

Pilocarpine and prevention of radiation induced xerostomia in HNSCC

Abstract

Stated purpose: To evaluate the efficacy and safety of concomitant pilocarpine with radiation therapy for the prevention of radiation induced xerostomia in Head & Neck cancer.

Material & methods: A prospective, randomized, study was carried out on sixty treatment naïve histopathologically proven patients of squamous cell carcinoma of head and neck. All the patients received 64Gy/32Fraction/6.2wks with and without pilocarpine. The study group received concomitant Pilocarpine hydrochloride 5.0 mg four times a day, starting three days prior to start of radiotherapy, continued for 3-months. Patients were evaluated at four points for xerostomia using subjective and objective scale. The Zimmermans Xerostomia Questionnaire and Visual Analogue Scale were used for evaluation of results. The statistical analysis was done by Paired sample T test and Mann-Whitney U-Test.

Results: The average Zimmerman Xerostomia scores of the pilocarpine group as compared to the control group were: First assessment-100mm Vs 100mm; Second assessment-48mm Vs 37mm; Third assessment-57mm Vs 41mm; Fourth assessment-62 Vs 44mm. The average LENT SOMA grades for the study group and the control group along with SEM respectively were: First assessment 1 Vs 1; Second assessment 2.7 (SEM-8.510X10⁻²) Vs 3 (SEM-0.000); Third assessment 2.3 (SEM-0.1150) Vs 2.5 (SEM-9.285X10⁻²); Fourth assessment 2.3 (SEM -0.1150) Vs 2.5 (SEM -9.285X10⁻²). The RTOG Salivary Gland Morbidity Scores for the study group and the control group respectively were: First assessment -0 Vs 0; Second assessment -1.8 Vs 2 (p Value-0.595); Third assessment -1.6 Vs 1.8 (p Value -0.094); Fourth assessment -1.6 Vs 1.8 (p Value-0.054).

Conclusion: The objective assessment of xerostomia done by these scales were favorable in the study group as compared to the control group signifying that concomitant pilocarpine preserved better salivary gland function.

Keywords: pilocarpine, prevention of radiation induced xerostomia, concomitant pilocarpine with radiation therapy

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Atri R, Dhull AK, Kaushal V

Department of Radiation Oncology, BD Sharma Post Graduate Institute of Medical Sciences, India

Correspondence: Rajeev Atri, Department of Radiation Oncology, BD Sharma Post Graduate Institute of Medical Sciences Rohtak, Haryana, India, Tel 919354180865, Email AnilKDhull@gmail.com

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Abbreviations: HNSCC, head and neck squamous cell carcinoma; HNC, head and neck cancer; KPS, Karnofsky performance status; Zn, zinc; Mn, manganese; Fe, ferric; WDSCC, well differentiated squamous cell carcinoma; MDSCC, moderately differentiated squamous cell carcinoma; PDSCC, poorly differentiated squamous cell carcinoma; M:F Ratio, male: female ratio; SD, standard deviation; SEM, standard error of mean

Introduction

Radiotherapy alone, or in combination with surgery or chemotherapy, is the main modality used in the treatment of head and neck cancer. For cure, radiation doses more than 60Gy are needed though the tolerance of normal organs e.g. salivary gland varies between 32Gy (TD5/5) to 46Gy (TD50/5).¹ Out of all the radiation reactions, xerostomia, the subjective sensation of dry mouth is one of the commonest and most troublesome. It may be an inconvenience when mild, or a debilitating condition when severe. The decreased salivary flow causes chronic oral discomfort and functional problems. Xerostomia is the main clinical effect that interferes with nutrition, use of dentures and oral hygiene. It predisposes patients to oral candidiasis and dental problems e.g. dental caries.¹⁻³ Pilocarpine has been used for prevention and treatment of radiation-induced xerostomia with variable success. The present prospective, randomized, study was carried out to evaluate the efficacy and safety of concomitant pilocarpine with radiation therapy for the prevention of radiation

induced xerostomia in patients receiving radical radiotherapy for head and neck cancer.

Materials and methods

From March 2003 to July 2004, a prospective randomized study was carried out on sixty treatment naïve patients of head & neck cancer, suitable for radical radiotherapy. All these patients had histopathologically proven squamous cell carcinoma of head & neck region. Excluded from the study were, patients of early head & neck cancer suitable only for brachytherapy, patients on palliative radiotherapy, patients who had received radiotherapy or chemotherapy earlier, patients planned to receive concurrent chemoradiation, patients having distant metastasis, patients having Karnofsky Performance Status <70, pregnant or lactating females and the patients having contraindications to the use of pilocarpine (e.g. glaucoma etc.)

The patients were staged according to AJCC - 2002 staging system.⁴ The sixty patients were divided in two groups of 30 patients each by draw of lots. All the patients were planned to receive a total target radiation absorbed dose of 64 Gy/32Fraction/6.2wks (2Gy/Fraction, 5 days/week) on a Telecobalt machine. The study (Pilocarpine) group comprised of randomly selected thirty patients who, in addition to above radical radiotherapy received tablet Pilocarpine hydrochloride 5.0 mg four times a day, starting three days prior to start of radiotherapy and continued for 3-months. Control group comprised of randomly selected thirty patients who received the similar radical

external radiotherapy without concomitant pilocarpine. The radiation reactions were graded according to RTOG criteria⁵ and tumor control was assessed using WHO criteria.⁶

Patients were evaluated for xerostomia using Zimmerman⁷ Xerostomia Questionnaire for subjective assessment and LENT SOMA Scale for objective assessment.⁸ The Zimmerman Xerostomia Questionnaire includes parameters like dryness of mouth and tongue, comfort status of mouth and tongue; sleep impairment attributed to dryness of mouth, speech impairment attributed to dryness of mouth and difficulty in denture wearing. It utilizes a Visual Analogue Scale for subjective documentation of xerostomia. The Zimmermans Xerostomia status was assessed at four points in time: before start of treatment, the day radiotherapy was completed, at 3-months, and at 6-months.

LENT SOMA scale for objective assessment of xerostomia includes following parameters: normal moisture, scant saliva, absence of moisture, stickiness of saliva, presence of coated mucosa etc. It was used in the present study for objective evaluation of the radiation induced xerostomia. The LENT SOMA scale status was assessed at four points in time: before start of treatment, the day radiotherapy is completed, at 3-months, and at 6-months.

Results

The radiation reactions in study and control group respectively were as follows: cutaneous radiation reactions; Grade I- 2(7%) vs 1(3%), Grade II-25 (83%) vs 27 (87%), Grade III- 3(10%) vs 3(10%); Mucosal radiation reactions; Grade I- 1(3%) vs 0(0%), Grade II- 19 (64%) vs 20 (67%), Grade III- 10(33%) vs 10(33%). Complete response in the study and the control group respectively was as follows: Stage II-5/6 (83%) vs 2/2 (100%); Stage III-8/14 (57%) vs 7/12 (58%); Stage IV-1/10 (10%) vs 2/16 (12.5%). Partial response in the study and the control group respectively was as follows: Stage II-16 (17%) vs 0/2 (0%); Stage III-6/14 (43%) vs 5/12 (42%); Stage IV-8/10 (80%) vs 12/16 (75%). No response in the study and the control group respectively was as follows: Stage IV-1/10 (10%) vs 2/16 (12.5%).

Zimmerman Xerostomia scores for various parameters in the pilocarpine group as compared with control group respectively have been shown in (Table 1). Higher the Zimmerman Xerostomia Score on a scale of 0-100, better is the salivary gland function. The average Zimmerman Xerostomia score for all parameters (dryness of mouth and tongue, comfort status of mouth and tongue, sleep impairment, speech impairment and difficulty in chewing and swallowing) combined (Figure 1), of the pilocarpine group as compared to the control group was as follows: First assessment -100mm vs 100mm; Second assessment -48mm vs 37mm; Third assessment -57mm vs 41mm; Fourth assessment -62 vs 44mm. There was overall trend of better salivary gland function in study group as compared to control group. The average Zimmerman Xerostomia score variation with stage was as follows: Stage II; 77.2mm vs 66.2mm, Stage III; 66.2mm vs 49.3mm, Stage IV; 55.2mm vs 43.6mm. The average Zimmerman scores were better in stage II patients and were worst in stage IV patients in both the study and the control group.

Objective LENT SOMA scale for assessment of xerostomia is divided into four grades: grade-1 normal moisture; grade-2 scant saliva; grade-3 absence of moisture, stickiness of saliva; grade-4 absence of moisture, coated mucosa. Lower the LENT SOMA grade on a scale of 1-4, better is the salivary gland function. The average LENT SOMA grades as measured at the time of various assessments

for the study group and the control group along with Standard Error of Mean (SEM) respectively were as follows: First assessment 1Vs 1; Second assessment 2.7 (SEM-8.510X10⁻²) Vs 3 (SEM -0.000); Third assessment 2.3 (SEM -0.1150) Vs 2.5 (SEM -9.285X10⁻²); Fourth assessment 2.3 (SEM - 0.1150) Vs 2.5 (SEM -9.285X10⁻²). The LENT SOMA grades were maximum at the time of completion of radiotherapy which improved to some extent in both groups at 6-months. Table 2 & 3 shows that xerostomia grade was higher in control group as compared to pilocarpine group, signifying that better salivary gland function was preserved with use of pilocarpine.

Table 1 Patient characteristics in radical radiotherapy for HNC

Characteristics		Patient Group	
		Pilocarpine Group n=30	Control Group n=30
Age (years)	Range	31- 80	31- 70
	Mean	51	50.9
	±S.D-9.22		±S.D-8.77
Gender	Male	29	29
	Female	1	1
	M:F Ratio	29:1	29:1
Karnofsky Performance status	>=70	30	30
	I	0	0
Tumor stage (AJCC-2002)	II	6	2
	III	14	12
	IV	10	16
	Floor of mouth	4	4
Primary site	Tonsil	9	3
	Base of tongue	17	22
	Soft palate	0	1
	WDSCC	7	4
Histopathology	MDSCC	22	25
	PDSCC	1	1

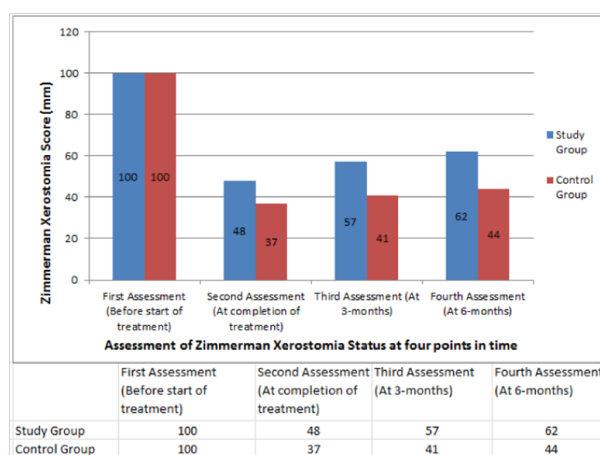


Figure 1 Average Zimmerman Xerostomia Score (n=60) in radical radiotherapy for head & neck cancer.

The RTOG Salivary Gland Morbidity Scores as measured at the time of various assessments for the study group and the control group respectively were as follows: First assessment -0 Vs 0; Second assessment -1.8 Vs 2 (p Value-0.595); Third assessment -1.6 Vs 1.8 (p Value -0.094); Fourth assessment -1.6 Vs 1.8 (p Value-0.054). The RTOG Salivary Gland Morbidity Scores were maximum at the time of completion of radiotherapy, which improved to some extent in both

the groups at 6 months. The average recovery in grades was 0.2 in both the study and the control group between the second and the final assessment. However, in both the groups pretreatment values were not achieved.

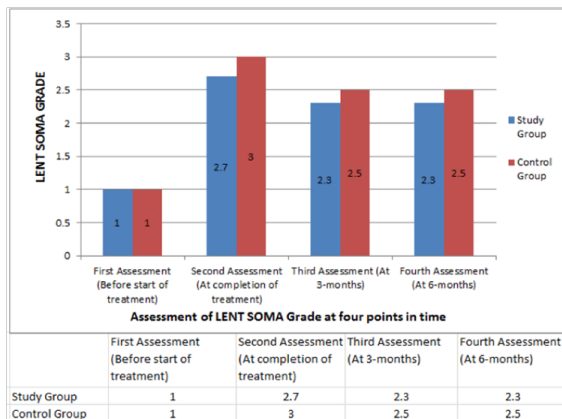


Figure 2 Average LENT SOMA grade in radical radiotherapy for head & neck cancer.

The frequency and severity of known side effects of pilocarpine were specifically enquired and documented. The adverse effects were nonspecific symptoms such as nausea (5/30), palpitations (2/30), excessive lacrimation (4/30), rhinitis (4/30), urinary frequency (3/30) and sweating (11/30). These were generally of mild degree.

Discussion

Xerostomia is a major complication in patients who are receiving curative radiotherapy for head and neck cancer. Having no threshold dose, the magnitude depends both on the volume of salivary tissue irradiated and dose of radiation delivered. Xerostomia and its associated symptoms have a considerable, negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties.¹⁻³ Treatment of radiation induced xerostomia calls for good hydration, optimal oral hygiene and prophylaxis of candidiasis. Therapeutic options are artificial saliva substitutes, mouth wetting

agents and drugs like pilocarpine and amifostine.⁹ However radiation induced xerostomia is better avoided than dealt with.¹⁰ It has been shown that preemptive use of oral pilocarpine hydrochloride prior to and concurrent with therapeutic irradiation in head and neck cancer patients has a positive effect upon retention of a beneficial level of post irradiation salivary function with no jeopardy of tumor control.⁷⁻¹² Pilocarpine is being used for prevention and treatment of radiation-induced xerostomia with a good measure of success.

The mechanism of action of radiation induced xerostomia is unknown. The main damage to serous salivary tissue is because of intracellular leakage of proteolytic enzymes in secretory granules after radiation induced per-oxidative damage. It is noteworthy that pretreatment with atropine which inhibits salivation and leads to an increase in secretory granules found in acinar cells, resulted in increased radiation damage to salivary glands. Pilocarpine by depleting heavy metals such as Zn, Mn, and Fe found in secretory granules, leads to reduction in metal-catalyzed lipid peroxidation of lysosomal membranes and subsequent serous cell autolysis seen following radiation.¹³ The improvement of xerostomia may also be due to stimulation of residual function of non-irradiated parts of parotid and other salivary glands/minor salivary glands. As consistent with our findings, some studies have also suggested that stimulation of these salivary glands by pilocarpine is responsible for better salivary gland function in irradiated patients.¹⁴⁻¹⁶

It is known that xerostomia begins within first week of radiotherapy. This has been the rationale to begin pilocarpine administration during radiotherapy Zimmerman et al.,⁷ showed that concomitant administration of pilocarpine with radical radiotherapy followed by continuation of pilocarpine for three months is adequate for favorable outcome in prevention and treatment of radiation induced xerostomia. Similar schedule of pilocarpine administration was followed in our study. Pilocarpine was well tolerated by all patients of study group and side effects were mild as reported in other studies.^{7,8,18,19} Discontinuation of pilocarpine because of side effects was not required in any of the patients.

Table 2 Average Zimmerman Xerostomia score in radical radiotherapy for HNC

	First Assessment		Second Assessment		Third Assessment		Fourth Assessment	
Zimmerman Xerostomia Score	Pilocarpine Group (n=30)	Control Group (n=30)	Pilocarpine Group (n=30)	Control Group (n=30)	Pilocarpine Group (n=30)	Control Group (n=30)	Pilocarpine Group (n=30)	Control Group (n=30)
Parameters	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)	Mean (mm) (SEM)
Dryness of mouth	100	100	48 (1.6089)	39 (1.6491)	57 (1.5365)	42 (1.6283)	62 (1.6574)	44 (1.6082)
p-value			P=0.000		P=0.000		P=0.000	
Comfort status of mouth	100	100	43 (1.4015)	32 (1.4794)	50 (1.7234)	36 (1.4637)	58 (1.4762)	40 (1.4948)
p-value			P=0.000		P=0.000		P=0.000	
Sleep impairment	100	100	60 (1.5796)	44 (1.6077)	64 (1.6811)	48 (1.6252)	70 (1.7237)	53 (1.5573)
p-value			P=0.000		P=0.000		P=0.000	
Speech impairment	100	100	50 (1.6774)	42 (1.6344)	60 (1.6451)	50 (1.5967)	68 (1.5989)	68 (1.5989)
p-value			P=0.001		P=0.000		P=1.000	
Difficulty in eating	100	100	43 (1.4596)	27 (1.3561)	50 (1.6341)	30 (1.4158)	62 (1.5132)	33 (1.4700)
p-value			P=0.000		P=0.000		P=0.000	

P value<0.05 statistically significant for each group, the distance from left side of scale were measured in millimeters, and then averaged and compared

Table 3 Objective xerostomia grade in pilocarpine and control groups in radical radiotherapy for HNC

	Maximum	Minimum	Median	Mode	SD (Standard Deviation)
Pilocarpine Group	3	1	2	2	0.65
Control Group	3	2	2.5	3	0.51

Several studies have shown significant improvement in radiation induced xerostomia when pilocarpine was given along with radiotherapy in HNC where whole of parotid glands received more than 45 Gy.⁷⁻¹² Our study has also shown improved subjective and objective xerostomia grades, which correlated positively, but results were not statistically significant. The average xerostomia scores were better in stage II patients and were worst in stage IV patients in both the study and the control group. This may be explained by the fact that radiation fields generally smaller in stage II patients, making sparing of salivary glands possible.

The possibility of tumor protection by pilocarpine is a valid concern that needs to be addressed. In *in vitro* studies, pilocarpine does not alter tumor cell killing by gamma irradiation.⁷ The tumor response rate of radiation treatment was almost similar in both the groups in the present study. The present study agrees with previous *in vitro* studies where pilocarpine did not alter tumor cell kill by gamma irradiation.

Conclusion

In the present study the Pilocarpine given during and continued for three months after radiotherapy has shown to reduce symptoms of xerostomia during treatment and lower the degree of post radiation salivary dysfunction than that occurring in a similar cohort of patients who had not received pilocarpine.

Acknowledgments

None.

Conflicts of interest

Authors declare there are no conflicts of interest.

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