

A comparative study evaluating the role of benzydamine versus povidone iodine in oral mucositis during concomitant chemoradiation in locally advanced head and neck cancer

Abstract

In India newly diagnosed head and neck cancer constitutes 13.9% of all cancers which is 12.8% of all cancer deaths. Concurrent Chemoradiation is considered the standard of care in locally advanced head and neck carcinomas. Nearly all patients receiving concurrent chemoradiation in the head and neck develop some degree of mucositis. Of these patients treated, some patients develop severe mucositis. Due to this, the patient's quality of life is affected, hospital admission rates are higher, the use of total parenteral nutrition is increased and interruption of treatment is more frequent, all of which compromises tumor control. Severe mucositis causes more treatment interruptions jeopardizing radical treatment outcomes. In the present study, the patients was divided randomly in two groups and all patients received standard fractionation chemoradiation with conventional radiotherapy 64 Gy/32 fractions/6.2 weeks and concomitant injection cisplatin 100 mg/m² three week for three cycles. In group I every patient did gargling with Povidone iodine 2%, and in group II every patient did gargling with Benzydamine 0.15%, four times a day, starting from the first day of radiotherapy till fifteenth day after completion of radiotherapy. At the end of treatment, grade III mucositis was observed in 50% patients in group-I while in 13% in group-II. From this study, we conclude that Benzydamine gargling is better than Povidone iodine gargling in decreasing the severity of chemoradiation induced oral mucositis in head and neck cancers.

Keywords: mucositis, oropharynx, concomitant chemoradiation, head and neck cancer, benzydamine, povidone iodine

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Abbreviations: EBRT, external beam radiation therapy; LAHNC, locally advanced head and neck cancer; HNC, head & neck cancer; ICD, international classification of diseases; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase

Introduction

Concomitant chemoradiation is considered the standard of care in Locally Advanced Head and Neck Cancer (LAHNC).^{1,2} Concomitant chemoradiation in head and neck cancer is associated with some degree of mucositis. Some of the approved oral gargling agents are available for the use of patients to control severity of mucositis in patients of head and neck cancer.³ Benzydamine, available as the hydrochloride form, is a locally-acting non-steroidal anti-inflammatory drug with local anesthetic and analgesic properties for pain relief and anti-inflammatory treatment of inflammatory conditions of the mouth and throat. It is widely used in treating painful inflammation of the mouth and throat conditions including tonsillitis, sore throat and mucositis.⁴ Povidone iodine is a stable chemical complex of polyvinyl pyrrolidone (povidone, PVP) and elemental iodine. Povidone Iodine is broad spectrum antiseptic used for topical application and also as gargles. Povidone iodine liberates iodine in contact with the skin and mucosa causing antiseptic action.

Materials and methods

In the present study total 60-patients of LAHNC were enrolled and were divided randomly by computer generated randomization in two groups of 30-patients and all these patients received standard conventional chemoradiation with 64 Gy/32-fractions/6.2-weeks and concomitant chemotherapy with injection cisplatin 100 mg/m² repeated every three week for three cycles. Every patient did gargling four times a day, starting from first day of radiotherapy till fifteenth day after completion of radiotherapy with Povidone iodine 2% solution in group-I and Benzydamine 0.15% solution in group-II. In these study RTOG criteria was used for assessment of mucositis.

Results and discussion

Male to female ratio was 18:1 and median age of presentation was 54-years. Majority of patients in both groups were from rural population (73.3%). The percentage of alcoholics in group I and II were 63% and 67% respectively. In both groups, majority of the patients presented with chief complaints of swelling in neck (28.3%), followed by pain while swallowing (25%). In both the groups, oropharynx (57%) was the most common International Classification of Diseases (ICD) site followed by larynx (30%). At the end of treatment, grade I mucositis was noticed in 10% patients of group-I, and 43% patients of group-

II. 40% patients in group-I and 43% patients in group-II developed grade II mucositis. Grade III mucositis was observed in 50% patients in group-I, while only 13% patients presented in group-II. No patient in either of the group developed grade-IV mucositis. The mean time of onset of grade III mucositis was 4.7 versus 5.3 weeks in group-I and group-II respectively.

At the end of treatment, complete response (CR) was seen in 33% of patients of group-I and 30% of group-II, whereas partial response (PR) was seen in 67% & 70% each in group-I & II respectively. At 6th month of follow-up, CR was seen in 43% patients in group-I and 40% in group-II, whereas PR was seen in 57% & 60% each in group-I & II respectively.

The highest levels of biochemical toxicities had been graded as per WHO criteria. The grade 1 toxicities related to SGOT (serum glutamic-oxaloacetic transaminase) & SGPT (serum glutamic-pyruvic transaminase) were observed in 2 (6.7%) patients in group-I whereas no patient in group-II has grade 1 toxicity. The grade 2 toxicities were observed in 6.7% patients in group-I and 3% patients in group-II. None of the patients in any of the groups reported any renal toxicity.

Weight loss was assessed weekly, during treatment and at the completion of treatment as per SWOG (South West Oncology Group) criteria. At the end of treatment, 40% of patients in group-I and 53% of patients in group-II experienced grade II weight loss. In most of the patients, nausea/ vomiting leading to inadequate oral intake appeared to be the factors for weight loss.

The number of cancer patients in our third world country are quite high and LAHNC consisting of 13.9% of all cancers. According to hospital based cancer registries in India, head and neck cancers account for 29.8 to 50.4% of all cancers in males and 11.4 to 21.6% of all cancers in females. The incidence of Head & Neck Cancer (HNC) in our institute in past 20-years constitutes 30-40% of all the malignancies.⁵

The mainstay of treatment in LAHNC is concomitant chemoradiation. The most common complication in radical chemoradiation is mucositis which usually leads to interruption of treatment. Hence in the present study, we put our sincere efforts to draw the inference for the prevention of mucositis using different oral solutions and their comparisons.

The 2014 MASCC/ISOO (Multinational Association of Supportive Care in Cancer/The International Society of Oral Oncology) panel recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (Level I Evidence). The guidelines also suggest the use of povidone iodine oral gargle present inadequate or conflicting data, concluding with the designation 'No guideline possible'.⁶

A study by Roopashri et al.⁷ compared benzydamine, chlorhexidine and PVP-I, and found evidence of efficacy for all interventions, but concluded that benzydamine was the superior agent. In fact, the incidence of mucositis was not statistically different in the study and control groups.⁷

Khosro et al.⁸ conducted double-blind placebo-controlled

randomized clinical trial to assess the efficacy of Benzydamine oral rinse in prevention and management of radiation-induced oral mucositis in patients undergoing radiotherapy in head and neck malignancies. They observed that up to the end of third week, two groups did not show any difference in the severity of mucositis. However, by the end of week 4, the mean score of placebo group was more than that of treatment group (1.81 vs 1.27, $P = 0.001$). This trend continued to end of week 7 (1.98 vs 1.43, $P = 0.001$). Hence they concluded that Benzydamine oral rinse can be considered as an effective, safe and well-tolerated medication for prevention of radiation-induced oral mucositis and alleviating its symptoms.⁸

Epstein et al.⁹ conducted a randomized prospective comparative trial in 145-patients of head and neck carcinoma undergoing Conventional Radiotherapy, regimens up to cumulative doses of 50 gray (Gy). They compared the efficacy of Benzydamine with placebo and concluded that Benzydamine significantly reduced erythema and ulceration by approximately 30% compared with the placebo and also greater than 33% of Benzydamine subjects remained ulcer free compared with 18% of placebo subjects. Benzydamine significantly delayed the use of systemic analgesics compared with placebo as well as, effective, safe, and well tolerated for prophylactic treatment of radiation-induced oral mucositis.⁹

In other study on 81-patients, Kazemian et al.¹⁰ concluded that benzydamine 0.15% oral rinse was safe and well tolerated and significantly reduced RT-induced mucositis. In the benzydamine group, the frequency of mucositis grade 3 was 43.6% in contrast to 78.6% in other group ($P = 0.001$). Grade 3 mucositis was 2.6 times more frequent in the placebo group. Intensity of mucositis increased up to fourth week of treatment in both groups to grade 2. In the treated group the grade of mucositis was approximately constant to the end of therapy; but in the control group it raised to grade 3 ($p < 0.001$). The highest grade of mucositis during the treatment time was significantly different between two groups ($p = 0.049$). However, concerns have been raised that at least some of the negative findings reported in the literature may be misleading, as a number of studies have used final concentrations of povidone iodine solution and benzydamine solution that are well below the recommended effective concentration. The present study was done to systematically assess the prevention and decreasing the severity of oral mucositis present in the literature regarding the treatment of oral mucositis.¹⁰

In our study, at the end of treatment, grade I mucositis was observed in 3 (10%) and 13 (43.3%) patients of group-I and group-II respectively, Grade II mucositis was observed in 12 (40%) and 13 (43%) patients and Grade III mucositis was observed in 15 (50%) and 4 (13%) patients of group-I and group-II respectively. None of the patients developed grade IV mucositis. There was no difference in prevention of grade II mucositis in both the groups while benzydamine gargling reduces the incidence of grade III mucositis which is statistically significant.

The mean time of onset of grade-I mucositis was 1.6 versus 3.0 weeks, grade-II mucositis was 2.8 versus 4.0 weeks and grade III mucositis was 4.7 versus 5.3 weeks in group-I and group-II respectively. The difference between them is not statistically significant (Tables 1)(Table 2).

Table 1 Study characteristics.

Study Number	Study Author	Year	Total patients	Patient gargle with Benzydamine (Grade III Mucositis)	Patient gargle with Povidone Iodine (Grade III Mucositis)
1.	Roopashri et al. [7]	2011	100	25 (4%)	25 (24%)
2.	Khosro et al. [8]	2015	51	26	-
3.	Epstein et al. [9]	2001	145	69 (30%)	-
4.	Kazemian et al. [10]	2009	81	17 (43.6%)	-
5.	Kangalingam et al.	2017	23		
6.	Madan et al.	2008	80	-	20
7.	Hashemi et al.	2015			
8.	Adamietz et al.	1998	40	-	20 (20%)

Table 2 Baseline characteristics of all patients.

Characteristics		GROUP I (n=30)		GROUP II (n=30)	
		Number of Patients	Percentage	Number of Patients	Percentage
Age	Mean Age	30 (55.8)	-	30 (52.5)	-
Sex	Male	30	100%	27	90%
	Female	0	-	3	5%
Smoking History	Smoker	30	100%	30	100%
Rural/Urban Status	Rural	27	90%	17	56%
	Urban	3	10%	13	43%
	MDSCC	24	80%	21	70%
Pathology	WDSCC	4	13%	6	20%
	PDSCC	2	7%	3	10%
Clinical Stage	Stage III	23	77%	20	66%
	Stage IV	7	23%	10	34%

Conclusion

Head & Neck Cancer (HNC) is the seventh most common type of cancer in the world and constitutes 5% of the entire cancers worldwide. The global burden of HNC accounts for 6,50,000 new cases and 3,50,000 deaths worldwide every year and a major proportion of regional malignancies in India. The incidence of Head & Neck Cancer (HNC) in our institute in past 20-years constitutes $\frac{1}{3}^{\text{rd}}$ of all the malignancies,⁵ hence remains the main focus of preventing radiation induced side-effects. From the present study, we conclude that Benzydamine gargling is better than Povidone iodine gargling in decreasing the severity of chemoradiation induced oral mucositis in head and neck cancers.

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None.

Conflict of Interest

Authors declare there is no conflict of interest in publishing the article.

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