Effect of Oral Pilocarpine on Post-Irradiation Xerostomia in Head and Neck Cancer Patients: A Single-Center, Single-Blind Clinical Trial

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Objective: *The authors determined the efficacy and safety of oral pilocarpine tablet in symptomatic relief of post-radiation xerostomia in head and neck cancer patients.*
Material and Method: *Thirty-three radiation-induced xerostomia patients were enrolled in a single-blind method to receive placebo 1-tablet three times daily in the first month and then oral pilocarpine (5 mg) 1-tablet three times daily for the next three months. Patients were evaluated for subjective symptomatic relief of xerostomia using questionnaires. Objective findings of xerostomia were also evaluated at the same time by two radiation oncologists.*
Results: *All 33 patients had received radiotherapy doses at least 4000 cGy to the parotid glands. Improvement of xerostomia symptoms was observed, with a mean total subjective xerostomia score improvement at the first 4 weeks of oral pilocarpine treatment ($p = 0.001$), and later throughout the present study. Objective xerostomia score also showed statistically significant improvement at the same time point. Adverse effects of pilocarpine included sweating, nausea, palpitation, and tearing, with sweating as the most common side effect. Adverse effects of placebo included mild headache, nausea, and vomiting.*
Conclusion: *Oral pilocarpine was effective and well tolerated in the treatment of radiation-induced xerostomia symptoms.*

Keywords: *Pilocarpine, Radiation-induced xerostomia, Head and neck cancer*

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Radiation therapy is commonly used either alone or in combination with surgery in the treatment of patients with head and neck cancer. Xerostomia is one of the disturbing side effects of radiotherapy to the head and neck area. The hallmarks of radiation-induced damage are acinar atrophy and chronic inflammation of the salivary glands. Early response, resulting in atrophy of secretory cells without inflammation, might be due to radiation-induced apoptosis. In contrast, late response with inflammation could be a result of radiation-induced fibrosis or necrosis[4]. Current management strategies include stringent dental and oral hygiene, parotid-sparing radiation technique by intensity-modulated radiotherapy (IMRT), and pharmacotherapy such as salivary substitutes and sialogogues[1].

Pilocarpine is a cholinergic parasympathomimetic agent that functions as a muscarinic agonist

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with mild beta-adrenergic activity. Many double-blinded, placebo-controlled randomized clinical studies demonstrated statistically significant improvement of post irradiation xerostomia[2,3,6,9]. This present study is the first trial to investigate the efficacy and safety of oral pilocarpine tablets (Salagen tablets) for the treatment of post-irradiation xerostomia as a single-blind placebo-controlled trial.

Material and Method

Patients

Written of informed consent was obtained from all potential study patients at the screening stage. Eligible patients had received external radiotherapy to the head and neck, with both parotid glands in the treated field at least 40 Gy and more than 6-month post-radiation before enrollment to the present study. All patients had a history of clinically significant xerostomia. They all showed some evidence of residual salivary function on physical examination as visible by moisture in the oral cavity. Patients with known asthma, narrow-angle glaucoma, hypertension, chronic obstructive pulmonary disease, heart disease, psychiatric disorders, and allergy to study drug were excluded.

The screening processes included history taking, physical examination, ophthalmologic examination, and 12-lead ECG.

Treatment

The duration of protocol was 20 weeks. Patients were seen before the start of treatment and at four-week intervals. Patients were treated as outpatients and scheduled for six clinic visits during the present study: admission (visit 1), week 4 (visit 2), week 8 (visit 3), week 12 (visit 4), week 16 (visit 5), and week 20 (visit 6); placebo was administered for the first four weeks. Pilocarpine tablets (5 mg) were administered from week 4 through week 16. All tablets (pilocarpine and placebo) were identical in appearance, color, and size. Patients were instructed to take one tablet three times a day at meal time with water. The last visit was follow up with no drug administration. The treatment protocol is shown in Fig. 1.

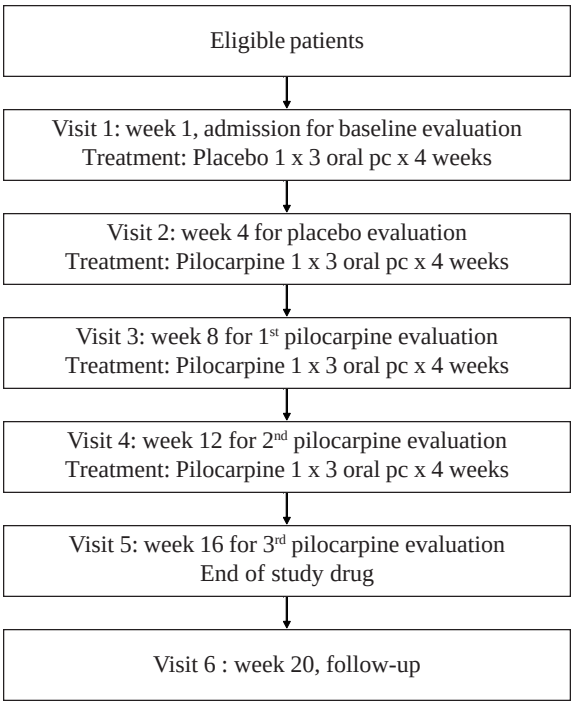

Fig. 1 Treatment protocol

Efficacy assessment

At each scheduled visit, a subjective xerostomia assessment of efficacy was undertaken; each patient was required to rate, on a scale of 1 to 10, each of 5 questions (overall mouth dryness, mouth comfort, ability to sleep, ability to speak, and swallowing function). The scale was set up with positive response on the left (score 0) and negative response on the right (score 10). The objective xerostomia assessment was also performed according to objective grades of the Late Effects of Normal Tissues Subjective, Objective, Management, and Analytic (LENT SOMA) scale (Table 1), by two radiation oncologists. If different grades were obtained by the two clinicians, the mean of the two-recorded grades was determined and was used as the result for each patient.

Safety assessment

Adverse events were recorded for each visit. An adverse experience was defined as any clinically significant change in physical signs or symptoms

Table 1. Objective grades of xerostomia according to the LENT SOMA scale

Grade	Description
1	Normal moisture
2	Scant saliva
3	Absence of moisture, sticky, viscous saliva
4	Absence of moisture, coated mucosa

occurring in any phase of the present study regardless of its relationship to the study drug.

Statistical analysis

Mean subjective and objective xerostomia at the baseline phase (visit 1), placebo phase (visit 2), pilocarpine phase (visits 3, 4, 5), and follow up phase (visit 6) were compared using student's t-test. Correlation of the subjective and objective xerostomia results was tested by bivariate correlation. The p-values reported were two-tailed and an alpha level of 0.05 was used to assess statistical significance. Statistical analyses were performed by using SPSS statistical software (version 13.0, SPSS Inc., 444 N. Michigan, Chicago, Illinois, USA).

Results

The mean age was 55.9 years (range 32-77 years). Most of the patients were male (63.6%). The most common primary site of disease was nasopharynx in 75.8%, followed by oral cavity (12.2%), oropharynx (6%), and larynx (6%). All the patients had the major part of both parotid glands in the radiation field of at least 4000 cGy. Radiotherapy was given by standard fractionation (2 Gy per day, 5 days per week) using cobalt-60 or linear accelerator. Baseline characteristics are given in Table 2.

The subjective xerostomia questionnaire was completed in 100% of eligible patients at baseline, 100% at visit 2, 100% at visit 3, 90.9% at visit 4, 78.8% at visit 5, and 69.7% at follow-up visit. Table 3 shows each specific symptom-related subjective xerostomia mean score at baseline visit, during study visits and follow-up visit. When compared to baseline, the mean total subjective xerostomia score was significantly improved at every time point from visit 3 throughout the end of the 20-week study period (Fig. 2).

Focusing on each symptom of subjective of xerostomia, the authors found that mouth dryness, ability to sleep, and ability to swallowing significantly improved in visit 3 (after one month of pilocarpine treatment).

There were improvements in oral comfort and speech, but slightly later than other symptoms (visit 4). Symptomatic benefit in total improvement was also seen in the follow up phase (visit 6) (Table 3). In the present study the subjective xerostomia scores and objective xerostomia grades were significantly correlated ($p = 0.001$).

Table 2. Baseline characteristics

No. of patients	33
Sex	
Male	21 (63.6%)
Female	12 (36.4%)
Age (year)	
Mean ± SD	55.9 ± 9.9
Primary site of cancer	
Nasopharynx	25 (75.8%)
Oropharynx	2 (6%)
Larynx	2 (6%)
Oral cavity	4 (12.2%)
Treatment	
Concurrent chemoradiotherapy	21 (63.6%)
Radiotherapy alone	5 (15.2%)
Postoperative radiotherapy	7 (21.2%)
Radiation dose (cGy)	
Mean ± SD	6763.6 ± 362.1
Months from radiotherapy to start of study	
Mean ± SD	22.5 ± 29.1

Table 3. Subjective xerostomia score at each visit

Time point	Mean subjective xerostomia score ± SD									
	Mouth dryness	p-value	Mouth comfort	p-value	Ability to sleep	p-value	Ability to speak	p-value	Ability to swallow	p-value
Visit 1 (n = 33) (baseline)	6.79±2.65	-	4.42±3.35	-	4.00±3.48	-	4.71±2.39	-	6.33±2.57	-
Visit 2 (n = 33)	6.21±2.76	0.274	3.75±3.04	0.373	3.50±3.19	0.415	4.50±3.05	0.701	6.71±2.18	0.524
Visit 3 (n = 33)	4.58±2.76	0.000	3.25±2.72	0.051	2.38±3.03	0.016	4.38±2.29	0.484	5.25±2.29	0.079
Visit 4 (n = 30)	4.21±2.30	0.000	2.17±2.91	0.003	2.21±2.90	0.004	3.42±3.34	0.023	4.71±2.87	0.006
Visit 5 (n = 26)	3.83±2.59	0.001	1.67±2.18	0.026	2.67±2.81	0.131	2.92±2.61	0.058	4.08±2.19	0.098
Visit 6 (n = 23) (follow-up)	4.29±3.35	0.108	1.00±1.19	0.012	2.43±2.88	0.023	2.57±2.70	0.026	5.00±2.89	1.000

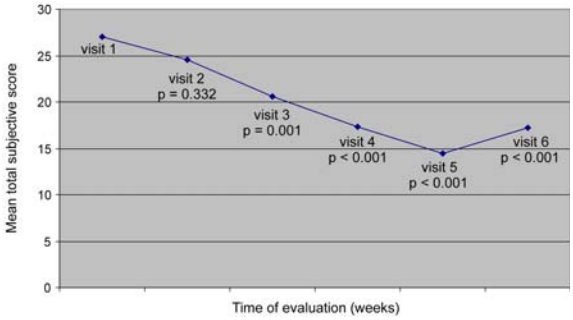

Fig. 2 Total Subjective Xerostomia score at each visit

Table 4. Objective xerostomia score at each visit

Time point	Mean objective xerostomia score	p-value
Visit 1 (n = 33) (baseline)	2.25 ± 0.44	-
Visit 2 (n = 33)	2.13 ± 0.54	0.083
Visit 3 (n = 33)	1.33 ± 0.56	0.000
Visit 4 (n = 30)	1.25 ± 0.44	0.000
Visit 5 (n = 26)	1.50 ± 0.51	0.000
Visit 6 (n = 23) (follow-up)	1.74 ± 0.45	0.001

In addition, the mean objective xerostomia score showed statistically significant improvement in visits 4, 5, and 6. The authors performed a subgroup analysis of the patients who received radiotherapy alone and those who received concurrent chemoradiotherapy, the groups were comparable in assessing their subjective and objective xerostomia score at each visit. The authors also found the same results in both groups in improvements of each symptom of subjective xerostomia and objective xerostomia score. However, it is difficult to compare and interpret whether this response was related to different prior therapies (RT alone vs. concurrent chemoradiotherapy) due to the small number of patients.

Adverse effects were generally mild. Ten patients (30.3%) reported sweating, three (9.1%) described nausea, two (6%) complained about palpitation, and two (6%) had mild tearing. In the first 4 weeks of placebo, one patient (3%) reported the development of mild headache, and two patients (6%) reported nausea and vomiting. No discontinuation because of adverse events took place in the present study.

Discussion

Previous studies[3,5,6,8] had indicated an improvement in salivary function in cancer patients following pilocarpine therapy. Most of these studies were double blinded, placebo-controlled trials with patients being randomized into two groups: placebo and study drug. In this current study, the authors determined the efficacy of pilocarpine in a different way by using placebo followed by the study drug in the same patient to avoid imbalance of baseline subjective xerostomia symptoms in each patient. Results of the present study also indicated symptomatic relief of mouth dryness and ability to sleep after 4 weeks of pilocarpine. However, some xerostomia symptoms, such as mouth comfort, speech, and swallowing, did not change immediately after the first dose of pilocarpine. According to the pharmacokinetic profile of this drug, its effect on saliva flow is dose-dependent and time-related, with peak effect at 1 hour and duration of 3-5 hours[7]. However, the treatment effects in the present study were sustained for 1 month after pilocarpine treatment completion in almost all xerostomia symptoms except mouth dryness.

Subjective and objective xerostomia score were significantly correlated in all visits ($p = 0.001$).

Adverse effects reported in the present study were those expected for a cholinergic agonist. Sweating was the most common side effect, followed by nausea, palpitation, and tearing. Adverse effects of placebo were manifested in a mild degree of headache and nausea/vomiting. There were no serious drug related adverse events in the present study.

The weak point of the present study is the high number of patients lost to follow up (10% in visit 4, 21% in visit 5, and 30% in the last visit). This is usually a significant problem in our center clinical trials. For the present study, the authors thought that the patients knew all the schedule of the protocol (6 visits: 4 visits with drug and 2 visits of follow-up alone), also the long distance patients have to travel to the tertiary care center.

Conclusion

As data from the present study suggested, pilocarpine tablet treatment offers a wide range of potential therapeutic effects in patients with radiation-induced xerostomia.

Acknowledgement

Pilocarpine (Salagen tablets) and placebo

tablets were provided by American-Taiwan Biopharm Co., Ltd. (Thailand).

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ผลของยาเม็ดพิโลคาร์ปีนในการรักษาภาวะน้ำลายแห้งจากการฉายรังสีในผู้ป่วยมะเร็งบริเวณศีรษะและลำคอ: การศึกษาทางคลินิกแบบ single-center, single-blind

อิ่มใจ ชิตาพนารักษ์, พิมพ์ขวัญ กำเนิดศุภผล, เอกสิทธิ ธราวิจิตรกุล, ยุพา สุมิตสวรรค์, พิชิต สิทธิไตรย์, เธียรไชย ภัทรสกุลชัย, วิชาญ หล่อวิทยา, วิมล สุขถมยา, นันทกา ภู่กัณหพันธ์, ภัทรินี ไตรสถิตย์

วัตถุประสงค์: *การศึกษานี้มีวัตถุประสงค์เพื่อประเมิน ประสิทธิภาพและความปลอดภัยของยาเม็ดพิโลคาร์ปีนในการบรรเทาอาการภาวะน้ำลายแห้งหลังการฉายรังสีในผู้ป่วยมะเร็งศีรษะและลำคอ*

วัสดุและวิธีการ: *เป็นการศึกษาแบบ prospective single-blind method ในผู้ป่วยที่มีภาวะน้ำลายแห้งจากการฉายรังสี จำนวน 33 ราย โดยผู้ป่วยทุกรายจะได้รับยาหลอก 1 เม็ด วันละ 3 เวลา ในเดือนแรก หลังจากนั้นจะได้รับยาเม็ดพิโลคาร์ปีน ขนาด 5 มิลลิกรัม 1 เม็ด วันละ 3 เวลา ต่ออีกเป็นเวลานาน 3 เดือน ผู้ป่วยจะได้รับการประเมินภาวะน้ำลายแห้งทุก 4 สัปดาห์ จนถึงสัปดาห์ที่ 20 ทั้งแบบ subjective โดยการตอบแบบสอบถามด้วยตนเอง และแบบ objective โดยการตรวจประเมินอาการของภาวะน้ำลายแห้ง โดยแพทย์รังสีรักษาจำนวน 2 ท่าน*

ผลการศึกษา: *จากการศึกษาพบว่าค่า mean total subjective xerostomia ของผู้ป่วยดีขึ้น อย่างมีนัยสำคัญทางสถิติตั้งแต่ 4 สัปดาห์แรกที่ได้รับยาเม็ดพิโลคาร์ปีน (p = 0.001) และยังคงพบความแตกต่างนี้ตลอดจนจบการศึกษา ส่วนค่าคะแนนของ objective xerostomia ก็พบว่าดีขึ้นอย่างมีนัยสำคัญทางสถิติในช่วงเวลาเดียวกันกับการประเมิน subjective xerostomia สำหรับผลข้างเคียงที่พบได้บ่อยคือ เหงื่อออก ส่วนอาการข้างเคียงอื่น ๆ ที่พบได้บ้าง ได้แก่ คลื่นไส้, ใจสั่น, น้ำตาไหล*

สรุป: *ยาเม็ดพิโลคาร์ปีน มีประสิทธิภาพที่ดี และผลข้างเคียงค่อนข้างน้อย ในการรักษาภาวะน้ำลายแห้งจากการฉายรังสี*