients (7.5%) in the study arm, whereas 11 patients had grade-III mucositis (27.5%) in the control arm. The p-value was 0.03 (Fisher exact 0.018) and thus there was statistically significant difference seen between the two arms.

**Table 1: Grades of mucositis in the study and control arm at the end of third week.**

| Mucositis grade At week 3 | Study arm No. of pts. (%) | Control arm No. of pts. (%) |
|---|---|---|
| **0** | 22 (55) | 16 (40) |
| **I** | 18 (45) | 22 (55) |
| **II** | 00 (00) | 02 (05) |
| **Total** | 40 | 40 |

**Table 2: Grades of mucositis in the study and control arm at the end of fifth week.**

| Mucositis grade at week 5 | Study arm No. of pts. (%) | Control arm No. of pts. (%) |
|---|---|---|
| **I** | 24 (60) | 23 (57.5) |
| **II** | 16 (40) | 14 (35) |
| **III** | 00 (00) | 03 (7.5) |
| **Total** | 40 | 40 |

After one month of radiotherapy only 4 patients (10.3%) in the study arm were found to have grade-II mucositis, compared to that of 6 patients in the control arm (15.7%) while 24 patients (61.5%) in the study arm had grade-0 mucositis compared to 17 patients (44.8%) in the control arm. One patient lost for follow-up in study arm while two patients lost for follow-up in control arm.

**Table 3: Grades of mucositis in the study and control arm at the end of seventh week.**

| Mucositis grade at week 7 | Study arm No. of pts. (%) | Control arm No. of pts. (%) |
|---|---|---|
| I | 14 (35) | 13 (32.5) |
| II | 23 (57.5) | 16 (40) |
| III | 03 (7.5) | 11 (27.5) |
| Total | 40 | 40 |

**Table 4: Grades of mucositis in the study and control arm after one month of radiotherapy.**

| Mucositis grade after one month | Study arm No. of pts. (%) | Control arm No. of pts. (%) |
|---|---|---|
| 0 | 24 (61.5) | 17 (44.8) |
| I | 11 (28.2) | 15 (39.5) |
| II | 04 (10.3) | 06 (15.7) |
| III | 00 (00) | 00 (00) |
| Total | 39 | 38 |

## DISCUSSION

Radiation induced Oral mucositis is a complication in the management of head and neck cancer. It is a result of imbalance between cell death and cell division. At first radiation causes mucosal erythema which ultimately results in confluent mucositis and may lead to hemorrhage and necrosis. It is treated with various locally applied and systemically taken agents are used. They are used mostly as supportive treatment to reduce pain, discomfort and secondary infections.[12,13]

In our study we have used 0.15% Benzydamine hydrochloride in 40 patients and compared with other 40 patients in which 2% Povidone-iodine is used. Povidone-iodine is commonly used and established in the treatment of radiation mucositis.

At the end of the third week of radiotherapy it was observed that, only 45% patients using Benzydamine developed grade-I mucositis, while 60% patients using Povidone iodine developed grade-I and grade-II mucositis. None of the patients using Benzydamine developed grade-II mucositis. No statistically significant difference was found between the two arms at the end of third week.

After fifth week, the patients using Benzydamine developed grade-I mucositis in 60% and grade-II mucositis in 40% patients whereas patients using Povidone iodine developed grade-II (35%) and grade-III (7.5%). It is important to observe that none of the patients using Benzydamine developed grade-III mucositis even at the end of fifth week. There was no statistically significant difference seen among the arms.

At the end of the seventh week of radiotherapy, most of the patients using Benzydamine had grade-I mucositis (35%) as compared to the patients using Povidone iodine (32.5%). Grade-II mucositis was seen in 57.5% patients using Benzydamine and 40% patients using Povidone iodine. It is important to note that grade-III mucositis was seen in 3 patients (7.5%) using Benzydamine, whereas 11 patients (27.5%) using Povidone iodine developed grade-III mucositis and there was significant statistical difference (P-value 0.03, Fisher exact 0.018). It shows that by the end of the seventh week of radiotherapy Benzydamine seems to be effective in delaying the progression of severity and decreasing the intensity of oral mucositis.

After one month of radiotherapy only 10.3% patients using Benzydamine were found to have grade-II mucositis, compared to that of 15.7% patients using Povidone-iodine. 61.5% patients using Benzydamine had completely resolved mucositis compared to 44.8% patients using Povidone-iodine. Only one patient lost for follow-up in study arm while two patients lost for follow-up in control arm. These findings suggest that Benzydamine seems to be effective in accelerating resolution and decreasing the duration of mucositis. Previous studies done by Roopashri G. et al and Epstein J.B. et al have the nearly similar results as our study.[14,15]

## CONCLUSION

We conclude that Benzydamine is effective for prophylaxis and treatment of radiation-induced oral mucositis in head and neck cancers. However, these results required further evaluation with larger number of patients.

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