Effectiveness of oxygen nebulization at preventing radiotherapy-induced mucositis in patients with nasopharyngeal cancer

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ABSTRACT

Purpose: To evaluate the effectiveness of oxygen nebulization at preventing radiotherapy-induced mucositis in patients with nasopharyngeal cancer.

Methods: Sixty patients with nasopharyngeal cancer treated with simultaneous integrated boost intensity-modulated radiotherapy were randomly assigned to oxygen nebulization or ultrasonic nebulization groups; treatment was once daily for 20 minutes. All patients received routine oral care. We compared saliva pH and volume, food intake, and change in oral mucosa during radiotherapy, and dry mouth and sore throat after radiotherapy between the two groups.

Results: There were significant differences in the incidence of grade III or IV mucositis, saliva volume and pH, and dry mouth and sore throat between the two groups when the total dose was 33 Gy (\(p < 0.05\) or \(p < 0.01\)).

Conclusion: Oxygen nebulization reduces radiotherapy-induced mucositis and relieves symptoms such as dry mouth and sore throat in patients with nasopharyngeal cancer.

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1. Introduction

Radiotherapy remains the preferred treatment for nasopharyngeal cancer; the most common adverse reaction is acute oral mucosa reaction to radiotherapy. The reaction is characterized by dry mouth, oropharyngeal pain, oral inflammation, pseudomembrane formation, easily broken mucous membranes, bleeding, ulcer formation, and eating disorder, All of which has a serious influence on radiotherapy, even leading to its suspension. Therefore, preventing and controlling oral mucosa reaction to radiotherapy effectively is
a clinical problem that should be resolved. Oxygen nebulization is used for patients with chronic obstructive pulmonary disease [1] and infantile acute laryngitis [2], but its effect in the treatment of oral mucosa reaction to radiotherapy is unknown; therefore, we examined the effect of oxygen nebulization therapy in patients with nasopharyngeal cancer during radiotherapy in this study.

2. Design and methods

2.1. Participants

Between December 2011 and December 2012, we enrolled 60 patients with a pathological diagnosis of nasopharyngeal cancer at our department, and assigned them to experimental (n = 30) and control (n = 30) groups using the random number method. Inclusion criteria: (1) pathological diagnosis of nasopharyngeal; (2) received radiotherapy for the first time; (3) Karnofsky functional status score ≥ 70 points; (4) no oral mucosal inflammation, cavities, dentures, or other oral diseases; (5) no synchronous chemotherapy or radiotherapy sensitization agent use during radiotherapy; (6) adherence to treatment as required. The grouping method was as follows: we obtained 60 random numbers with the random number table, removed the same numbers, and then assigned these random numbers to patients according to time of hospital admission. We ranked the numbers from small to large and placed the first 30 in the experimental group; the remaining numbers were placed in the control group. Table 1 lists the characteristics of the two groups in terms of age, sex, and dose. All patients completed the whole research process.

2.2. Methods

2.2.1. Radiotherapy

All subjects were treated with simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT). SIB-IMRT uses 6-MV X-ray, 2.2-Gy gross tumor volume (GTV) dose (visible tumor imaging and neck lymph node metastasis), 2.0-Gy clinical target volume (CTV) 1 dose (high-risk areas), and 1.8-Gy CTV2 dose (low-risk areas) each time for a total 30 times, and GTV dose to test dose of 66 Gy five times per week.

2.2.2. Nursing intervention

Patients in the experimental group received oral care every day to maintain oral health, rinsed their mouths daily before and after radiotherapy and after eating, and received oxygen nebulization after radiotherapy each day. The drugs used were 10 mL saline, 240,000 U gentamicin, 600 U chymotrypsin, and 5 mg dexamethasone, with an oxygen flow rate of 8 L/min for 20 min per session, until the end of radiotherapy. The control group received the same oral care during radiotherapy as the experimental group. During radiotherapy, control group patients received ultrasonic nebulization at the end of radiotherapy daily, using the same drugs as the experimental group for 20 min per session.

2.2.3. Outcome measures

Before radiotherapy, three primary nurses were trained to evaluate the effects. After radiotherapy was administered at 10 AM every Monday, the nurses in charge performed the following: (1) Oral pH measurement using precise test paper (Xingxia Xiangrui Technology Development, Beijing) and measuring the average of two points: the center of the tongue and on one side of the tongue. (2) Saliva collection using an Azov mong Trading (Shanghai) triangle funnel; patients gargled with water before saliva collection, then chewed two sticks of blueberry-flavored chewing gum for five minutes without swallowing while chewing. After the chewing gum had been spat out, the triangle funnel was affixed to the patient’s jaw, and the patient lowered their head, allowing all of the saliva collected in their mouth to flow out; bubbles were filtered out. (3) Observed oral mucosa injury in patients. Based on the World Health Organization classification [3], radioactive oral mucosa injury was graded 0–IV. Grade 0: no mucosal response; grade I: mucosal hyperemia; grade II: mottled mucositis; grade III: 50% flaky mucositis in 50% of the area exposed to radiotherapy, or with obvious pain; grade IV, flaky mucositis accounting for >50% of the exposure area or severe reaction + need to stop treatment or stopping oral nutrition. (4) Evaluated dry mouth and degree of oropharyngeal pain using the visual analog scale ruler [4]. The ruler is numbered 0–10; patients rate their own discomfort: 0: no symptoms, 1–4: mild discomfort, 5–7: medium discomfort, 8–10: severe dry mouth or oropharyngeal pain.

2.2.4. Statistical analysis

We used SAS 9.0 for statistical analysis. We compared the oral mucosa reaction between the two groups with nonparametric tests; oral pH, saliva, and nebulization comfort of the two groups were compared by t-test.

3. Results

3.1. Comparison of oral mucosa reaction

Compared to the control group, significantly fewer patients in the experimental group had grade III–IV mucosal reaction after receiving up to 33 Gy radiotherapy, at the end of radiotherapy, and the following one week (p < 0.05, Table 2). As no patient in either group developed grade 0 or IV reaction, we merged grade 0 and I, and grade III and IV reactions to reduce statistical error during statistical analysis.

3.2. Comparison of oral pH and salivary flow rate

Salivary flow rate and pH of the experimental group remained higher than that of the control group (p < 0.05, Table 3).
Comparison of oral mucosa reaction by grade.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>33-Gy radiotherapy</th>
<th>End of radiotherapy</th>
<th>One week after end of radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–I</td>
<td>II</td>
<td>III–IV</td>
</tr>
<tr>
<td>Experimental</td>
<td>30</td>
<td>21</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>12</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>X2min</td>
<td>4.86</td>
<td>11.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.028</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.3. Comparison of dry mouth and oropharyngeal pain at the end of radiotherapy

Oxygen nebulization drug therapy was better than ultrasonic nebulization in preventing radiation-induced oral mucositis, dry mouth, sore throat, and other clinical reactions (p < 0.05, Table 4).

### 4. Discussion

#### 4.1. Analysis of the causes of adverse reactions caused by oral cavity radiotherapy

At present, radiotherapy is the first choice for treating nasopharyngeal carcinoma. Oral mucosa reaction to radiotherapy is one of the most common complications in patients with nasopharyngeal carcinoma. The oral environment is moist and rich in blood supply, and the stratified squamous epithelium, which renews itself quickly, is highly sensitive to radiation. Salivary gland (parotid, submandibular, sublingual) secretion decreases after radiotherapy, and saliva decreases, which causes the oral pH to decrease, leading to dry mouth and disorder of the oral microenvironment. At the same time, radiation can damage the mucosa directly, narrowing or blocking the local microcirculatory vasculature, resulting in mucosal hyperemia and edema, causing ischemia and hypoxia and causing the oral mucosa reaction to radiotherapy. Currently, the first choice for treating nasopharyngeal carcinoma is typically IMRT technology. A clinical randomized controlled phase III study confirmed the protective effect of IMRT on parotid gland function [5]; however, it is difficult to avoid radiation damage to the gland. SIB-IMRT increases radiotherapy efficacy; at the same time, the increased radiotherapy dose exacerbates the oral mucosa reaction. Urgent measures are required to alleviate acute mucosal reactions in patients and improve patient tolerance of radiotherapy. The flow rate of the salivary gland is related to the average radiation dose: the tolerance dose of the minor salivary glands is 10–15 Gy. When the major salivary glands receive the average dose of 20–40 Gy, their function will gradually decline, and if the average dose exceeds 40 Gy, the major salivary gland function will decrease dramatically (>75% loss) [6]. Gland secretions decrease following radiotherapy mainly because of gland cell apoptosis, decreased cell numbers, and reduced secretory function. Normal salivary gland secretion is about 0.5 mL/min. Parotid and submandibular gland secretion respectively account for 60–65% and 20–30% of salivary gland secretions; gland damage causes dry mouth. This study also showed that during radiotherapy, the oral pH and salivary flow rate in patients decrease when the radiation dose increases; despite the drug inhalation treatment methods, the patients developed oral mucositis, dry mouth, and oropharyngeal pain, which is consistent with the current literature [7]. Preventing oral mucosa reaction to radiotherapy effectively and relieving dry mouth and sore throat or other discomfort is a clinical problem urgently requiring resolution.

#### 4.2. Oxygen nebulization can prevent or reduce oral mucosa reaction to radiotherapy, dry mouth, and sore throat

Rodriguez et al. found that severe hypoxia was a key factor in wound non-healing, where hypoxic conditions impede many aspects of the wound healing process, such as angiogenesis, fibroblast proliferation, and inflammatory reaction [8]. Balin and Prantt proved that there is obvious oxygen toxicity when oxygen pressure >137 mmHg (1 mmHg = 0.133 kPa), where the oxygen tension for skin fiber propagation should not exceed 137 mmHg; appropriate supplemental oxygen improves local microcirculation and promotes oral mucosal cell proliferation [9]. Oxygen inhibits bacteria, and the inhibitory effect is divided into specific and nonspecific suppression. Specific inhibitory effects mainly inhibit anaerobic bacteria by increasing the oxygen pressure around the wound; it inhibits bacterial growth by causing bacterial metabolic disorder. Nonspecific inhibition inactivates bacterial enzymes, leading to bacterial metabolic disorder and inhibiting microbial growth. Oxygen

### Table 3 – Comparison of oral pH and salivary flow rate (X ± s).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>33-Gy radiotherapy</th>
<th>End of radiotherapy</th>
<th>One week after end of radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pH</td>
<td>Saliva (mL/5 min)</td>
<td>pH</td>
</tr>
<tr>
<td>Experimental</td>
<td>30</td>
<td>6.25 ± 0.50</td>
<td>3.61 ± 1.01</td>
<td>5.29 ± 0.42</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>5.83 ± 0.43</td>
<td>2.73 ± 1.10</td>
<td>4.85 ± 0.47</td>
</tr>
<tr>
<td>t</td>
<td>3.45</td>
<td>3.22</td>
<td>3.84</td>
<td>2.77</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
</tbody>
</table>
nebulization uses high-flow oxygen (8 L/min) to achieve this, improving local mucosal oxygen pressure and local tissue oxygen supply during treatment and promoting oral mucosa healing by improving tissue hypoxia [6], promoting angiogenesis and achieving anti-inflammatory effects [10]. At the same time, it increases effective control of local inflammation, promoting resolution of inflammation and improving local blood circulation; it also reduces pain and relieves or dissipates subjective pain.

This study showed that compared to the control group, the experimental group, which received oxygen nebulization treatment instead of ultrasonic nebulization during radiotherapy, experienced oral mucositis, dry mouth, and sore throat to a lesser degree. During radiotherapy, salivary gland secretion in both groups decreased when the radiation dose was increased, and the salivary flow rate decreased. However, salivary flow rate and pH of the experimental group remained higher than that of the control group. According to our analysis, oxygen nebulization drug therapy was better than ultrasonic nebulization in preventing radiation-induced oral mucositis, dry mouth, sore throat, and other clinical reactions. However, further research into an effective method of preventing oral mucosa reaction or other discomfort during radiotherapy in patients with nasopharyngeal carcinoma is still required to alleviate patient discomfort, which would translate into better acceptance of treatment.

Table 4 – Comparison of dry mouth and oropharyngeal pain at the end of radiotherapy (X ± s).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Dry mouth</th>
<th>Oropharyngeal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>30</td>
<td>5.23 ± 1.85</td>
<td>5.40 ± 1.83</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>6.87 ± 1.87</td>
<td>7.17 ± 1.97</td>
</tr>
<tr>
<td>t</td>
<td>−3.40</td>
<td>−3.60</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Conflicts of interest statement

No conflict of interest has been declared by the authors. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES