A Randomized Study to Assess the Effectiveness of Orally Administered Pilocarpine During and After Radiotherapy of Head and Neck Cancer

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Abstract. Background: This prospective randomized study was undertaken to assess the effectiveness of oral pilocarpine chloratum (Salagen) during and after radiotherapy. Patients and Methods: Between October 1999 and December 2003, 66 patients received 60 Gy of irradiation to their head and neck cancer. Half of the patients received 5 mg oral pilocarpine 3 times a day from the beginning of radiotherapy over a period of 12 weeks. The control group received similar doses of pilocarpine only in the second 6-weeks following irradiation. Patient saliva secretion was recorded, and a visual analog scale measuring overall and daily xerostomia, difficulty in sleeping, speaking, eating and wearing dentures was employed. Results: Pilocarpine, given concomitantly with radiotherapy, statistically improved the salivary flow and induced better patient comfort by the end of radiotherapy. Patient comfort and symptoms related to xerostomia greatly decreased compared to patients receiving pilocarpine after irradiation in the second 6-week period of therapy. The patients' quality of life, saliva production and symptoms related to xerostomia showed significant progress by the end of the 12 weeks. Conclusion: The results suggest that stimulated salivary glands suffer less decrease in saliva production during radiotherapy. The stimulated saliva flow reduced the side-effects of irradiation.

The incidence of head and neck cancer is steadily increasing. Besides surgery, radiation therapy (RT) continues to be one of the primary treatments, despite efforts to develop new treatment modalities (1-3). Of the side-effects associated with curative irradiation of these sites, xerostomia or oral dryness of the mouth is the most annoying for the patients. Due to the atrophic effects on secretory function, vascular and connective tissue changes caused by RT, salivary gland function decreases (particularly the serous component) (4, 5), causing decreased saliva production. Hypo-salivation can lead to enhanced formation of dental caries, recurrent candidiasis, compromised mucosal integrity, impaired speech, chewing, swallowing and difficulty in wearing dentures. Patients often complain of chronic oral pain and mouth burning. This decreases the general quality of life and well-being of the irradiated patients (6).

There is a dose-response relationship between the received irradiation and remaining salivary flow (7, 8). Patients usually receive a dose exceeding 50 Gy. Symptoms appear in the first week of RT and, by the end of RT, salivary gland function has diminished greatly.

The treatment for radiation-induced xerostomia is usually palliative (9). The use of mouth rinses, saliva substitutes, topical fluoride and gustatory stimulants (e.g., candy, chewing-gum) is inadequate (10-13).

Pilocarpine, a cholinergic parasympathomimetic agent, with predominantly muscarin action, stimulates cholinergic receptors on the surfaces of the exocrine glands, causing a reduction of the symptoms of mouth dryness, even in patients with no measurable salivary flow at rest (14, 15).

Pilocarpine was shown, in the early 1960’s, to increase salivary secretion (16) and, then, has been used both topically (in mouthwashes) and systemically (per os) to relieve symptoms of post-irradiation xerostomia (10, 17-23). Currently, there is debate concerning the early concomitant pilocarpine use during RT (24-27). In this study, the short term-effects and effectiveness of per os-administered pilocarpine chloratum (Salagen) were assessed during and after radiotherapy.
Patients and Methods

Between October 1999 and December 2003, 70 patients were treated with head and neck cancer external beam irradiation as a part of our complex protocol (28).

The patients were distributed randomly into two groups and received a minimum of 50 Gy of Tele-Cobalt irradiation to the head and neck region. The patients had retained at least both parotids and two of their other major salivary glands. Patients were excluded from the study if they had clinically significant uncontrolled cardiac, renal or pulmonary problems, ophthalmic or other chronic diseases that could potentially interfere with the evaluation of the safety and efficacy of pilocarpine. Patients receiving tricyclic antidepressants or antihistamines with anticholinergic effects, β-blockers or pilocarpine for ophthalmic indications were also excluded from the study (29).

All patients received 60 Gy of irradiation, in 10-Gy weekly fractions, for 6 weeks. Five doses were given on 5 consecutive days followed by 2 rest days, until the end of RT.

The patients in the first group (During RT - D) received daily 3x5 mg pilocarpine chloratum (Salagen, Novartis Hungária Kft, Budapest, Hungary) orally, from the beginning of RT, for the subsequent 12 weeks. In the control group (After RT - A), patients took oral pilocarpine only at the end of RT in the last 6 weeks of the study. The patients were instructed to take pilocarpine 1 hour prior to eating, for standardization of administration. Compliance was not objectively measured. Three patients dropped out from group D and one from group A, since they failed to appear at controls. Assessment of the remaining 66 patients was done. The patients’ descriptive statistics and baseline values are shown in Table I.

Data regarding the site of the primary tumor, previous treatment, radiotherapy ports and prescribed tumor dose were recorded. For a period of 12 weeks, patients were asked to fill out a visual analog score (VAS) questionnaire used in previous studies, which measured the severity of the various components of xerostomia (24), including overall and daytime xerostomia, ability to sleep, speak, swallow and wear dentures. Responses consisted of a single line drawn across a 100-mm scale. For each group, the distances from the left side of the scale were measured in millimeters. Only 3 patients in both groups had dentures at the onset of therapy. Non-stimulated, prior to eating, for standardization of administration. Compliance was not objectively measured. Three patients dropped out from group D and one from group A, since they failed to appear at controls. Assessment of the remaining 66 patients was done. The patients’ descriptive statistics and baseline values are shown in Table I.

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Results

Table I. Measured baseline values of patients before treatment.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.12±11.21</td>
<td>57.85±9.42</td>
<td>58.98±10.34</td>
</tr>
<tr>
<td>Received dose (Gy)</td>
<td>60.0±0.0</td>
<td>60.0±0.0</td>
<td>60.0±0.0</td>
</tr>
<tr>
<td>Overall xerostomia (%)</td>
<td>90.42±12.49</td>
<td>88.30±19.02</td>
<td>89.36±16.0</td>
</tr>
<tr>
<td>Daily xerostomia (%)</td>
<td>86.52±18.49</td>
<td>88.91±17.59</td>
<td>87.71±17.95</td>
</tr>
<tr>
<td>Eating disturbances (%)</td>
<td>88.30±15.88</td>
<td>82.21±24.05</td>
<td>85.26±20.45</td>
</tr>
<tr>
<td>Sleeping disturbances (%)</td>
<td>88.82±17.22</td>
<td>85.70±14.23</td>
<td>87.26±15.75</td>
</tr>
<tr>
<td>Saliva secretion (ml)</td>
<td>7.00±2.55</td>
<td>6.92±2.66</td>
<td>6.96±2.59</td>
</tr>
</tbody>
</table>

There were no differences in primary tumor localization or the total prescribed dose of pilocarpine between the two groups. The daily dose and treatment energy were the same in the two groups. Prior to therapy, there were no statistically significant differences in saliva secretion, overall and daytime xerostomia, ability to sleep, speak, and swallow at p=0.005 significance level with both Mann-Whitney U-test and Student’s t-tests. Descriptive statistics and the initial baseline values of the examined groups are provided in Table I.

Saliva secretion. Changes in saliva secretion are shown in Figure 1. The 10-minute non-stimulated saliva secretion decreased from 7.0±2.54 ml to 2.18±1.61 ml by the end of RT, and increased to 4.0±1.75 ml by the end of the study in group A. In group D, initial saliva secretion decreased from 6.92±2.65 ml to 4.77±2.66 ml by the 6th week. This was a significantly lower decrease (Student’s t-test p<0.001; Mann-Whitney U-test p<0.001) than in group A. Final saliva secretion on the 12th week in group D was 5.79±2.66 ml, which was a significantly smaller change (Student’s t-test p<0.001; Mann-Whitney U-test p<0.001) than that observed in group A. The recorded saliva secretion was always significantly better in group D (Student’s t-test p<0.05; Mann-Whitney U-test p<0.05).

Overall xerostomia. Changes in overall xerostomia VAS are presented in Figure 2. The overall mean xerostomia VAS decreased from an initial value of 90.42±12.49% to 34.78±24.13% by the 6th week and increased to 72.6±24.7% by the 12th week in group A. In group D, a minor increase of symptoms was observed on VAS compared to group A (Student’s t-test p<0.001; Mann-Whitney U-test p<0.001). Xerostomia VAS was 64.12±24.51% at RT end and 87.0±11.57% at 12 weeks. The recorded VAS after initiation of RT was always significantly better in group D (Student’s t-test p<0.001; Mann-Whitney U-test p<0.001).

Daily xerostomia. The changes in daily xerostomia VAS are presented in Figure 3. Daily xerostomia VAS decreased from an initial value of 86.51±18.49% to 47.87±31.35% by
the end of RT and increased to 73.84±22.6% by the 12th week in group A. In group D, a minor increase of symptoms was observed on VAS compared with group A (Student’s t-test p<0.001; Mann-Whitney U-test p<0.001). Xerostomia VAS was 67.84±26.49% in the 6th week and 88.69±10.82% at 12 weeks. The recorded VAS was always significantly better after the beginning of RT in group D (Student’s t-test p<0.05; Mann-Whitney U-test p<0.05).

Sleep disturbances (nocturnal xerostomia). The changes in sleeping patterns due to oral dryness and burning are presented as VAS in Figure 4. The nocturnal average
baseline values were 88.3±15.87% in group A and 82.21±24.15% in group D. VAS was 55.03±30.78% in group A and 62.03±28.07% in group D at the end of RT. There was a significant increase of symptoms due to nocturnal xerostomia by the 6th week (Student’s t-test \( p<0.05 \); Mann-Whitney U-test \( p<0.05 \)). However, there was a statistically significant difference between the two groups favoring group D only in the 10th (Student’s t-test \( p<0.05 \); Mann-Whitney U-test \( p<0.001 \)) and 12th (Student’s t-test \( p<0.001 \); Mann-Whitney U-test \( p<0.001 \)) weeks of the study.

**Speaking disturbances.** The changes in speaking disturbances due to xerostomia are presented as VAS in Figure 5. From an initial VAS of 85.57±18.09% in group A and 91.15±24.04% in group D, there was a statistically significant increase of symptoms (Student’s t-test \( p<0.001 \); Mann-Whitney U-test \( p<0.001 \)) by the end of RT. From the 6th week, there was an increase in VAS to 70.18±21.54% in group A and 85.42±12.9% in group D. The recorded VAS was always significantly better in group D (Student’s t-test \( p<0.005 \); Mann-Whitney U-test \( p<0.005 \)).

**Eating disturbances.** The changes in eating experiences due to oral dryness and burning are presented in Figure 6. Eating difficulty due to xerostomia decreased from 88.81±17.22% to 44.27±24.79% by the end of RT on the 6th week, and increased to 72.27±25.29% by the end of the study in group A. In group D, the initial VAS decreased from 85.97±14.23% to 56.36±25.63% by the 6th week. This was a significantly smaller decrease (Student’s t-test \( p<0.001 \); Mann-Whitney U-test \( p<0.001 \)) than that observed in group A. Final VAS on the 12th week in group D was 86.48±10.84%, which was a significantly lower change (Student’s t-test \( p<0.01 \); Mann-Whitney U-test \( p<0.01 \)) than that observed in the other group. The recorded eating disturbances by VAS were always significantly better in group D (Student’s t-test \( p<0.01 \); Mann-Whitney U-test \( p<0.01 \)).

**Ability to wear dentures.** The number of patients wearing dentures at the onset of therapy was three in both groups. This was too few for a meaningful statistical analysis, however the patients seemed to tolerate their dentures better in group D after RT.

**DMF and periodontal status.** There were no differences in the DMF and periodontal status of patients at 6 and 12 weeks in the two groups. The observed period may have been too short to allow the development of major differences, especially when the patients’ oral status was prepared for RT.

**Side-effects.** The dose (3x5 mg) used in our study was safe. The side-effects were mild and tolerable; they did not indicate the discontinuation of pilocarpine usage. Adverse experiences were primarily sweating, rhinitis and urinary frequency.

**Discussion**

Radiation therapy is highly successful in the treatment of lymphomas and certain solid tumors arising in the head and neck region (28). Unfortunately, the salivary glands often must be included in the radiation field, and patients have life-long effects in the form of xerostomia due to poor or absent salivary flow, as well as changes in the consistency of the saliva. The lack of salivary protection negatively influences nutrition, dentition, sleep, speech and pleasure in eating, thus greatly decreasing comfort (9, 31, 32). Attempts to improve oral function and reduce the high rate of dental caries included topical fluoride and antifungal agents. The palliative use of mouth rinses, saliva substitutes, topical fluoride and gustatory stimulants (e.g., candy, chewing-gum) have proved inadequate (10, 11, 13, 22).

Several studies have shown that oral pilocarpine is beneficial in short-term post-irradiation use to control the symptoms and discomfort related to xerostomia (10, 17, 19-23, 33). In these studies, pilocarpine was administered several weeks or months after radiotherapy. Under these circumstances, the saliva production of both the major and minor salivary glands was increased (34, 35), thus greatly relieving the symptoms of late post-irradiation xerostomia.

Rieke et al. showed pilocarpine to be safe and free of major side-effects, even in doses up to 15 mg 3 times a day (36). These patients had undergone previous RT and had established xerostomia before treatment. This group also found that pilocarpine decreased the symptoms of RT-related xerostomia effectively.

Zimmerman et al. concomitantly administered pilocarpine with RT. The controls in this study did not receive any form of the drug during the time of the study. In this setup pilocarpine effectively induced saliva production and decreased the symptoms of xerostomia (24). In another study, no significant difference was noted in the level of saliva, xerostomia, or other symptoms between patients treated with pilocarpine during RT and the control group. However, the stimulated patients reported a better overall quality of life (25).

Data derived from the present study indicate that pilocarpine hydrochloride (Salagen) given concomitantly with RT induced statistically significant changes and corroborated our preliminary results (26, 27). Salivary flow decrease was lower in the group treated with Salagen from the beginning of RT. The drug also induced better patient comfort in head and neck cancer, with the exception of difficulty in sleeping, when administered from the beginning.
of RT. Patient comfort and symptoms related to xerostomia greatly decreased compared to patients who received pilocarpine after RT only in the second 6 weeks of treatment. The patient quality of life, saliva production and symptoms related to xerostomia showed significant progress in the concomitantly-treated group by the end of 12 weeks. These results suggest that a stimulated salivary gland suffers a smaller decrease in saliva production capability during RT. The increased saliva flow reduces the side-effects of RT.

Conclusion

We recommend the concomitant use of oral pilocarpine chlororatum (Salagen) during RT to relieve the symptoms of xerostomia. The stimulated saliva secretion may help to preserve salivary gland function.

References