Clinical Investigation

Is Pilocarpine Effective in Preventing Radiation-Induced Xerostomia? A Systematic Review and Meta-analysis

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Received May 26, 2015, and in revised form Sep 29, 2015. Accepted for publication Nov 4, 2015.

Summary

Pilocarpine has been used in the treatment of xerostomia; however, it is still uncertain whether it has a preventive effect on radiation-induced xerostomia. Our systematic review and meta-analysis demonstrated that concomitant administration of pilocarpine during radiation could increase unstimulated salivary flow rate and reduce clinician-rated xerostomia grade. It may also relieve patients’ xerostomia at 6 months, and possibly at

Purpose: To evaluate the efficacy of concomitant administration of pilocarpine on radiation-induced xerostomia in patients with head and neck cancers.

Methods and Materials: The PubMed, Web of Science, Cochrane Library, and ClinicalTrials were searched to identify randomized, controlled trials studying the effect of concomitant administration of pilocarpine for radiation-induced xerostomia. Included trials were systematically reviewed, and quantifiable outcomes were pooled for meta-analysis. Outcomes of interest included salivary flow, clinician-rated xerostomia grade, patient-reported xerostomia scoring, quality of life, and adverse effects.

Results: Six prospective, randomized, controlled trials in 8 articles were included in this systematic review. The total number of patients was 369 in the pilocarpine group and 367 in the control group. Concomitant administration of pilocarpine during radiation could increase the unstimulated salivary flow rate in a period of 3–6 months after treatment, and also reduce the clinician-rated xerostomia grade. Patient-reported xerostomia was not significantly impacted by pilocarpine in the initial 3 months but was superior at 6 month. No significant difference of stimulated salivary flow rate could be confirmed between the 2 arms. Adverse effects of pilocarpine were mild and tolerable.

Conclusions: The concomitant administration of pilocarpine during radiation increases unstimulated salivary flow rate and reduces clinician-rated xerostomia grade

Acknowledgment—The authors thank biostatistician Dr May M. C. Wong, Faculty of Dentistry, University of Hong Kong, for assistance with data analysis.

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The project was supported by a grant (no. 81371160) from the National Natural Science Foundation of China.

Conflict of interest: none.
Introduction

Radiation therapy plays an important role in the multidisciplinary therapy of head and neck cancer, either as an adjunctive method or as the main treatment regimen. Among the acute and chronic side effects of radiation therapy, xerostomia is one of the most common complaints. Xerostomia is the subjective dryness of mouth, which may be associated with reduced salivary flow or changes in the composition of saliva (1, 2). Individuals with xerostomia often complain of difficulties in speech and swallowing, impairment of taste, and deterioration of dental hygiene, greatly impairing patients’ quality of life (QoL) (3).

Some treatment options have been put forward to relieve radiation-induced xerostomia, including salivary substitutes and sialogogic agents (4). Pilocarpine, a cholinergic agonist, stimulates saliva production and has been approved by the US Food and Drug Administration for the treatment of xerostomia. Preventive regimens are more promising, including submandibular gland transfer before radiation therapy, and parotid gland sparing techniques with 3-dimensional conformal or intensity modulated radiation therapy (IMRT) (5, 6). However, only selected candidates are suitable for submandibular gland transfer. Studies have confirmed the significant role of IMRT in preventing xerostomia and maintaining normal oral functions (7-11). Even with IMRT, however, the salivary glands may still overlap the planning target volume partially, resulting in some degree of salivary gland impairment and xerostomia (8, 12, 13).

An early clinical trial revealed that the concomitant administration of pilocarpine during radiation therapy was effective in preventing radiation-induced xerostomia in patients with head and neck cancers (14). However, its exact efficacy is under investigation, and to date, no reported trial has been convincing enough to validate the efficacy of pilocarpine for the prevention of xerostomia. Compelling evidence is needed before concomitant pilocarpine can be recommended for routine use. Therefore, we aimed to conduct a systematic review and meta-analysis to evaluate the efficacy of concomitant administration of pilocarpine on radiation-induced xerostomia in patients with head and neck cancers.

Methods and Materials

Search strategy

We performed a comprehensive search in PubMed, Web of Science, Cochrane Library, and ClinicalTrials for relevant articles using different combinations of the following key words: “pilocarpine” or “salagen” and “radiation” or “radiotherapy” and “xerostomia” or “dry mouth” or “hyposalivation.” All articles published up to September 1, 2014 were reviewed in the initial stage, without any other limitations on the publication type and language. We also hand-searched the reference lists of eligible studies and relevant conference abstracts. This process was repeated until no additional studies were found.

Selection criteria

Two authors independently reviewed and selected articles according to the following inclusion criteria: (1) Included studies should be randomized controlled trials. (2) Eligible patients were diagnosed with head and neck cancers, and underwent radiation therapy as primary or adjuvant therapy. (3) Patients took pilocarpine daily during radiation therapy. (4) Patients in the control group received placebo, or no intervention for xerostomia prevention. (5) The sample size of patients receiving pilocarpine should be larger than 10.

Data extraction

Two authors independently reviewed the included articles and extracted data using a pre-established form, covering information about author, publication year, study design, country, sample size, tumor sites, exposed volume of salivary glands, intervention regimen, major endpoints, and duration of observation. The completed forms were checked by a third author. Any inconsistency was resolved through discussion and consensus.

Assessment of risk of bias in included studies

The Cochrane Collaboration’s tool (Cochrane Handbook version 5.1.0) for assessing risk of bias in randomized trials was adopted in this systematic review (15). Two authors independently evaluated the risk of bias of included trials in 6 domains. We also corresponded corresponding authors for further clarity of randomization, concealment, blinding method, and incomplete outcome data. If available information was insufficient to eliminate a bias, we would define it as “unclear risk” rather than “low risk.”

Data analysis

Outcome variables were extracted for meta-analysis. For salivary flow rates, clinician-rated xerostomia grades, and patient-reported xerostomia scores, we calculated mean

12 months. However, it had no effects on stimulated salivary flow rate.
differences (MDs) with 95% confidence intervals (CIs) between groups during and after the course of radiation therapy (months). Mean differences were based on the fixed-effect model, because the estimate of between-study variance is poor when the number of studies is small (16). The fixed-effect meta-analysis provided the best pooled intervention effect estimate (17). Heterogeneity was evaluated with the Pearson $\chi^2$ test and $I^2$ test. All assessments and calculations were performed using Review Manager (version 5.3; Oxford, United Kingdom) and SPSS Statistics (version 22.0) (SPSS, Chicago, IL).

**Results**

**Selection of trials**

Of 495 reports initially identified (Fig. 1), 471 were excluded by title and abstract. The remaining 24 reports were screened at full-text level. Relevant references were manually searched, and 2 additional reports were added. According to the predefined inclusion and exclusion criteria, 8 reports of 6 clinical trials were included (18-26) (Table 1).

**Description of the included studies and data analysis**

All 6 trials in 8 articles were prospective trials. The trial by Fisher et al (19) was conducted in multiple centers in the United States, and the trial by Burlage et al (18) was conducted in 2 medical centers in the Netherlands, whereas the other included trials were single-centered.

The total number of patients was 369 in the pilocarpine group, and 367 in the control group. The mean age of patients was approximately 60 years in 5 trials (18-20, 22-26). However, in the trial by Haddad et al (21), the mean age of patients was 43 years, possibly owing to its different composition of tumors; most (76.9%) were nasopharyngeal carcinomas. The subtypes of tumors were reported according to their sites in every trial. The oropharynx, the oral cavity, and the larynx were the most commonly involved tumor sites, respectively accounting for 33.6%, 20.3%, and 19.5% (18-21, 23-26). More than 50% of the bilateral parotid glands received a dose of 50 Gy in most of the trials. An exception was the trial by Burlage et al (18): to study the influence of different exposed volumes of parotid glands, they recruited patients with a range of parotid volumes and divided them into 3 groups, which had an irradiated volume of parotid gland of 25%-45%, 46%-75%, and $\geq$75%, respectively.

A dose of 5 mg pilocarpine per administration was consistent in all the studies. Patients were instructed to take pilocarpine either 3 times daily, or 4 times. Patients took pilocarpine during radiation therapy and continued for different periods ranging from 2 weeks to 3 months. The period of follow-up varied from 5 weeks to 1 year after treatment (20, 22).

Studied endpoints included objective, clinician-rated, and patient-reported indicators evaluating the alleviation of radiation-induced xerostomia. Objective data could be the salivary flow rate calculated as mL/min, including stimulated and unstimulated salivary flow rates. Clinician-rated grades of xerostomia according to the known scales were reviewed, such as the Late Effects of Normal Tissues Subjective, Objective, Management, and Analytic (LENT SOMA) scale, and the Radiation Therapy Oncology Group Acute Xerostomia Toxicity scale (27-29). Patient-reported xerostomia was measured using a visual analogue scale or Likert scale when responding to xerostomia-related

**Fig. 1.** Selection process for studies included in the systematic review. Abbreviation: RT = radiation therapy.
questions, such as the 1-item questionnaire by Gornitsky in 2004, the 6-item questionnaire by Johnson in 1993, and the 12-item questionnaire by Buralle in 2008. (20, 30-32). Because these questionnaires all focused on xerostomia and the aspects evaluated were similar, we extracted mean patient-reported scores, representing the overall xerostomia, at each time point. The scores were standardized on a 0-100 scale for final synthesis (32).

The impact of xerostomia on patients’ QoL was evaluated through validated questionnaires, such as the McMaster University Head and Neck Questionnaire, and the University of Washington-Quality of Life Questionnaire. Finally, adverse effects of pilocarpine were qualitatively assessed by reviewing records in the included clinical trials. Studies containing one or more of the above endpoints were included and thoroughly reviewed.

Risk of bias in included studies

The 6 included studies were all prospective, randomized clinical trials. It was difficult to gain information regarding allocation concealment and eliminate the risk of selection bias. In the trial by Fisher et al (19), eligible patients from multiple centers were registered to a treatment arm by Radiation Therapy Oncology Group headquarters, and patient factors were balanced by the headquarters other than by institutions. Most of the other studies, though, neglected to describe their methods of performing allocation. Considering performance bias, in the trial by Nyarady et al (23), the control group received neither pilocarpine nor placebo, so double-blinding was violated. Unclear information about the number of early dropouts was considered to be bias-producing. Intention-to-treat analysis was regarded as an ideal statistical method in such circumstances. In the study by Gornitsky et al (20), a missing data replacement technique was used, using mean values from corresponding groups. In the study by Fisher et al (19) the schedule for data collection of the University of Washington Quality of Life Questionnaire at the completion of radiation therapy was not carried out (Fig. 2).

Efficacy and safety of concomitant pilocarpine for radiation-induced xerostomia

Salivary flow rate

Three included studies measured unstimulated salivary flow rate. Their data at each time point were synthesized to calculate the MDs between groups. At baseline the

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### Table 1: Main characteristics of randomized, controlled trials included in the systematic review and meta-analysis of concomitant pilocarpine for radiation-induced xerostomia

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N (Pilo/Scr)</th>
<th>Patient characteristics</th>
<th>Pilocarpine group</th>
<th>Control group</th>
<th>Outcomes</th>
<th>Indicators</th>
<th>Time points</th>
<th>Duration of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buralle (2008)</td>
<td>169 (85/84)</td>
<td>Age (y): 18-60: 54% &gt;60: 46%</td>
<td>Pilocarpine (5 mg q.i.d. continued for 14 d after RT)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>PFCP; LENT SOMA; PRX</td>
<td>Before RT, at 6 wk, 6 mo, 12 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Fisher (2003)</td>
<td>249 (124/125)</td>
<td>Age (y): 60-70 Gy to the oral cavity and oropharynx, &gt;50% of the major salivary gland to doses &gt;50 Gy</td>
<td>Pilocarpine (5 mg q.i.d. continued for 3 mo)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>USF, SSF, RTOG; UW-QOL</td>
<td>Before RT, at the end of RT, at 3, 6 mo after treatment</td>
<td>6 mo</td>
</tr>
<tr>
<td>Scaranitanto (2006)</td>
<td>58 (29/29)</td>
<td>Age (y): 59.8</td>
<td>Pilocarpine (5 mg 5 times daily during RT; q.i.d. for 5 wk after RT)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>USF, SSF, PRX; 1-item; QOL; AEs</td>
<td>Before RT, at the end of RT, 5 wk after RT</td>
<td>5 wk</td>
</tr>
<tr>
<td>Haddad (2002)</td>
<td>60 (31/29)</td>
<td>Total dose of 58 Gy</td>
<td>Pilocarpine (5 mg t.i.d. continued for 3 mo)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>PRX; 6-item; LENT SOMA</td>
<td>6 mo after the end of RT</td>
<td>6 mo</td>
</tr>
<tr>
<td>Nyarady (2006)</td>
<td>70 (35/35)</td>
<td>Total dose of 60 Gy</td>
<td>Pilocarpine in the last 6 wk</td>
<td>Placebo</td>
<td>USF, SSF, PRX; 6-item</td>
<td>Baseline and weekly during RT, and 1, 3, 6 mo after RT</td>
<td>8 wk</td>
<td></td>
</tr>
<tr>
<td>Warde (2002)</td>
<td>130 (65/65)</td>
<td>Total dose of 50 Gy</td>
<td>Pilocarpine (5 mg t.i.d. continued for 1 mo after RT)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>PRX; 6-item; MU-HNRQ; AEs</td>
<td>Baseline and weekly during RT, and 1, 3, 6 mo after RT</td>
<td>6 mo</td>
</tr>
<tr>
<td>Ringash (2005)</td>
<td>57</td>
<td>Total dose of 60 Gy</td>
<td>Pilocarpine (5 mg t.i.d. continued for 12 wk)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>PRX; 6-item; MU-HNRQ; AEs</td>
<td>Baseline and weekly during RT, and 1, 3, 6 mo after RT</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

**Abbreviations:** AEs = adverse effects of pilocarpine; LENT SOMA = objective grades of the Late Effects of Normal Tissues Subjective, Objective, Management and Analytic; MU-HNRQ = McMaster University Head and Neck Questionnaire; PFCP = stimulated parotid flow rate complication probability; PRX = patient-rated xerostomia scoring (PRX 1-item) by Gornitsky in 2004; PRX (6-item) by Johnson in 1993; PRX (12-item) by Buralle in 2008; q.i.d. = four times daily; QOL = quality of life; RT = radiation therapy; RTOG criteria = Radiation Therapy Oncology Group acute morbidity scoring criteria; SSF = stimulated salivary flow; t.i.d. = three times daily; USF = unstimulated salivary flow; UW-QOL = University of Washington Quality of Life Questionnaire.
unstimulated salivary flow rates were similar between the pilocarpine and control groups (MD $-0.02$ mL/min; 95% CI $-0.13$, 0.09; $P = .68$). During radiation therapy the concomitant administration of pilocarpine increased the amount of unstimulated saliva per minute. Immediately after radiation therapy the unstimulated saliva flow rate of the pilocarpine group was significantly increased (MD $0.28$ mL/min; 95% CI 0.18, 0.37; $P = .0001$). The advantageous effect of pilocarpine continued for 3 months after radiation therapy; however, the increased rates declined over time. At 5-6 weeks, the increase of unstimulated saliva was 0.15 mL/min (95% CI 0.07, 0.24; $P = .0005$), and at 3 months the increased rate was 0.10 mL/min (95% CI 0.00, 0.20; $P = .04$). By 6 months after radiation therapy the difference between groups was insignificant (MD $0.10$ mL/min; 95% CI $-0.02$, 0.22; $P = .09$) (Fig. 3).

A significant decrease in stimulated saliva flow rate after radiation therapy was observed in 2 trials. However, no significant difference was detected between arms (18, 20, 25).

**Clinician-rated scoring of xerostomia**

Two included studies measured the xerostomia grade using the LENT SOMA scale. Available data were synthesized at 6 months. The severity of xerostomia was less in the pilocarpine group (MD $-0.41$ points; 95% CI $-0.65$, $-0.17$; $P = .0008$) (Fig. 4).

**Patient-reported scoring of xerostomia**

Four included studies provided patient-reported xerostomia scores. Xerostomia was complained of during radiation therapy and persisted in the following 12 months. At baseline, xerostomia scores were similar between the pilocarpine and control groups (MD $-0.46$; 95% CI $-4.76$, 3.84; $P = .83$). After radiation therapy, patients in the pilocarpine group did feel a little better than those in the control group (MD $-9.40$; 95% CI $-17.96$, $-0.83$; $P = .03$). However, at 1-3 months after radiation therapy, patients’ scorings of xerostomia were not significantly different. Thereafter at 6 months, the xerostomia scores in the pilocarpine group were better than those in the control group (MD $-7.59$; 95% CI $-14.49$, $-0.69$; $P = .03$). At 12 months we included only 1 trial, by Burlage et al (18), indicating the favorable effect of pilocarpine (MD $-16.50$; 95% CI $-29.07$, $-3.93$; $P = .01$) (8, 13) (Fig. 5).

**Quality of life**

Two trials adopted validated questionnaires to assess QoL. XXXX et al used the McMaster University Head and Neck Head and Neck Symptom Scale questionnaire, revealing no difference between the pilocarpine and the placebo groups during or after radiation therapy. The QoL declined significantly during radiation therapy but gradually returned to the baseline score by 6 months after treatment. The patient-reported xerostomia, in contrast with the QoL, worsened and persisted in both arms (24, 26). Fisher et al used the University of Washington Head and Neck Symptom Scale questionnaire in their trial. Even though the unstimulated saliva increased in the pilocarpine group, no improvement in QoL during the follow-up 6 months was reported (19, 25).

**Adverse effects of pilocarpine**

Several included articles reported adverse effects of pilocarpine, including nausea, lacrimation, sweating, rhinitis, mild headache, and urinary frequency (21, 23, 26). The observed adverse effects were usually mild and tolerable. Meta-analysis was not performed because included studies failed to report quantifiable outcome measures. On the basis of the original report from the largest trial, no statistical difference was reported between the pilocarpine group and the placebo group (25). Only 1 patient receiving pilocarpine discontinued the medication because of excessive sweating (18).

**Discussion**

The efficacy of pilocarpine on the treatment of radiation-induced xerostomia has been studied since the 1990s (31). The morbidity of radiation-induced xerostomia is better avoided than treated (21). Thus, the preventive effect of...
3.1.1. At baseline

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Pilocarpine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Fisher 2003</td>
<td>1.8</td>
<td>1.1</td>
<td>110</td>
<td>2</td>
<td>1.1</td>
<td>115</td>
<td>2.4%</td>
<td>-0.20 [-0.49, 0.09]</td>
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</tr>
<tr>
<td>Gornitsky 2004</td>
<td>2.7</td>
<td>0.97</td>
<td>29</td>
<td>2.4</td>
<td>0.97</td>
<td>29</td>
<td>0.8%</td>
<td>0.30 [-0.20, 0.80]</td>
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</tr>
<tr>
<td>Nyarady 2006</td>
<td>0.69</td>
<td>0.26</td>
<td>33</td>
<td>0.7</td>
<td>0.25</td>
<td>33</td>
<td>13.2%</td>
<td>-0.01 [-0.13, 0.11]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>172</td>
<td></td>
<td></td>
<td>177</td>
<td>16.4%</td>
<td>-0.02 [-0.13, 0.09]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.11, df = 2 (P=0.01); I² = 36%</td>
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<tr>
<td>Test for overall effect: Z = 0.41 (P=0.68)</td>
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</table>

3.1.2. After radiotherapy

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Pilocarpine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher 2003</td>
<td>1.4</td>
<td>1.02</td>
<td>89</td>
<td>0.9</td>
<td>1.02</td>
<td>77</td>
<td>2.1%</td>
<td>0.50 [0.19, 0.81]</td>
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<tr>
<td>Gornitsky 2004</td>
<td>0.6</td>
<td>0.26</td>
<td>33</td>
<td>0.4</td>
<td>0.17</td>
<td>33</td>
<td>17.7%</td>
<td>0.18 [0.07, 0.29]</td>
<td></td>
</tr>
<tr>
<td>Nyarady 2006</td>
<td>0.48</td>
<td>0.27</td>
<td>33</td>
<td>0.22</td>
<td>0.15</td>
<td>33</td>
<td>17.9%</td>
<td>0.28 [0.15, 0.37]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>151</td>
<td></td>
<td></td>
<td>139</td>
<td>22.0%</td>
<td>0.28 [0.18, 0.37]</td>
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</tr>
<tr>
<td>Heterogeneity: Chi² = 2.30, df = 2 (P=0.32); I² = 13%</td>
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<td>Test for overall effect: Z = 5.70 (P&lt;0.00001)</td>
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3.1.3. At 5-6 week

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Pilocarpine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<tr>
<td>Gornitsky 2004</td>
<td>0.6</td>
<td>0.26</td>
<td>16</td>
<td>0.5</td>
<td>0.17</td>
<td>15</td>
<td>8.4%</td>
<td>0.10 [-0.05, 0.25]</td>
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</tr>
<tr>
<td>Nyarady 2006</td>
<td>0.58</td>
<td>0.26</td>
<td>33</td>
<td>0.4</td>
<td>0.17</td>
<td>33</td>
<td>17.7%</td>
<td>0.18 [0.07, 0.29]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>49</td>
<td></td>
<td></td>
<td>48</td>
<td>26.2%</td>
<td>0.15 [0.07, 0.24]</td>
<td></td>
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<tr>
<td>Heterogeneity: Chi² = 0.71, df = 1 (P=0.40); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.46 (P=0.0005)</td>
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3.1.4. At 3 month

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Pilocarpine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Fisher 2003</td>
<td>0.7</td>
<td>0.32</td>
<td>85</td>
<td>0.6</td>
<td>0.32</td>
<td>81</td>
<td>21.0%</td>
<td>0.10 [0.00, 0.20]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td></td>
<td>81</td>
<td>21.0%</td>
<td>0.10 [0.00, 0.20]</td>
<td></td>
</tr>
</tbody>
</table>

3.1.5. At 6 month

<table>
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<th>Study or Subgroup</th>
<th>Pilocarpine Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher 2003</td>
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<td>0.35</td>
<td>68</td>
<td>0.5</td>
<td>0.35</td>
<td>69</td>
<td>14.5%</td>
<td>0.10 [-0.02, 0.22]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>68</td>
<td></td>
<td></td>
<td>69</td>
<td>14.5%</td>
<td>0.10 [-0.02, 0.22]</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Unstimulated salivary flow rates during and after course of radiation therapy. Depicts mean differences between the pilocarpine group and the control group. Abbreviation: CI = confidence interval.

Fig. 4. Mean difference of clinician-rated xerostomia grades between the pilocarpine group and the control group at 6 months. Abbreviation: CI = confidence interval.
Burlage et al (34) discovered that pilocarpine could in-
crease unstimulated salivary flow rate kept descending.
This phenomenon could be due to different mechanisms of
salivary gland damage induced by radiation in different
time phases. In the early phase after radiation, the main
mechanism of xerostomia is attributable to plasma mem-
brane damage, which could be prevented by pilocarpine or
other specific receptor agonists(33). An in vivo study by
Burlage et al (34) discovered that pilocarpine could in-
crease proliferation of undamaged cells in the early phase
when there was a sufficient number of remaining progenitor
cells. In the late phase (approximately 120 days later),
salivary flow rate further deteriorated, because of acinar
cell apoptosis and the damaged extracellular environment
(35). Thus the concomitant application of pilocarpine was
hypothesized to be effective only in the early phase of
radiation-induced xerostomia. The protective effect may
also have accounted for the decreased clinician-rated
xerostomia grade at 6 months.

Although the unstimulated saliva flow improved in the
pilocarpine group, pilocarpine had no effect on stimulated
salivary flow rate. It was suggested that the parotid glands,
which produce stimulated saliva, might be more vulnerable
to radiation(36), and the recoverability of the parotid
glands after radiation might be weaker than the mucous
salivary glands. However, the assumption was rejected by
subsequent studies (37, 38), which showed that the func-
tional loss was quite comparable between the parotid and
submandibular glands (37). The inconsistent response to
pilocarpine between the unstimulated and stimulated saliva
might result from the sialagogic effect of pilocarpine.
daily administration of pilocarpine was presumed to keep the salivary glands in the stimulated condition. When secreting at a maximum rate, no more saliva could be secreted even with another stimulus, hence the stimulated saliva showed no significant change. Our finding was similar to those from the study by Wasserman et al (39), who observed a significant increase in unstimulated saliva production but found no difference in stimulated saliva flow in patients receiving the radioprotective agent of amifostine.

With respect to the patient-reported xerostomia, pilocarpine alleviated symptoms at 6 months, and possibly at 12 months (although only 1 study provided 12-month data). Considering the minimally important difference of 5-10% improvement required to prove the clinical value of pilocarpine, the patient-reported xerostomia at 6 months was of borderline significance (40). The discrepancy between patient-reported xerostomia and unstimulated saliva might be attributed to the varied and uncontrolled radiation doses of the submandibular glands and minor salivary glands, which would affect mucin secretion and was a critical factor for the patient-reported xerostomia scores (11, 41-43).

Two included trials found concomitant administration of pilocarpine during radiation therapy could not significantly improve QoL compared with the placebo group (19, 24). One potential reason may be that the adopted QoL questionnaire did not adequately measure xerostomia (24, 44). Fisher et al (19) explained that the ameliorated xerostomia was not perceived to be ideal, negatively affecting patients’ self-appraisal of their status. Another possibility is that the radiation-induced mucositis produces similar dysfunctions as xerostomia, and thus reduces the QoL (19). Jellema et al (45) evaluated patients’ xerostomia and QoL using the Radiation Therapy Oncology Group acute morbidity scoring criteria and the European Organization for Research and Treatment of Cancer QLC-C30. They found a significant impact of clinician-rated xerostomia on QoL, and the effect size increased over time even as the incidence of xerostomia decreased. The inconsistency in different studies indicates that the correlation between saliva flow, clinician- or patient-rated xerostomia, and QoL is complicated and should be further clarified in future studies.

The effect of pilocarpine on increasing unstimulated saliva needs to be highlighted even in the IMRT era. Intensity modulated radiation therapy is most useful in sparing the parotid glands (46) and can be combined with pilocarpine to obtain a complementary outcome. Even with IMRT, xerostomia is still a common side effect (13). Patients with N2c lymph node disease will often have marginal sparing of bilateral parotid glands, and large tumors of base of tongue may preclude submandibular glands sparing. Such circumstances will cause unavoidable radiation-induced xerostomia, which underlines the role of pilocarpine. Furthermore, IMRT produces long-term relief of xerostomia (8), whereas pilocarpine has more of a short-term benefit. Therefore, the combination of pilocarpine and IMRT is promising in preventing xerostomia and warrants further investigation.

Certain limitations in this systematic review should be taken into account. First, the number of included studies is limited, which underlines the necessity to combine available evidence for clinical guidance. Relevant outcomes should be interpreted carefully, and further high-quality trials are proposed. Second, the long-term efficacy of pilocarpine has to be further investigated, because no study in our analysis tracked outcomes beyond 12 months. Last, the adopted patient-reported or clinician-rated instruments for grading xerostomia, or the QoL questionnaires, are diverse, bringing about difficulty in comparing studies. A guideline concerning the design and implementation of future clinical trials should be recommended.

Conclusions

The concomitant administration of pilocarpine during radiation can increase unstimulated salivary flow rate and reduce clinician-rated xerostomia grade after radiation. It may also relieve patients’ xerostomia at 6 months, and possibly at 12 months. However, it has no effects on stimulated salivary flow rate. More high-quality trials are needed, with standardized outcome measures including the normalized measurement of salivary flow, clinician-rated xerostomia grade, patient-reported xerostomia, and a specialized QoL questionnaire.

References


