Effectivity of 0.15% benzydamine on radiation-induced oral mucositis in nasopharynx carcinoma

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ABSTRACT

Background: Nasopharynx carcinoma is the most common malignant tumour in head and neck region. Radiotherapy is the first choice of treatment for nasopharynx carcinoma that had not been metastases. The most common oral complications in radiotherapy is mucositis (± 80%). 0.15% benzydamine hydrochloride (HCl) oral rinse can be used to prevent radiation-induced oral mucositis.

Purpose: The aim of this research was to study the effectivity of 0.15% benzydamine HCl oral rinse for prevention of radiation-induced oral mucositis in nasopharynx carcinoma.

Methods: Samples were divided into 2 groups. Group A was using 0.15% benzydamine HCl oral rinse for 10 days. Group B was using placebo oral rinse for 10 days. Evaluation was conducted 3 times: first day, fifth day and tenth day of radiotherapy. The scoring used Spijkervet’s mucositis α score.

Results: Independent t test analysis for initial occurrence of oral mucositis showed no significant difference between 2 groups. Paired t test analysis showed significant difference between initial mucositis α score and mucositis α score in tenth day in each group. Independent t test analysis showed no significant difference in mucositis α score in tenth day between 2 groups.

Conclusion: In conclusion 0.15% benzydamine HCl oral rinse was not effective to prevent radiation-induced oral mucositis in nasopharynx carcinoma.

Key words: 0.15% benzydamine hydrochloride, prevention, radiation-induced oral mucositis, nasopharynx carcinoma

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INTRODUCTION

Nasopharynx carcinoma (NPC) is the most common of malignant tumor in head and neck region and also in the Department of Ear, Nose and Threat. NPC also showed increasing number from year to year.\(^1\)\(^2\) NPC is a malignant tumor located in the nasopharynx, which manifestation including initial symptoms in the nose and ear, and late symptoms because of the expansion of primary tumor to surrounding organ in nasopharynx, or regional metastases to lymph nodes in the neck.\(^2\)

Radiotherapy is the first choice of treatment for NPC that had not been distant metastases.\(^1\)\(^3\) This therapy is aimed to eradicate cancer cells with ionizing radiation. Radiotherapy is also occasionally associated with dysfunction and disintegration of healthy tissue during and after therapy, including oral mucosa, through delayed of cell maturation and development.\(^4\)

During the treatment of the head and neck radiotherapy, oral cavity is always in the risk of exposure of radiation. Therefore, oral complications are expected, such as radiation-induced oral mucositis, which is the most common oral complications (± 80%). Oral mucositis generally begin about ± 1–2 weeks after the start of radiotherapy (± 1000 cGy–2000 cGy). Oral mucositis is associated with significant pain, inability to tolerate food and fluids, affect speech, and further compromising patients’ response to complete planned radiotherapy, thus it can prolong the duration of radiotherapy.\(^4\)\(^10\)

Planning of the precise therapy before radiotherapy is aimed to prevent radiation-induced oral mucositis.\(^5\)\(^11\) In several literatures, to prevent radiation-induced oral mucositis, 0.15% benzydamine hydrochloride (HCl) oral rinse was used. Benzydamine HCl is a nonsteroidal rinse with anti-inflammatory, local anesthetic, antipyretic and antimicrobial activities.\(^9\)\(^12\) This oral rinse can be effective in preventing oral mucositis.\(^5\)\(^7\)\(^13\) According to the medical records in the ENT Oncology Outpatient Clinic of Dr. Soetomo Hospital, there had not been any effort to prevent radiation-induced oral mucositis in NPC’s patients. No attention to radiation-induced oral complications is given yet. The purpose of this research was to study the effectiveness of 0.15% benzydamine HCl oral rinse for prevention of radiation-induced oral mucositis in NPC.

MATERIALS AND METHODS

The design of this research used randomized controlled trial. Population of this research was NPC patients in the Department of Radiotherapy Dr. Soetomo Hospital who received radiotherapy. Inclusion criteria of the sample was cooperative sample, stage III & IV NPC without distant metastases (loco-regional advanced), histopathology results showed undifferentiated carcinoma (WHO type 3), which planned to receive fractional dose radiation 200 cGy per day, five times a week, man & woman, 30–60 years old, not undergoing chemotherapy, no symptoms about oral mucositis and xerostomia, no infection disease, no allergy, no systemic disease (liver and nephrotic disease, hypertension and diabetes mellitus), no consumption of drugs that could cause xerostomia (antidepressant, antihistamin, antihypertension, opiate, sedative and diuretic drugs), and no consumption of systemic analgesic drugs. Exclusion criteria of the sample was absent of visit and not using oral rinse as it was planned, could not undergo radiotherapy as it was planned, allergy to benzydamine HCl or other signs of side effect, and refused to continue this research.

Samples were divided into 2 groups. Group A was using 0.15% benzydamine HCl oral rinse 120 ml for 10 days, rinse or gargle 15 ml for 60 seconds, three times daily. Each time before the radiation was conducted, samples were using oral rinse under supervision from researcher. Group B was using placebo oral rinse 120 ml for 10 days, with the same protocol as group A. There was no intervention before, including dental treatment. Evaluation was conducted 3 times: first day, fifth day and tenth day of radiotherapy. The results of evaluations were recorded in the dental records.

The assessment of oral mucositis used Spijkervet’s mucositis α score. This scoring technique was specifically developed to measure tissue changes relative to dose-response relationships and the effects of preventative mucositis strategies. Spijkervet states that the mucositis scores developed by this technique are basically useful for research and are of limited value clinically because the total score α does not always reflect the clinical condition of the patient. This scoring distinguishes the most common and significant local clinical signs of radiation mucositis that represent the order or progression of mucosal radiation damage (k) that includes no mucositis, white discoloration, erythema, pseudomembranes, and ulceration. Eight anatomical areas (n) of the mouth are scored (right and left buccal mucosa, hard palate, soft palate, dorsum of tongue, right and left border of tongue, and floor of mouth), although any one area might include several subareas with different local signs of mucositis observed in that area. The length (k) of each identical local sign for each subarea is measured (in centimetres) and then summed and corresponds with a value E (1 ≤ 1 cm, 2 = 1.0–2.0 cm, 3 = 2.1–4.0 cm, 4 ≥ 4 cm). The degree of mucositis for each subarea was defined as the product of the values k and E; the score for mucositis in an area was defined as the sum of these products. Finally, the overall Spijkervet’s mucositis α score is calculated as the mean of the scores assigned to the number of irradiated areas (n).\(^6\)

Data analysis used descriptive and inferential (Independent t-test, Paired t-test, Mann-Whitney test and Fisher’s Exact test), with level of significance (α) was 0.05 (5%).
Table 1. Homogenity test between group A and Group B

<table>
<thead>
<tr>
<th>Data type</th>
<th>Group A</th>
<th>Group B</th>
<th>Statistic test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Man</td>
<td>7 (70%)</td>
<td>7 (77.88%)</td>
<td>Fisher’s exact test</td>
<td>1.000**</td>
</tr>
<tr>
<td>- Woman</td>
<td>3 (30%)</td>
<td>2 (22.22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rate (years)</td>
<td>45.10</td>
<td>45.11</td>
<td>Independent t-test</td>
<td>0.997**</td>
</tr>
<tr>
<td>- SD</td>
<td>7.95</td>
<td>6.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Elementary</td>
<td>7 (70%)</td>
<td>5 (55.56%)</td>
<td>Mann-Whitney test</td>
<td>0.476**</td>
</tr>
<tr>
<td>- Junior school</td>
<td>2 (20%)</td>
<td>2 (22.22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- High school</td>
<td>1 (10%)</td>
<td>2 (22.22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPC Stage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- III</td>
<td>4 (40%)</td>
<td>4 (44.44%)</td>
<td>Fisher’s exact test</td>
<td>1.000**</td>
</tr>
<tr>
<td>- IV</td>
<td>6 (60%)</td>
<td>5 (55.56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHI-S (first day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rate</td>
<td>2.60</td>
<td>2.26</td>
<td>Independent t-test</td>
<td>0.426**</td>
</tr>
<tr>
<td>- SD</td>
<td>0.88</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: **: no significant different (p > 0.05)

RESULTS

This research was completed in 3 months and included 19 samples. Group A was 10 samples and group B was 9 samples. Statistic analysis (Table 1) showed the homogenity of sex, age, level of education, NPC stage and Oral Hygiene Index Simplified (OHI-S) in the first day of radiotherapy, between group A and B (p > 0.05). Independent t-test analysis for initial occurence of oral mucositis between group A and group B (Table 2) showed p = 0.504 (p > 0.05), it meaning there was no significant difference between 2 groups.

Paired t test analysis showed significant difference between initial mucositis $\alpha$ score and mucositis $\alpha$ score in tenth day in each group (Table 3 & 4). Independent t test analysis showed no significant difference in mucositis $\alpha$ score in tenth day between 2 groups (Table 5).

DISCUSSION

The design of this research was randomized controlled trial. This clinical trial was an experimental trial with human being as the sample. This research was phase III clinical trial because it aimed to evaluate new treatment, compared with placebo.14 The homogenity between 2 groups (Table 1) must be tested to know about the factor that could affect mucositis $\alpha$ score. If there was any difference between 2 groups, the reason of difference was only because of the experiment that were given in both groups.14 Table 1 showed that group A and B were homogen.

Initial occurence of oral mucositis between 2 groups showed no significant difference among them (Table 2). It meant that 0.15% benzydamine HCl was not effective to delay the initial occurence of oral mucositis, as in placebo. This was similar with Putwatana et al.,15 that comparing benzydamine with natural agents, glycerine payayor (herbal product) was found to be superior in preventing and relieving radiation-induced oral mucositis than benzydamine hydrochloride. Although 0.15% benzydamine HCl also had antimicrobial effect, it could

Table 2. Independent t-test analysis for initial occurence of oral mucositis between group A and group B

<table>
<thead>
<tr>
<th>Initial occurence of oral mucositis</th>
<th>Group A</th>
<th>Rate</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>of oral mucositis</td>
<td>A</td>
<td>7.20</td>
<td>1.14</td>
<td>0.504**</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>7.56</td>
<td>1.13</td>
<td></td>
</tr>
</tbody>
</table>

Notes: ** : no significant difference (p > 0.05)

Table 3. Paired t-test analysis for mucositis $\alpha$ score in group A (The 1st, 5th and 10th day of radiotherapy)

<table>
<thead>
<tr>
<th>Mucositis $\alpha$ score</th>
<th>Group A</th>
<th>N</th>
<th>Rate</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>9</td>
<td>10</td>
<td>0.00</td>
<td>0.00</td>
<td>**</td>
</tr>
<tr>
<td>5th day</td>
<td>9</td>
<td>10</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>10th day</td>
<td>9</td>
<td>10</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

Notes: *: significant difference (p < 0.05); **: could not be analyzed

Table 4. Paired t-test analysis for mucositis $\alpha$ score in group B (The 1st, 5th and 10th day of radiotherapy)

<table>
<thead>
<tr>
<th>Mucositis $\alpha$ score</th>
<th>Group B</th>
<th>N</th>
<th>Rate</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>9</td>
<td>9</td>
<td>0.00</td>
<td>0.00</td>
<td>**</td>
</tr>
<tr>
<td>5th day</td>
<td>9</td>
<td>9</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>10th day</td>
<td>9</td>
<td>9</td>
<td>1.86</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *: significant difference (p < 0.05); **: could not be analyzed
not delay this disorders. It might because rinsing was not
guaranteed to have enough contact between antimicrobial
agent with microorganism, so 0.15% benzydamine HCl as
antimicrobial could not help the antiinflammation effect.
But the research of Epstein et al. and Worthington et
al. stated the opposite things. These differences because
the method to assess oral mucositis was different. Epstein
et al. used mucositis score based on subjective and
clinical manifestation of oral mucositis (erythema,
elucration and pain). Worthington et al. recommended
in additional large trials to determine benefit, dosage, and
administration method. While Spijkervet’s mucositis α
score used in this research was a special method for research
so the assessment is accurate. This method assessed clinical
changes of radiation-induced oral mucosa in qualitative
and qualitative ways (white discoloration, erythema,
pseudomembrane and ulceration), not subjective complaint
or dysfunction of oral cavity. It is important to note that,
whereas the score developed by the Spijkervet technique
will not always reflect the clinical state of the patient, it does
quantify the degree of tissue change or damage. Besides
that, the differences might be caused by initial occurrence of
oral mucositis was not due to the microba, but because of the
radiotherapy’s side effect. Thus the use of antimicrobial
agent did not have effect, and the antiinflammation was
playing the role. The antiinflammation effect depends
on oral hygiene, tissue resistance to radiotherapy, total
dose of radiotherapy and how long the patient received
radiotherapy. In this research, oral hygiene in the first day
of radiotherapy between 2 groups was homogenous (Table
1), but it meant both groups had bad oral hygiene, so it
might stimulate the initial occurrence of oral mucositis.
This was similar with Köstler et al. and Berger & Kilroy,
which reinforced oral hygiene as a important
direct factor that could affect the degree of severity and
duration of mucositis. Besides oral hygiene, there were
also radiation source, daily doses, cumulative doses and
irradiated mucosa volume. The side effect of radiotherapy,
especially sensitive to cell with faster proliferation such as
tumor cell, but this effect also affect healthy tissue in the
radiation field, so tissue resistance was decreased because
of radiotherapy.

There was significant differences between the rates
of mucositis α score in the first and the tenth day of
radiotherapy in each group (Table 3 and 4). This fact
could be caused by the initiation of oral mucositis in both
groups, so mucositis α score could be assessed already.
There was no significant different of mucositis α score’s
rates between group A and group B in the tenth days.
(Table 5). It meant that 0.15% benzydamine HCl was
not effective, as in the placebo. This was similar with
Rosenthal and Trotti, Hancock et al. which stated that
the risk for developing radiation-induced oral mucositis
depends on different factors, such as anti cancer treatment
protocol, age and diagnosis of the patient, level of oral
hygiene during therapy, genetic factors. Kartabrata et al.
and Beck, said that disintegration of lining mucosa was port
d’entry of microorganism and caused local infection which
potentially disseminated through blood stream. According to
Stokman et al., Epstein et al. and Kazemian et al.,
there was significant different of mucositis score between
group using benzydamine with placebo as a prevention
because it proved could prevent or reduce the severity
and the risk of secondary infection and bleeding because
of benzydamine’s antiinflammation effect. Besides, those
research used different definition of prevention, that
was to prevent or reduce clinical manifestation of oral
mucositis. While in this research, the definition was to
prevent the occurrence of oral mucositis. Therefore, it can
be concluded that 0.15% benzydamine HCl oral rinse was
not effective to prevent radiation-induced oral mucositis in
nasopharynx carcinoma. It will need further research and
better cooperation between specialists of oncology radiation
and oral medicine.

### Table 5. Independent t-test analysis for mucositis α score between group A and group B in 1<sup>st</sup>, 5<sup>th</sup> and 10<sup>th</sup> day of radiotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Rate</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>0.00</td>
<td>0.00</td>
<td>- ***</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>0.00</td>
<td>0.00</td>
<td>- ***</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>0.00</td>
<td>0.00</td>
<td>- ***</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>0.00</td>
<td>0.00</td>
<td>- ***</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>1.37</td>
<td>0.79</td>
<td>0.245**</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>1.86</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

Notes: **: no significant difference (p > 0.05); ***: could not be analyzed

### REFERENCES


