Bang Med J Khulna 2022; 55; 13-18

ORIGINAL ARTICLE

Role of pilocarpine to prevent radiation induced xerostomia in locally advanced head and neck squamous cell cancer

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Abstract

Background: *Radiotherapy of head and neck region generally includes irradiation of the salivary glands. That results in glandular dysfunction which leads to xerostomia. Xerostomia, the subjective sensation of dry mouth which significantly deteriorates the quality of life.*

Aim and objective: *To compare the effects of pilocarpine HCL with basic oral care vs only basic oral care for controlling xerostomia in patients with locally advanced Head and neck squamous Cell Carcinoma patients having definitive concurrent chemoradiotherapy.*

Material and Method: *A prospective observational hospital based study was carried out in the Department of Oncology, Khwaja Yunus Ali Medical College & Hospital from July 2017 to June 2018 on sixty patients of locally advanced HNSCC. All the patients received 66 Gy/33 Fraction/6.5 wks with concurrent weekly cisplatin (40mg/m²). The study group received concomitant Pilocarpine HCL 5 mg three times a day, starting three days prior to start of radiotherapy, continued for 3 months. Patients were evaluated before start of treatment, weekly during radiotherapy and after completion of radiotherapy two weekly over telephone upto 3 months and finally at 6 months using Zimmermen Xerostomia Questionnaire with Visual Analogue Scale and Xerostomia Grading Scale.*

Result: *Overall incidence of xerostomia was significantly lower in pilocarpine group ($p<0.05$). The average Zimmerman Xerostomia scores of the pilocarpine group as compared to the control group: Dryness of mouth were significantly lower ($p<0.05$) in each of the assessment after the start of radiotherapy. Significant p value is also found in measurement of comfort status of mouth, sleep impairment, speech impairment and difficulty in eating.*

Conclusion*: Pilocarpine given concomitantly and after radiotherapy has shown to reduce symptoms of xerostomia and lower the degree of post radiation salivary dysfunction than that occurring in the patients who had not received pilocarpine.*

Keywords: *Radiation, Xerostomia, Pilocarpine, Head-Neck Cancer*

Introduction

The majority of patients (more than 60%) present with locoregionally advanced disease and are managed with combined modality approaches.[1] Treatment of locally advanced HNC generally consists of either a combination of surgery and radiotherapy or definitive recently concomitant chemotherapy.[2] Almost all head and neck cancer patients undergoing radiotherapy experience some degree of xerostomia. Its incidence varied in the range of 60% to 93% in the era of conventional radiotherapy. With concurrent chemo-radiation, there is an increased incidence of salivary gland dysfunction (by about 70%) when compared with radiation alone.[3-4] The major salivary glands are the parotid, submandibular, and sublingual. The parotid and the submandibular glands are the main contributors to salivary flow, contributing approximately 90% of salivary volume. The parotid gland produces purely serous secretions, creating watery saliva, while the submandibular and sublingual glands produce predominantly mucous secretions, which are more viscous. Several minor salivary glands present in the oral cavity and the pharynx are minor contributors, secreting less than 10% of the saliva. In the unstimulated state, the submandibular gland produces most of the saliva, whereas in the stimulated state the parotid gland is responsible for most of the saliva

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produced. Total salivary flow can be up to 1.5 liter a day in healthy person.[5] The salivary gland cells, although well differentiated, are extremely radiosensitive with serous acini more than the mucous.[6] It depends on the number and size of fractions, linear energy transfer and response modifiers.[7] Radiation-induced damage to the salivary glands alters the volume, consistency and pH of secreted saliva. The secretions become more tenacious and acidic during radiotherapy.8 Saliva is comprised of 90% water and exerts antimicrobial, digestive, antacid and lubricative properties. Inadequate salivary function creates multiple complications, including dental caries, a propensity to oral infections, sleep disturbances, oral pain, and difficulty in talking, chewing and swallowing. Xerostomia has a profound negative impact on quality of life. Xerostomia and its associated symptoms have a considerable, negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties. There should therefore be more focus on the management of xerostomia, which is often neglected in palliative care.[9] Both subjective and objective improvement of xerostomia had been seen with oral pilocarpine in the study of Chitapanarux et al 2008.[10] Pilocarpine is a drug of parasym- pathomimetic activity which acts mainly as a muscarinic agonist having mild beta-adrenergic activity also. Administration of pilocarpine results in pharmacologic stimulation of exocrine glands in humans and leads to diaphoresis, salivation, lacrimation, and gastric and pancreatic secretion.[11]

Although the use of pilocarpine was approved for the treatment of xerostomia in chronic phase, the concurrent use had also been proven in reducing the severity of xerostomia in a prospective, randomized, placebo-controlled trial of 60 patients by Haddad & Karimi 2002.[12] Pilocarpine, given concomitantly with radiotherapy, statistically improved the salivary flow and induced better patient comfort by the end of radiotherapy randomized, double-blind, placebo- controlled study of 66 patients by NYÁRÁDY et al 2006.[13] The Food and Drug Administration currently approves pilocarpine for the treatment of radiation induced xerostomia.[14] The aim of this study was to evaluate the effects of addition of oral pilocarpine to the basic and supportive management in the prevention of xerostomia of patients receiving radiation HNSCC. No statistical data were available in Bangladesh perspective.

Materials and methods

Methods: Prospective observational study had been conducted from July 2017 to June 2018 among the patients with biopsy proven locally advanced head and neck squamous cell carcinoma at department of Oncology, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajgonj A total 60 patients were enrolled in the study with 30 patients belonged to each study group. All patients were treated with external beam radiotherapy with concomitant cisplatin based chemotherapy. The patients of group A received Tab Pilocarpine hydrochloride 5 mg, three times a day, starting three days prior to start of radiotherapy and continued for three months after completion of EBRT, where the patients of group B did not received pilocarpine. The patients who were below 18 or above 70 years having ECOG performance status score more than 2 with history of prior surgery or radiotherapy to the head and neck region, having contraindications to the use of pilocarpine (e.g. glaucoma). Serious concomitant medical illness including severe heart disease, uncontrolled diabetes mellitus, uncontrolled hypertension or renal diseases and uncontrolled infection were excluded from the study. All patients were evaluated properly with clinical examination and relevant investigations before enrollment. Purposive sampling technique was done.

External beam radiotherapy: Radiotherapy was delivered by using a Linear Accelerator (LINAC) machine in all patients (both arm-A and arm-B) in this study. Before irradiation, dental examination was performed carefully. Unless the teeth were damaged severely, dental extraction was avoided. Instruction for oral hygiene were given to prevent dental decay and to reduce the risk of subsequent infection during radiotherapy. The patients were properly immobilized in the supine position. CT simulation was done from the base of skull to the top of the aortic arch with the patient with 3 mm slice thickness. Treatment planning was done by 3D conformal radiotherapy planning with delineation of the targets properly. 10mm GTV to CTV margin and 5mm CTV to PTV margin were used 1151 Contouring was done as per RTOG contouring atlas. The total delivered dose was 66 Gy in 33 daily fractions (one fraction per day, five days per week) over 6.5 weeks for both Arm - A and B. Dose of critical structure like spinal cord, thyroid gland, parotid gland were kept within tolerance limit.

Verification of field and dose distribution was monitored properly before and during treatment and correction set up error was done if needed.

Chemotherapy: All the patients had received Cisplatin 40 mg/m² weekly with proper hydration.

Assessment: Patients were evaluated on subjective basis based on Zimmerman Questionnaire. A 100 mm visual analogue scale was used to record the responses to each five Zimmerman Xerostomia questions. The scale was set up with positive responses on the right (at 100 mm) and negative responses on the left (at 0 mm). The patients marked their responses on the scale in relation to these extremes. Then the mean scores were analyzed. Other toxicities (even xerostomia also) were assessed by the national cancer institute "Common Terminology Criteria for Adverse Events (CTCAE), v.5.0 weekly during radiotherapy and after completion of radiotherapy two weekly over telephone up to 3 months and finally at 6 months.

Data analysis: Data analysis was performed using the SPSS (Statistical Package for Social Science) software program for Windows, version 22.0. The results were presented through tables, figures, and diagrams. Microsoft excel had been used for creating graph. All reported p-values are two-sided, and statistical significance was considered at $p < 0.05$ with95% confidence interval, determined through the Chi-square test.

Ethical consideration: The research protocol received approval from the Institutional Review Board and the Ethical Committee of Khwaja Yunus Ali Medical College & Hospital.

Results

Patient and tumor characteristics: Majority of the patients were diagnosed after 40 years of age and average age of diagnosis was 58±8.7 years and 55.2+9.1 years for arm A and B respectively. Most of the patients in both arm were male. Larynx and buccal mucosa were major primary sites. 22 patient in Arm A and 21 patients in Arm B had stage IV HNSCC whereas only 8 and 9 patients in Arm A and Arm B respectively had stage III disease. Majority patients in this study had well differentiated variety of HNSCC. 21 (70%) patients in Arm A and 13 (43.3%) of patients in Arm B belonged to ECOG performance status 0. Only 1 patient from arm A and 3 patients from Arm B had ECOG PS 2 (Table I).

Table I

Patient and tumor characteristics of both study Arm

Characteristics	Arm A n = 30	Arm B n = 30
Mean age	58.2±8.7	55.1±9.1
Sex		
Male	18	23
Female	12	07
Socioeconomic status		
Lower	20	21
Middle class	10	09
Educational status		
Literate	15	21
Iliterate	15	09
Tumor size (T stage)		
T1	03	09
T2	06	09
T3	04	03
T4	17	09
Lymph nodes (N stage)		
NO	09	04
N1	06	13
N2	13	13
N3	02	00
Clinical stage		
Stage III	08	09
Stage IV	22	21
Histological differentiations		
Well	17	13
Moderate	13	16
Poor	00	01
Site of primary tumour		
Oral cavity	22	11
Oropharynx	01	01
Hypopharynx	00	00
Larynx	05	18
ECOG Performance status		
PS 0	21	13
PS 1	08	14
PS 2	01	03

Overall toxicities after radiotherapy: The most prevalent toxicities observed after radiotherapy were xerostomia, mucositis, skin reactions, dysphagia, nausea, excessive salivation, excessive sweating, vertigo and loss of taste sensation. The grade I mucositis occurs 50% in arm A and 43.32% in arm B. Grade II mucositis 30% and 40% in arm A and B respectively. No grade-III mucositis observed in Arm-A. Skin toxicity was

more or less same in Arm A and B. Grade I skin reaction occurs 23.32 % and 6.66% in Arm A and B correspondingly. Grade II skin reaction was 6.66% in both arms. Grade III skin reaction occurs 3.33% only in Arm A. All of them are managed accordingly. Nausea occurs 60% in Arm A and 53.3% in arm B. Dysphagia occurred 76.7% and 40% in Arm A and Arm B respectively. Loss of taste sensation occurs 36.66% and 46.66% in Arm A and B respectively. Dysphagia and excessive salivation were slightly higher in Arm A. 76.7% patients of Arm A experienced dysphagia in comparison to 40% in Arm B. 50% patients of Arm A experienced excessive salivation due to pilocarpine administration, while none of the patients of Arm B had such experience (Table II).

Table II

Toxicities in both study Arms during and after radiotherapy (n=60)

Variables	Arm A(n=30)	Arm B(n=30)
Mucositis -		
Grade I	15(50%)	13(43.3%)
Grade II	09(30%)	12(40%)
Grade III	00(00%)	2(6.7%)
Grade IV	00(00%)	0(00%)
Skin reaction -		
Grade I	07(23.3%)	08(26.7%)
Grade II	02(6.7%)	02(6.7%)
Grade III	01(3.3%)	0(0%)
Nausea	18(60%)	16(53.3%)
Xerostomia	00(0%)	25(83.3)
Dysphagia	23 (76.7%)	12 (40%)
Excessive salivation	15 (50%)	00(0%)
Excessive sweating	03 (10%)	00(0%)
Vertigo	03 (10%)	00(0%)
Headache	04 (12%)	00(0%)
Loss of taste sensation-	11(36.7%)	14(46.7%)

Xerostomia assessment: According to CTCAE grading, patients of Arm-A who received pilocarpine had significantly lower xerostomia than patients of Arm-B both during and after radiotherapy. In fact, no patients of Arm-A experienced xerostomia at all. Incidence of grade-I and grade-II xerostomia in Arm-B were 23% and 40% during radiotherapy. After completion of radiotherapy, 20% (3.3% grade-I and 16.7% grade-II) patients of Arm-B had been suffered from xerostomia within 6 months. Grade-III xerostomia had been experienced by none of the patients in this study (Table III).

Table III

Distribution of the study patients according to onset of Xerostomia during and after treatment (n=60)

Xerostomia during tteatment	Arm-A (n=30) No. (%)	Arm-B (n=30) No. (%)	x^2value	p-value
Grade I	0(0.0%)	7(23.3%)		
Grade II	0(0.0%)	12(40.0%)		
Grade III	0(0.0%)	0(0.0%)	42.8	<0.001s
Grade IV	0(0.0%)	0(0.0%)		
Total	30(100.0%)	30(100.0%)		
Xerostomia after completion of treatment	Arm-A (n=30) No. (%)	Arm-B (n=30) No. (%)	x^2 value	p-value
Grade I	0(0.0%)	01(3.3%)		
Grade II	0(0.0%)	05(16.7%)		
Grade III	0(0.0%)	0(0.0%)	60.0	<0.001 $
Grade IV	0(0.0%)	0(0.0%)		
Total	30(100.0%)	30(100.0%)		

Zimmerman Xerostomia Score: Assessment of xerostomia was done through Zimmerman Xerostomia score. A 100 mm visual analogue scale was used to record the responses to each five Zimmerman Xerostomia questions. The scale was set up with positive responses on the right (at 100 mm) and negative responses on the left (at 0 mm). The patients marked their responses on the scale in relation to these extremes.

Table IV

Average Zimmerman Xerostomia Score in Radical Radiotherapy for HNC

	First assessment		Second assessment		Third assessment		Fourth assessment	
Zimmerman Xerostomia Score Parameters	Arm-A (n=30) Mean (mm)	Arm-B (n=30) Mean (mm)	Arm-A (n=30) Mean (mm)	Arm-B (n=30) Mean (mm)	Arm-A (n=30) Mean (mm)	Arm-B (n=30) Mean (mm)	Arm-A (n=30) Mean (mm)	Arm-B (n=30) Mean (mm)
Dryness of mouth	100	100	60	40	65	42	74	46
p-value			P<0.001		P<0.001		P<0.001	
Comfort status mouth	100	100	55	32	58	36	70	40
p-value			P<0.001		P<0.001		P<0.001	
Sleep impairment	100	100	59	44	65	47	71	52
p-value			P<0.001		P<0.001		P<0.001	
Speech impairment	100	100	51	43	62	49	68	58
p-value			P<0.001		P<0.001		P<0.001	
Difficulty in eating	100	100	44	28	51	31	64	33
p-value			P<0.001		p<0.001		P<0.001	

Then the mean scores were analysed. Higher the Zimmerman Xerostomia score on a visual analogue scale of (0-100) mm, better is the salivary gland function. The average Zimmerman Xerostomia scores of the pilocarpine group as compared to the control group: Dryness of mouth were at First assessment (before start of

radiotherapy) - 100mm Vs 100mm; Second assessment (the day radiotherapy was completed) - 60mm Vs 40mm; Third assessment (at month 3 after completion of radiotherapy)- 65mm Vs 42mm; Fourth assessment (at month 6 after completion of radiotherapy) - 74mm Vs 46mm. P value<0.05, which was significant. Significantly better score was also found for comfort status of mouth, sleep impairment, speech impairment and difficulty in eating at every assessment in the patients of Arm-A (Table IV, Figure I)

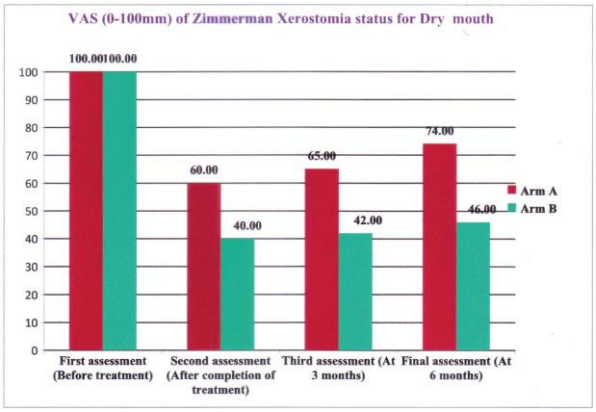

Figure 1: Assessment of Zimmerman Xerostomia status at four points in time on visual analogue scale about dry mouth

Discussion

One of the commonest complications experienced by head and neck cancer patients after radiotherapy is xerostomia. It has negative impact on oral health and can result in sore throat, altered taste, dental decay, poor tonal quality and difficulty in chewing and swallowing function. In this study, Pilocarpine is a parasympathomimetic sialogogue had been used during concurrent chemoradiotherapy for locally advanced head and neck squamous cell carcinoma. Mean age of the patients in this study were 58+8.7 years and 55.21+9.1 years for Arm-A and Arm-B. Male sex was predominant in both arms. Most patients had ECOG PS 0 or 1. Stage-IV was more common than stage-III. Oral cavity and larynx were the frequent primary sites.

None of the patients of Arm-A, who received pilocarpine during radiotherapy had experienced xerostomia during or after completion of radiotherapy which was significantly lower than Arm- B. Total 25 (83.3%) patients of Arm-B experienced xerostomia before or after radiotherapy, although none of them had grade-III xerostomia. Incidence of xerostomia was 75% after radiotherapy using 3DCRT in head & neck cancer as per Kawamoto et al. 2018.[16] The concurrent use had also been proven in reducing the severity of xerostomia in a prospective, randomized, placebo-controlled trial of 60 patients by Haddad & Karimi 2002.[12]

Zimmerman Xerostomia Questionnaire, Visual Analogue Scale and Salivary Gland Changes/ Xerostomia grading scale (Adapted NCI CTCAE criteria, version 4.03) had been used to grade the severity of xerostomia. The average Zimmerman Xerostomia scores of the pilocarpine group was significantly better in all aspects (Dryness of mouth, comfort status of mouth, sleep impairment, speech impairment and difficulty in eating) as compared to the control group ($p<0.05$). These findings indicated that salivary flow had been increased with the use of pilocarpine during radiation therapy. Even though some improvements had been seen in salivary flow at 3 to 6 months after treatment that correlates with the result of Fisher et al. 2003 and also Zimmerman et al. 2006.[14,17]

Besides xerostomia, the most prevalent toxicities were mucositis, skin reactions, dysphagia, nausea and loss of taste sensation. There were no life-threatening events after concurrent chemoradiotherapy in this study. Most of the toxicities were similar in two study arms. But dysphagia was higher in the control group as a consequence of higher incidence of xerostomia in control arm.

The frequency and severity of known side effects of pilocarpine were specifically enquired and documented. The adverse effects were nonspecific symptoms such as excessive salivation 50% (15/30), excessive sweating 10% (3/30), and vertigo 10% (3/30). These were generally of mild degree and managed accordingly. There was no requirement of hospital admission for those adverse effects. Excessive salivation occurred mainly in the first few weeks after radiation therapy as due to muscarinic effects of pilocarpine. This excess saliva was thick and mucoid in consistency. Although xerostomia starts mainly in the 3rd weeks after radiotherapy and parotid gland (Predominantly serous secretion) effected first, the excess salivation in some patients was logical and mucoid consistency was mainly due to minor salivary gland stimulation which is rarely affected by radiotherapy.[18-19]

Major limitations in this study were small sample size, no randomization and most importantly no evaluation of objective response regarding xerostomia. But it had been a difficult task to see the objective response because during pre-testing most of the study subjects were unable to follow the procedure to see the salivary flow rate and that's why this procedure had been omitted during the final study design.

Conclusion

Despite good local control and organ preservation, radiotherapy also has some complications. Xerostomia is an important acute and late sequelae of radiation therapy leading to patient anxiety and morbidity. Treatment of resultant dry mouth is at present poor. Pilocarpine had a better result in controlling radiation induced xerostomia and it is cheap with few side effects. So, pilocarpine may be used concurrently with radiotherapy as a routine practice.

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