Randomized Double Blind, Placebo-Controlled Study of Pilocarpine Administered During Head and Neck Irradiation to Reduce Xerostomia

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Abstract

Purpose : Pilocarpine hydrochloride administered during head and neck irradiation was evaluated for its ability to relieve xerostomia and its adverse effects.

Material and Method : A total of 60 head and neck cancer patients were enrolled in a randomized, double blind, placebo - controlled trial. Each patient had both parotid glands treated with a radiation dose of at least 50 Gy. Patients received jelly containing pilocarpine or placebo 5.0 mg (1 cc.) tid at meal times during radiation. Pilocarpine was administered beginning on the first day of radiation and continued until radiation was completed. Patients were evaluated for symptomatic relief by responding to questionnaires using a Visual Analogue Scale (VAS). Questionnaires measured relief of oral dryness, oral discomfort, difficulty in chewing and swallowing, speaking, and sleeping. Evaluation was conducted preradiation as a baseline, weekly during radiation and monthly until 6 months after radiation was completed.

Results : The baseline characteristics, disease and radiation technique including field arrangement and total dose, were not significantly different between the two groups. There was no statistically significant subjective difference in xerostomia, including oral dryness, oral discomfort, inability to chew and swallow, speak and sleep, during and postradiation between the two groups. The adverse effects were non-specific symptoms such as nausea, vomitting, dizziness, urinary frequency, palpitation, sweating and tearing. The adverse effects during radiation and postradiation were not significantly different between the two groups.

Conclusion : It was concluded that pilocarpine hydrochloride administered during head and neck irradiation produced subjectively insignificant benefit in relieving xerostomia with acceptable side effects.

Key word : Pilocarpine, Xerostomia, Radiation Therapy, Head and Neck, Cancer

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Xerostomia is the subjective feeling of dry mouth caused by a severe reduction in the salivary flow(1). Radiotherpy of patients with head and neck tumors usually causes damage to the salivary gland since these are frequently unavoidably included in the field of radiation(2). Salivary gland hypofunction commonly develops during radiation therapy(3). It is usually severe and often permanent(4). Xerostomia usually persists for several months to years and may or may not recruit depending on the volume of radiation, total radiation dose and individual patient variation. Degree of damage is known to be proportional to the volume of irradiated salivary tissue. Total dose exceeding 60 Gy causes permanent changes(fibrosis, secretory function) (5). Xerostomia, with secondary symptoms of increased dental caries, difficulty in chewing, swallowing and speaking and increased incidence of oral candidiasis and nutritional deficiency, can have a significant effect on the quality of life and the physical and psychological well-being of patients. Therapeutic approaches include improved oral hygiene, dietetic adjustments and artificial saliva. Salivary stimulants such as pilocarpine hydrochloride is a cholinergic agonist which stimulates salivary secretion(6). Treatment options including salivary substitutes and saliva stimulants are largely palliative and generally offer only short term relief of symptoms(7). In recent years, there have been preliminary results from a clinical trial which suggest that the use of pilocarpine, given during the course of radiotherapy, may reduce the secretory hypofunctional effect(8).

The purpose of this study was to evaluate the ability of pilocarpine administered during radiation to reduce xerostomia and to assess its adverse effects.

MATERIAL AND METHOD

Patients

This study was conducted at the Department of Radiology, Songklanagarind Hospital, between January 1998 and January 1999. Patients with histologically documented squamous cell carcinoma of head and neck who would receive definitive or postoperative radiation were eligible. Patients were excluded if they had significant uncontrolled cardiac, pulmonary, renal or occular disease or required tricyclic antidepressants or antihistamine with antichlolinergic effects, beta blocker, pilocarpine for opthalmic indications or chemotherapy.

Sixty head and neck cancer patients were randomized by a block of four technique into 2 groups of 30 patients each. Informed consent was obtained from all subjects before randomization. The study had institutional review board approval.

Radiation

All patients were treated with Cobalt-60 or 6 MV photon machine. The standard arrangement consisted of opposing lateral portals, loaded 1: 1 and / or anterior low neck field. Each patient had both parotid glands treated to a dose of at least 50 Gy with an equal daily dose of 1.8 to 2.0 Gy.

Pilocarpine hydrochloride/ Placebo

The drug consisted of pilocarpine jelly in dosages of 5.0 mg. All jelly was manufactured by the Songklanagarind Hospital Pharmacy. Drug and identically appearing placebo were self administered 3 times a day at meal times. Patients and investigators were unaware of which treatment was administered. Pilocarpine hydrochloride was administered beginning on the first day of radiation, and continued daily until completion of radiation. Compliance was not objectively measured.

Patient questionnaires

All patients were seen prior to initiation of treatment and at 1– week intervals during radiation and at 1- month intervals post complete radiation upto 6 months. At each scheduled visit, patients were requested to make a subjective assessment of their xerostomia using a visual analogue scale (VAS). The patients answered questions about their sensation of oral dryness, oral discomfort and difficulties in speaking, chewing and swallowing and sleeping. A 100-mm visual analogue scale was used to record the responses to each question. The VAS was set up with negative responses of, very dry, extremely uncomfortable or very difficult on the left (at 0) and positive responses of, not dry, comfortable or easy on the right (at 10). The patients were shown their previous scores before marking their responses on the scale in relation to the two

extremes. The scores represented the patients' condition at each visit.

Adverse effects

The severity of adverse effects was categorized as mild (spontaneous symptomatic relief), moderate (need drug for symptomatic relief) and severe degree (need to stop all treatment).

Statistical analysis

The changes in subjective response were calculated for each patient by subtracting the scores during and after radiation from the score prior to radiation. *T*-test was used to evaluate differences in change in score at each visit and chi-square was used to compare the frequency of side effects between the treatment groups. Statistical significance was accepted at P value < 0.05.

RESULTS

Of the 60 patients randomized to protocol, 53 received complete treatment and 47 patients were determined to be evaluable. The reasons for 6 placebo and 1 pilocarpine treated patients' withdrawal and 2 placebo and 4 pilocarpine treated patients' permanent discontinuation were intolerance to radiation mucositis and personal reasons. The baseline characteristics, disease and treatment of the patients according to treatment group are shown in Table 1. There were no significant differences between the two groups.

Preradiation (baseline) scores of all symptoms including oral dryness, oral discomfort, difficulty in chewing and swallowing, speaking and sleeping were not different between the groups as shown in Fig. 1. Mean differences between preradiation scores and weekly scores

Table 1. Baseline characteristics, disease, treatment of patients by group.

	Placebo gr.		Pilocarpine gr.	
	Number	%	Number	%
Sex				
Male	24	80	25	83
Female	6	20	5	17
Age* (year)	58 ± 12.95	-	57 ± 12.87	-
Performance Status				
ECOG1	28	93	30	100
ECOG2	2	7	0	0
Diagnosis				
Oropharynx	15	50	12	40
Nasopharynx	6	20	8	27
Others	9	30	10	32
Stage				
IV	14	47	16	53
III	7	23	6	20
Others	9	30	8	26
Surgery				
Without surgery	23	77	21	70
With surgery	7	23	9	30
Radiation field				
Width				
Spare submen.**	20	67	23	77
Without spare	10	33	7	23
Length				
***POL&ALN	25	83	29	97
***POL(whole neck)	4	13	0	0
***POL(upper neck)	1	3	1	3
Dose* (Gy)	66.09 ± 5.67	-	64.96 ± 9.03	-

* Mean ± standard deviation
** Submental region
*** POL = Parallel opposed lateral
ALN = Anterior lower neck

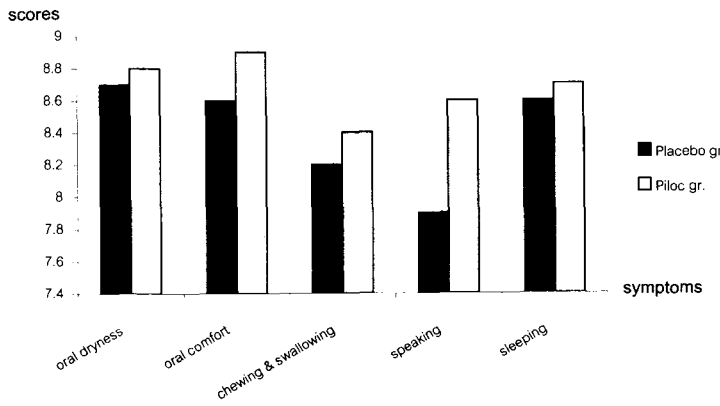

Fig. 1. Baseline scores of all symptoms by group.

during radiation and monthly scores postradiation of each symptom are shown in Figs. 2-6. None of the symptoms differed significantly between the two groups. The adverse effects that occurred during and postradiation were generally of mild degree (Fig. 7, 8) and there were no statistically significant differences between the two groups.

DISCUSSION

Koshima et al[9] suggests that serous cells of the salivary gland are relatively sensitive to ionizing radiation, whereas, mucous cells are more resistant. The parotid, which consists mainly of serous cells, is the most sensitive to radiation among the three major salivary glands [10,11]. However, the mechanism of irradiation-induced hypofunction of the salivary gland is not fully understood[12]. Various mechanisms, including mitotic and interphase death, direct DNA damage, effects of secondary metabolites and altered gene expression, have all been proposed to explain the salivary epithelial cell death observed. Studies on the seromucous secretory tissue of the rat submandibular gland

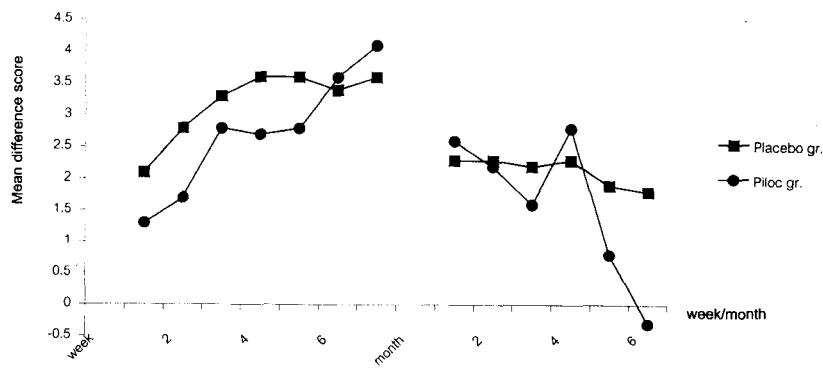

Fig. 2. Mean difference between preradiation scores and during and postradiation scores for oral dryness by group.

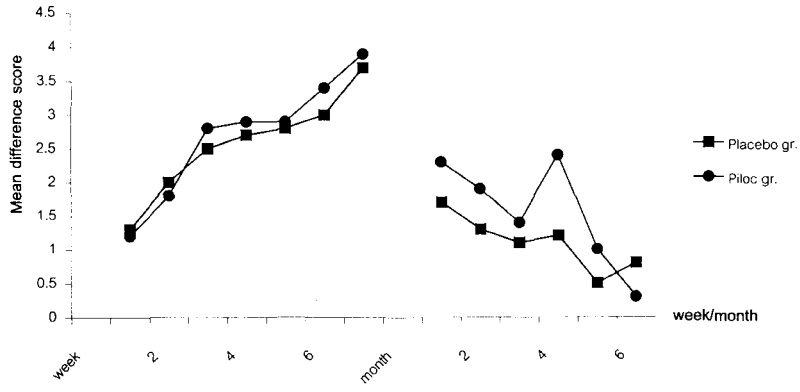

Fig. 3. Mean difference between preradiation scores and during and postradiation scores for oral discomfort by group.

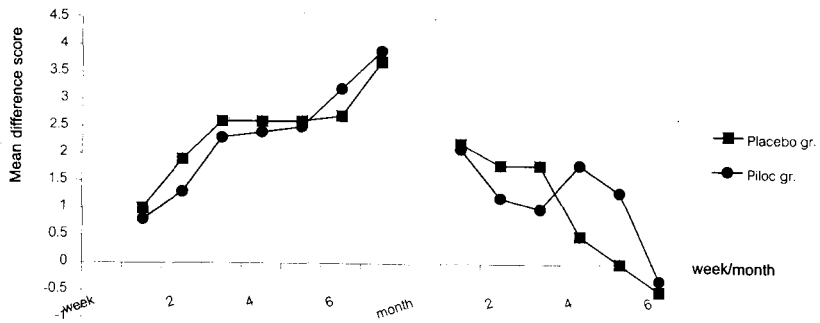

Fig. 4. Mean difference between preradiation scores and during and postradiation scores for difficulty in chewing and swallowing by group.

have suggested that secretory granules may play a role as a mediator agent in radiation-induced death of serous granular cells[13]. These granules contain relatively high amounts of proteolytic enzyme and heavy metal ions. Coppes et al[14] postulated that redox-active ions(copper, iron) play a major role in the process of radiation-induced injury of the salivary gland. They suggest that ionizing radiation disrupts the secretory granule membrane by metal-catalyzed induction of lipid peroxidation, which causes release of proteolytic enzymes into the cytoplasm which could reach the nuclear DNA and promote DNA damage by virtue of the hydroxyl radical. The exact source of this hydroxyl radical is unclear ; it could be generated *via* the iron or copper redox reactions. This process leads to irreversible, often lethal, cellular damage. The postradiation damage could result in immediate cell death or delayed reproductive death and loss of function[15,16]. Kim et al[10] explored the possibility of decreasing the radiation-induced damage of the salivary gland by modifying the amount of secretory granules. Animal studies have shown that pretreatment with cholinergic agonists, as well as alpha or beta adrenergic

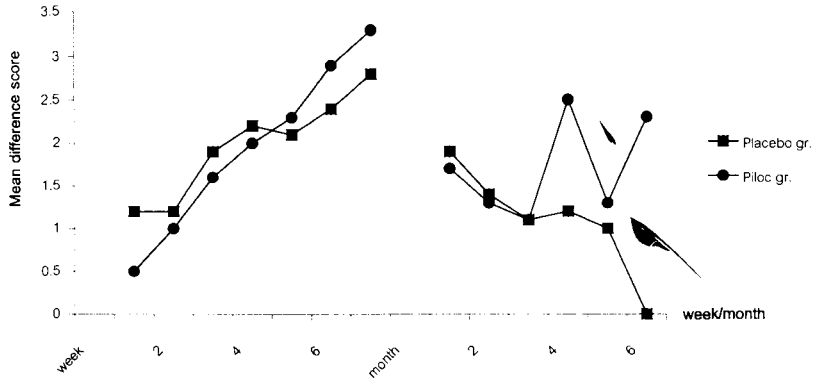

Fig. 5. Mean difference between preradiation scores and during and postradiation scores for difficulty in speaking by group.

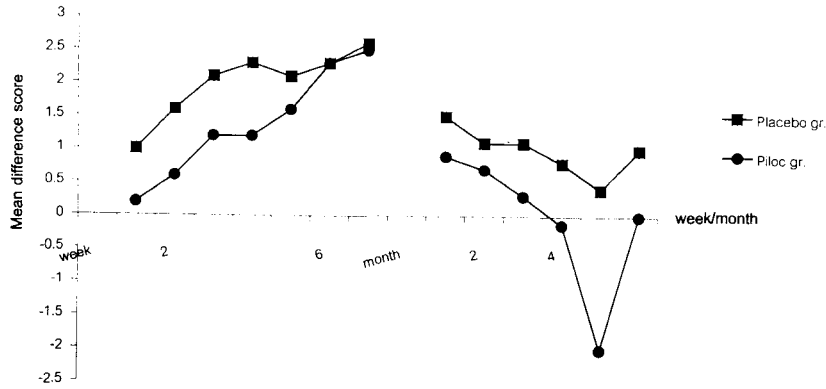

Fig. 6. Mean difference between preradiation scores and during and postradiation scores for difficulty in sleeping by group.

agonists, which act to degranulate salivary gland serous acinar cells, protect the salivary gland from radiation-induced damage based on histologic assessment(17).

The mechanism of protection of salivary gland function by pilocarpine is less certain. It is highly probable that the protection against radiation is, at least in part, a consequence of the mobilization of iron and copper out of cells into the secreted parotid gland saliva, which appears to be associated with degranulation (14,18).

A small clinical trial has demonstrated that concomittant use of pilocarpine during radiation for head and neck tumors can result in protection of salivary glands from radiation-induced damage. Significantly less subjective xerostomia was observed in pilocarpine treated patients compared to untreated patients(8). That study has a limitation in interpretation because pilocarpine was also given postradiation, therefore, the improvement of xerostomia may be a result of stimulating residual function of other salivary glands.

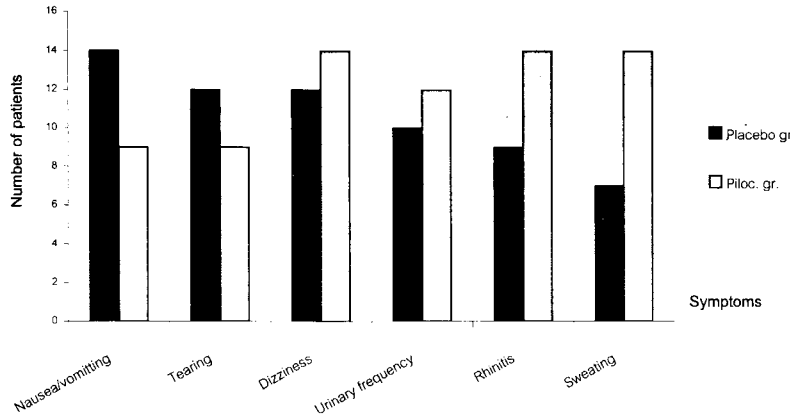

Fig. 7. Adverse effects (during radiation).

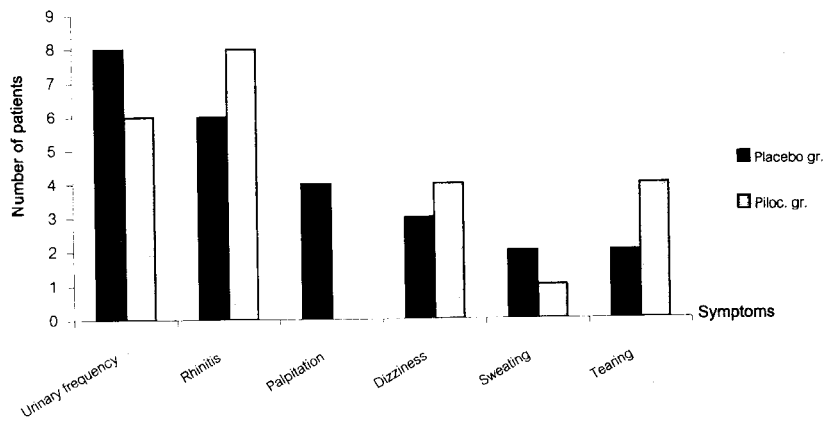

Fig. 8. Adverse effects (postradiation).

In the current study, all patients received pilocarpine only during radiation and certainly had xerostomia because a high dose of radiation was applied to both parotid glands. We emphasized subjective assessment for xerostomia because xerostomia is the subjective feeling of dry mouth and one study has shown that there was no correlation between increased salivary production and subjective improvement(19). There were differences between preradiation scores and subsequent scores, starting at the first week, for all symptoms, indicating that salivary gland hypofunction may have occurred since the first week of radiation. During the radiation period, mean differences between preradiation and weekly scores increased with time and reached a maximum at the end of radiation. This change could be from oral mucositis which influenced patient perception of xerostomia or from an actual increase in severity of salivary hypofunction. However, the data revealed no difference in change of scores from preradiation

to during radiation between the two groups. Mean differences between preradiation scores and monthly scores decreased with time. It seems there was an improvement of xerostomia, which could be from the disappearance of oral mucositis, from saliva from minor salivary glands distributed in the oral cavity, or from other functional major salivary glands. However, xerostomia of the two groups was still not significantly different.

In conclusion, the results of this study showed that patients administered pilocarpine during radiation did not experience less xerostomia than those in the placebo group. The adverse effects were non-specific symptoms such as nausea, vomitting, dizziness, palpitation, tearing, rhinitis, urinary frequency and sweating, and were generally of mild degree. During and postradiation adverse effects were not significantly different between the two groups and not different from those reported in other studies. Further study is needed to define the mechanism of radiation-induced xerostomia as well as to define the method for protection against this condition.

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การศึกษา Randomized double blind, placebo–controlled ของการให้ยาพิโลคาร์ปีนระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก เพื่อลดอาการของภาวะน้ำลายแห้ง

ดวงใจ แสงถวัลย์, พ.บ., สมชาย วัฒนอาภรณ์ชัย, พ.บ.*, เต็มศักดิ์ พึ่งรัศมี, พ.บ.**

การศึกษามีจุดประสงค์เพื่อประเมินผลของการให้ยาพิโลคาร์ปีนไฮโดรคลอไรด์ระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก ในแง่การลดอาการของภาวะน้ำลายแห้ง และประเมินผลข้างเคียงของยาพิโลคาร์ปีน โดยทำการศึกษาแบบ randomized double blind, placebo – controlled ในผู้ป่วยมะเร็งระบบ หู คอ จมูก จำนวน 60 ราย ผู้ป่วยแต่ละรายจะได้รับการฉายรังสีอย่างน้อย 50 Gy ครอบคลุมต่อมน้ำลายพาโรติค ทั้ง 2 ข้าง และได้รับยาพิโลคาร์ปีนหรือ placebo ที่อยู่ในรูปเยลลี่ 5 มิลลิกรัม (1 ซีซี.) วันละ 3 ครั้ง เริ่มตั้งแต่วันแรกของการฉายรังสีจนกระทั่งถึงวันที่ครบการฉายรังสี การประเมินอาการของภาวะน้ำลายแห้งจะประเมินในแง่ความรู้สึกโดยใช้แบบคำถาม Visual Analogue Scale (VAS) ประเมินอาการปากแห้ง ความไม่สบายในช่องปาก ความลำบากในการเคี้ยวและกลืน การพูด การหลับ โดยประเมินในช่วงก่อนการฉายรังสี ระหว่างการฉายรังสีทุกสัปดาห์ หลังการฉายรังสีทุกเดือนจนกระทั่งครบ 6 เดือน ผลการศึกษา พบว่าลักษณะทั่วไปของผู้ป่วย ลักษณะโรค และการฉายรังสี ทั้งในแง่พื้นที่ฉายรังสีและปริมาณรังสี ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ระหว่างผู้ป่วยกลุ่มที่ได้รับและไม่ได้รับยาพิโลคาร์ปีนระหว่างการฉายรังสี การประเมินในแง่อาการของภาวะน้ำลายแห้ง พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วย 2 กลุ่ม ทั้งในระหว่างและหลังการฉายรังสี อาการข้างเคียงที่พบเป็นอาการที่ไม่เฉพาะเจาะจง ได้แก่ คลื่นไส้อาเจียน เวียนศีรษะ ปัสสาวะบ่อย ใจสั่น เหงื่อออก น้ำตาไหล ซึ่งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วยทั้ง 2 กลุ่มทั้งในระหว่างและหลังการฉายรังสี จากการศึกษานี้สรุปได้ว่าการให้ยาพิโลคาร์ปีนระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก ไม่ได้ลดอาการของภาวะน้ำลายแห้งอย่างมีนัยสำคัญทางสถิติ และผลข้างเคียงที่เกิดจากยาพิโลคาร์ปีนอยู่ในระดับที่ปลอดภัยต่อผู้ป่วย

คำสำคัญ : พิโลคาร์ปีน, ภาวะน้ำลายแห้ง, รังสีรักษา, ระบบ หู คอ จมูก, มะเร็ง

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