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ORIGINAL ARTICLE

Role of benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients treated with radiotherapy (>50 Gy) with or without chemotherapy

Madhup Rastogi[1] · Rohini Khurana[1] · Swaroop Revannasiddaiah[2] · Isha Jaiswal[1] · Sambit S Nanda[3] · Pooja Gupta[4] · Kundan S Chufal[5] · M L Bhatt[6]

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Abstract
Purpose Benzydamine is recommended for prophylaxis of oral mucositis (OM) in head and neck cancer (HNC) patients for radiation doses (<50 Gy). This study evaluates role of benzydamine for higher radiation doses (>50 Gy) with or without chemotherapy.
Methods One hundred twenty patients of HNC with planned radiation doses of ≥60 Gy were randomized to group A (control radiotherapy alone), group B (study radiotherapy alone), group C (control chemoradiotherapy), or to group D (study chemoradiotherapy). Groups A and C were advised saline mouth rinses, and in groups B and D, additional benzydamine rinses (0.15%) were advised. Mucositis grading was done with both WHO (WHO-M) and CTCAE (CTC-M) version 4.0 (common terminology criteria for adverse events) weekly.
Results Patient characteristics are presented in the table. Patients in group B had lesser grade 3 WHO-M and CTC-M as compared to group A, 62.1 vs. 36.4% ($p = 0.038$) and 51.7 vs. 27.3% ($p = 0.043$), respectively. The rates of Ryle's tube feeding (RTF), intravenous fluid supplementation (IVF), and hospitalization were also lesser in group B as compared to A, 34.5 vs. 21.2% ($p = 0.18$), 27.6 vs. 9.1% ($p = 0.06$), and 6.9 vs. 0% ($p = 0.21$), respectively. WHO-M and CTC-M in groups C and D were not statistically different, 64.3 vs. 43.3% ($p = 0.091$) and 53.6% vs. 43.3% ($p = 0.30$), respectively. The rates of RTF, IVF, and hospitalization were all lesser but $p > 0.05$.
Conclusion Benzydamine significantly reduces OM even at doses >50 Gy in HNC patients. Its role in patients receiving concurrent chemotherapy further needs to be evaluated.

Keywords Benzydamine · Radiotherapy · Concurrent · Chemotherapy

✉ Madhup Rastogi
drmadhup1@rediffmail.com

[1] Department of Radiation Oncology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Vibhuti Khand, Gomti Nagar, Lucknow 226010, India

[2] Department of Radiotherapy, Government Medical College, Haldwani, India

[3] Department of Radiotherapy, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

[4] Department of Radiotherapy, Medanta The Medicity, New Delhi, India

[5] Department of Radiotherapy, Batra Hospital and Medical Research Centre, New Delhi, India

[6] Department of Radiotherapy, King George's Medical College, Lucknow, India

Introduction

Head and neck carcinoma (HNC) is the most common malignancy among males and the fifth most common among females in India. Head and neck squamous cell carcinoma (HNSCC) is the most common of all HNC. The habit of tobacco chewing and smoking is associated with such high incidence of HNSCC [1]. In developing countries like India, only 20% patients present in early stage are treated with single modality treatment either with radiotherapy or surgery, whereas 80% patients present in locally advanced stage often use combined modality treatment [2].

Treatment intensifications in the management of head and neck cancers have come at a cost of increased and at times debilitating morbidities. Of all the toxicities, oral mucositis (OM) poses a significant challenge for the patients as well as the physician. The overall incidence of grade 3/4 OM in

patients treated with conventional fractionation of radiotherapy with or without concurrent chemotherapy ranges from 40 to 80% in various studies [3]. Grade 3–4 OM worsens the quality of life (QOL) of patients during the treatment and leads to treatment interruptions which further impacts the locoregional control and possibly survival as well [4].

Several prophylactic treatments for management of OM like sucralfate, prostaglandins, corticosteroids, vitamins, and anti-oxidants are available but have not been proven to be very effective. Of the several guidelines existing [5], the most evidence-based and comprehensive guidelines come from the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) [6]. Updated guidelines from MASCC/ISOO, [7] recommend the use of benzydamine oral rinse for prevention of radiation induced OM in HNC patients treated with moderate doses of radiation therapy (<50 Gy). However, the role of benzydamine in prophylaxis of OM for patients of head and neck cancers receiving higher dose of radiation (>50 Gy) and in patients with treated with concurrent chemoradiotherapy remains unknown.

We did this prospective randomized study with a hypothesis that the use of benzydamine reduces the rates of OM in patients treated with higher radiation dose (>50 Gy) and also in patients treated with concurrent chemotherapy along with radiation therapy.

Materials and methods

One hundred twenty patients of histopathologically proven squamous cell carcinoma of the head and neck with age >18 years, Karnofsky performance status (KPS) ≥70, planned radiation dose of ≥60 Gy (either definitive or post-operative), hemoglobin ≥10 g/dL, leukocyte count ≥4000/mm^3, absolute neutrophil count ≥1500/mm^3, platelets ≥100,000/mm^3, creatinine clearance ≥50 mL/min, and normal liver function tests were included in this study. Patients with significant comorbid conditions, those with history of prior radiotherapy or history of other malignancies in last 5 years (except basal cell carcinoma, squamous cell carcinoma in situ), those who are pregnant or lactating, and those with reported allergy to benzydamine (0.15%) were excluded from the study.

Study design

This was a non-blinded, prospective, randomized trial. Randomization was done as per computer-generated random numbers. Eligible patients were first stratified into radiotherapy (RT) or chemoradiotherapy (CRT) arms as per indications mentioned in the treatment section below. Patients in the RT arm were further randomized into group A (control radiotherapy alone) or group B (study radiotherapy alone), and similarly, patients in the CRT arm were further randomized into group C (control chemoradiotherapy) or group D (study chemoradiotherapy). Groups A and C were advised saline mouth rinses, and in groups B and D, additional benzydamine rinses (0.15%) were advised for prophylaxis of oral mucositis. Sample size required to detect an expected difference of 20% in the present study arms was calculated to be around 200 each in groups A–D. Owing to limitation of resources, sample size was restricted to 120. A consort diagram of the progress of the trial is summarized in Fig. 1.

Treatment

Post-operative patients were assessed for the need of adjuvant radiotherapy (close margin, T3/T4 stage, multiple levels of lymph node positivity, lymphovascular space invasion, and perineural invasion) or adjuvant chemoradiotherapy (margin positive or extracapsular extension). All patients treated with definitive radiotherapy (except stage I/II patients) received concurrent chemoradiotherapy, if found suitable.

The dose of post-operative radiation (PORT) was 60–64 Gy, and for definitive radiotherapy was 66–70 Gy at 2 Gy per fraction over 6–7 weeks. Patients were immobilized in a customized thermoplastic device in supine position with the arms by the side. Patients were planned with three-dimensional conformal radiation therapy (3D-CRT). Cisplatin (35 mg/m^2 body surface area intravenous weekly) was used in patients suitable for chemoradiotherapy.

Patients in the control groups (groups A and C) and study groups (groups B and D) were instructed to rinse the oral cavity with 10 mL of their respective rinses for at least 1 min, 4–6 times a day. The first mouth rinsing was performed

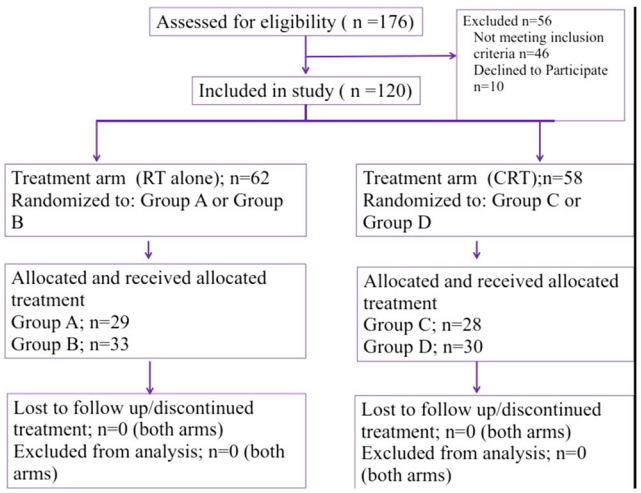

Fig. 1 A consort diagram of the progress of the trial

under professional supervision. Control group patients rinsed with saline gargles (made by adding one half tablespoon salt to 1-L water and kept at room or refrigerated temperatures, depending on patient preference), and patients in the study group additionally rinsed with commercially available benzydamine hydrochloride (0.15%) gargle.

Toxicity evaluation

Patients were examined weekly during and till 4 weeks after completion of RT. Mucositis and pain were recorded and graded as recommended by WHO and CTCAE (common terminology criteria for adverse events version 4.0). Radiation was withheld in emergence of grade 3/4 toxicity. Additionally, rates of Ryle's tube feeding (RTF), requirement of intravenous supplementation, and hospitalization rates were also recorded for all patients.

Statistics

Descriptive analysis was used for patient characteristics. Chi-squared test/Fisher's exact test was used to compare toxicity between the arms. SPSS Software version 19.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses, and all p values were based on a two-sided hypothesis. p value <0.05 were considered significant for all statistical analysis.

Results

Patients

Median age of the patients in groups A–D were 54 (range 34–76 years), 55 (32–86 years), 50 (19–73 years), and 50 (20–73 years), respectively. Median KPS for all groups was 80 (range 70–90). The rest of the patient characteristics are summarized in Table 1.

Treatment and toxicity

Fifteen patients (of 29; 52%), 13 patients (40%), 15 patients (53%) and 16 patients (53%), respectively, in groups A–D underwent surgery, and the rest of the patients were treated with definitive radiotherapy or chemoradiotherapy. Median radiotherapy dose received by patients in groups A and B were 60 Gy (range 56–66 Gy) and in groups C and D were 66 Gy (range 60–70 Gy). Median number of chemotherapy cycles received by patients in groups C and D were 4 (range 2–6).

Radiotherapy alone arm (groups A and B): Median duration of radiation treatment was significantly longer in group A as compared to group B (56 vs. 44 days; $p = 0.042$). Patients in group B had lesser grade 3 WHO-M and CTC-M as compared to group A, 62.1 vs. 36.4% ($p = 0.038$) and 51.7 vs. 27.3% ($p = 0.043$), respectively. The rates of RTF, IVF, and hospitalization were also lesser in group B as compared to A, 34.5 vs. 21.2% ($p = 0.18$), 27.6 vs. 9.1% ($p = 0.06$), 6.9 vs. 0% ($p = 0.21$), respectively.

Chemoradiotherapy arm (groups C and D): Median duration of radiation treatment was longer in group C as compared to group D, though not statistically significant (57 vs. 46 days; $p = 0.08$). WHO-M and CTC-M in groups C and D were less but not statistically different, 64.3 vs. 43.3% ($p = 0.091$) and 53.6 vs. 43.3% ($p = 0.30$), respectively. The rates of RTF, IVF, and hospitalization were all lesser but $p > 0.05$.

Follow-up and response to treatment

Median follow-up in the radiotherapy arm (groups A and B) and the chemoradiotherapy arm (groups C and D) was 8 months (range 2–15 months) and 9 months (range 2–14 months) respectively. Four, three, four, and five patients in groups A–D, respectively, had recurrence at the time of last follow-up. No patient died in any of the study groups.

Table 1 Summarized patient characteristics in different treatment groups

Groups/attributes	Group A	Group B	Group C	Group D
Patient number (n)	29	33	28	30
Sex (M/F)	25/4	28/5	24/4	28/2
Primary site (oral cavity/non-oral cavity)	15/14	19/14	11/17	17/13
Stage (AJCC 2010)				
II	3	3	0	1
III	10	13	7	14
IV	16	17	21	15

KPS Karnofsky performance status, *RT* radiotherapy, *AJCC* American Joint Committee on Cancer

Discussion

The management of cancer has evolved over the period of time, and with the use of supportive medicines, the accompaniments of treatment, once considered as debilitating, has become manageable. Treatment of various cancers including HNSCC has witnessed intensification in the form of escalation of radiotherapy doses as well as use of combination therapies like concurrent chemotherapy [8]. Of the many side effects, OM is a significant accompaniment of anticancer therapy and is associated with interruptions in treatment as well as responsible for decrease in QOL of patients [9].

OM involves mucous membrane of the oral and oropharyngeal cavity and has a dose-response relationship with radiotherapy doses. Particularly, the incidence has been found to be higher in patients treated with higher radiation doses (>50 Gy), in those treated with concurrent chemotherapy or altered fractionation, and also in patients where the irradiated area predominantly involves oral cavity and oropharynx [10]. OM affects the patients in a multifactorial manner, causing significant pain and decrease in oral intake, and this may be further aggravated by superimposed infections [10]. This is also associated with loss of weight, increased use of resources, and increase in the cost of treatment [11].

Management of OM encompasses nutritional support, control of pain, treatment of concomitant infections as well as treatment of any complications like bleeding and ulceration [12]. Frequent oral rinses (4–6 times with saline) are recommended for the prophylactic management of OM in patients receiving radiation therapy for HNC. Benzydamine [13–18] has been found to be effective in reducing OM as well as associated pain across multiple studies. Epstein et al. [14] in their double-blinded, multicentric, randomized study found that use of benzydamine in patients treated with moderate dose of radiation reduced rates of erythema and ulceration and also use of analgesics significantly ($p < 0.05$ for all endpoints). Similarly, Kazemian et al. [5] found the frequency of mucositis more than grade 3 to be 43.6 vs. 78.6% in the benzydamine group compared to the placebo group ($p = 0.001$).

Although, no studies have been reported regarding the use of benzydamine in patients treated with high dose of radiation therapy (>50 Gy) or in patients treated with concurrent chemotherapy, we in our study found a significant reduction in the rates of grade 3 mucositis in patients treated with radiation dose >50 Gy (62.1 vs. 36.4%; $p = 0.038$) and lesser, although not a statistically significant reduction in rates of grade 3 or higher OM in patients treated with concurrent chemotherapy (64.3 vs. 43.3%; $p = 0.091$). We also found lesser rates of RTF, IVF supplementation, and hospitalization rates in patients treated withhigher radiation dose arm (Group B compared to Group A) but not in the concurrent chemotherapy arm (Group D compared to Group C).

One limitation of our study is inadequate sample size of the treatment groups studied. We restricted the number of patients based on the available resources with us. Nevertheless, the results of our study should be taken as hypothesis generating and not confirmatory, and this should lend support to the design and conduct of large, multicentric, randomized study in this regard to further validate the findings of our study.

Conclusion

Benzydamine oral rinses in addition with saline rinses significantly reduces the rates of oral mucositis, Ryle's tube feeding, intravenous supplementation, and hospitalization in patients of head and neck cancers treated with radiation doses >50 Gy and up till 70 Gy. The role of benzydamine in patients treated with concurrent chemotherapy or biological therapy needs to be further studied.

Compliance with ethical standards All patients signed an informed consent before entry into the study and the study was approved by the Institutional Ethics Committee.

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