ORIGINAL ARTICLE

Propolis mouthwash for preventing radiotherapy-induced mucositis in patients with nasopharyngeal carcinoma: A randomized control trial

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Malaysia. The gold standard treatment of NPC is radiotherapy (RT), as NPC is a radiosensitive tumour. Although RT is successful in treating NPC, patients cannot avoid the resulting RT complications. Oral mucositis is the most frequently encountered debilitating complication of RT and has no specific preventive treatment. The aim of this study was to evaluate the efficacy and safety of a 2.5% propolis mouthwash for preventing RT-induced mucositis in patients with NPC.

Materials and methods: The study was a prospective, double-arm, randomised control trial with intervention. The patients were randomly divided into an experimental group receiving propolis mouthwash and a placebo group receiving normal saline mouthwash. All patients were instructed to rinse their mouths with 7mL mouthwash three times daily for six weeks. The severity of oral mucositis was then evaluated by the World Health Organization Oral Toxicity Scale at the second, fourth, and sixth weeks of the study.

Results: In total, 17 patients completed the study: 10 patients used the propolis mouthwash and seven used the placebo mouthwash. The mean mucositis scores for the propolis mouthwash compared to the placebo at the second, fourth, and sixth weeks were 0.10 vs. 1.14, 0.50 vs. 2.00, and 1.20 vs. 2.86, respectively, and the differences between the two groups were statistically significant (p<0.001).

Conclusion: A 2.5% propolis mouthwash was both safe and effective for reducing the severity of oral mucositis following RT for NPC.

KEYWORDS:
Nasopharyngeal carcinoma, radiotherapy, mucositis, propolis mouthwash

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common cancer of the head and neck in Malaysia and is the fifth most common of all cancers among all Malaysian residents.1 The gold standard treatment for NPC is radiotherapy (RT), as NPC tumours are radiosensitive. The Malaysia Clinical Practice Guidelines recommend that stage I NPC be treated with definitive RT to the nasopharynx and elective RT to the neck region, whereas stage II, III, and IVa NPC should be treated with concurrent chemoradiotherapy (CCRT). Only palliative treatment is available for stage IVb NPC (distant metastasis). The RT dose for the primary tumour site is 66-70 Gray (Gy) at 33-35 fractions for 6-7 weeks, and 54-70 Gy at 30-35 fractions for 6-7 weeks for the neck region. If the neck nodes are negative, the neck region dose is 54-60 Gy for 30 fractions for six weeks. These RT can successfully treat NPC, but they leave the patients with serious complications from the RT itself. Oral complications, such as oral mucositis, dysphagia, and taste changes, are commonly experienced by patients with NPC undergoing RT.

RT-induced oral mucositis is the most common debilitating ionizing radiation toxicity arising from RT. It is a normal tissue injury after exposure to RT and lasts between 7 and 98 days, starting with acute inflammation of the oral mucosa, tongue, and pharynx. The epithelial cells of the oropharyngeal mucosal lining desquamate, leading to basement membrane damage, loss of the protective barrier, and then to ulceration and infection. RT-induced oral mucositis occurs in almost 80% of head and neck cancer patients who undergo RT.1 The major consequences of RT-induced oral mucositis include hospital admission for pain management, total parenteral nutrition, and antibiotic administration in 62% of the patients, while 70% of the patients with grade 3 and 4 oral mucositis require feeding tube insertion. About 35% of the patients need to abandon their cancer protocol treatments due to the development of dose-limiting toxicity.1 No specific treatment will prevent RT-induced oral mucositis, but good oral care is known to aid in reducing the severity of mucositis. The mainstay of effective oral care is mouth rinses, as these can help in sweeping away debris and keeping the oral mucosa clean and moist.

Many published studies have tested alternative natural product treatments for the prevention of oral mucositis. Common products considered as alternative treatments have
often been honey-based products, which have been deemed very efficient at preventing or reducing the severity of oral mucositis in patients undergoing cancer treatment. In particular, stingless bee products are well known for their medicinal properties for treating numerous diseases. The present study is the first in Malaysia to seek out alternative preventive treatments for oral mucositis using propolis from the stingless bee as a mouthwash.

MATERIALS AND METHODS

Study Design
This was a prospective, double-arm, randomised control trial (RCT) with intervention. Its aim was to determine the efficacy of a 2.5% propolis mouthwash in preventing RT-induced mucositis among patients with NPC attending the Otorhinolaryngology, Head, and Neck Surgery (ORL-HNS) clinic at the Advanced Medical and Dental Institute (AMDI), Bertam. The study was approved by the ethical committee of the Human Research Ethics Committee of Universiti Sains Malaysia (HREC) (JEPeM USM Code: USM/JEPeM/20010025) and was conducted from 1 April 2020 until 30 June 2021. The sample population was selected from patients diagnosed with NPC attending the ORL-HNS clinic at AMDI, Bertam, who met the inclusion and exclusion criteria. The inclusion criteria were all patients diagnosed with NPC scheduled to undergo CCRT. Exclusion criteria were allergy to bee products, NPC stage T1 N0 M0, and age younger than 18 years.

Methods
All NPC patients who attended ORL-HNS clinic AMDI, Bertam, were screened for eligibility. Consent to participate in the study was obtained after the purpose, importance, and benefit of the study were explained to the patients and necessary documentation was given to the patients for consultation and for references. The patients were randomly divided into an experimental and a placebo group by using a ballot system. The experimental group was given a 2.5% propolis mouthwash, and the placebo group was given a normal saline mouthwash. All patients were provided with a pamphlet of instructions. The mouthwashes (propolis and saline) were provided by AMDI, Bertam, and were packaged in identical bottles labelled A and B.

The propolis was diluted in water at 60°C until it fully dissolved, and the volume was made up to 150mL for gargling. The solution was stored in a normal refrigerator to prevent fermentation of the propolis.

All patients were provided every week with a bottle of product containing 150mL of either 2.5% propolis or normal saline according to their respective groups. All the patients were instructed to rinse their mouths with 7mL (measured using syringe provided) of the assigned mouthwash for 60 seconds and then spit it out. This was done three times per day: on the RT days from Monday to Friday, the patients were instructed to perform the mouth rinse at 30 minutes before starting the RT, at 30 minutes after completing the RT, and then at 6 hours after the RT. During the rest days on Saturday and Sunday, the patients were instructed to rinse their mouths at 30 minutes after completing the RT, at 30 minutes before starting the RT days from Monday to Friday, the patients were instructed to perform the mouth rinse at 30 minutes before starting the RT, at 30 minutes after completing the RT, and then at 6 hours after the RT. The mucositis grading score over time also showed significant differences within each group (time effect). Table II shows significant differences in the mucositis grading for the propolis group between the second week and the sixth week (p=0.001) and between the fourth week and the sixth week (p=0.029). The normal saline group showed a significant difference in mucositis scores over time between the second week and the sixth week (p=0.009).

The mean difference in mucositis scores between the propolis and normal saline groups was 1.40 (1.02, 1.78), and this difference was statistically significant (p<0.001). Analysis of the mucositis grading scores based on the time–treatment interaction between the two groups revealed significant differences in all weeks (p=0.004, p<0.001, and p<0.001, for the second, fourth, and sixth weeks, respectively) (Table III).

Data analysis comparing the mean body weight pre and post RT within the propolis and normal saline groups, was made. The propolis group showed a mean weight difference of 8.0 (6.08, 9.92) kg pre and post treatment (p<0.001), while the normal saline group showed a mean weight difference of 11.87 (8.28, 15.47) kg pre- and post-treatment (p<0.001). The weight loss occurring between the pre and post treatments was statistically significant in both groups.

The mean weight difference between the propolis and normal saline groups was -2.564 (-17.05, 11.92), but this difference

RESULTS
We recruited 10 patients into the propolis group and 7 patients into the normal saline placebo group, for a total of 17 patients. No significant differences were noted in the baseline demographic characteristics, including race (p=0.60) and cancer staging (p=0.13), between the propolis and normal saline groups (Table I). The mean (SD) age of the patients was 47 (14.94) years in the propolis group and 47.29 (18.73) years in the normal saline mouthwash group (p=0.97). Most of the patients were Malay.

The distribution of the severities of mucositis was determined separately in the second, fourth, and sixth weeks of RT, based on the WHO Oral Toxicity Scale. The mean mucositis scores for the propolis vs. normal saline groups at the second, fourth, and sixth weeks of RT were 0.10 vs. 1.14, 0.50 vs. 2.00, and 1.20 vs. 2.86, respectively, and the differences between the two groups were statistically significant. The mean mucositis score for the normal saline group worsened throughout the assessment weeks, whereas the score for the propolis group improved.

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Table I: Demographic characteristics of respondents (n = 17)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propolis n=10</td>
<td>Normal saline n=7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47(14.94)*</td>
<td>47.29(18.73)*</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>7(70.0)</td>
<td>6(85.7)</td>
</tr>
<tr>
<td>Chinese</td>
<td>3(30.0)</td>
<td>1(14.3)</td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2(2.0)</td>
<td>4(57.1)</td>
</tr>
<tr>
<td>3</td>
<td>4(40.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>4a</td>
<td>3(30.0)</td>
<td>3(42.9)</td>
</tr>
<tr>
<td>4b</td>
<td>1(10)</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>

*Mean (SD); aIndependent t-test; bFisher's exact test.

Table II: The comparison of mucositis grading scores within the propolis mouthwash and normal saline mouthwash groups over time (time effect)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Propolis Mean score different (95% CI)</th>
<th>p-value^a</th>
<th>Normal saline Mean score different (95% CI)</th>
<th>p-value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2 vs Week 4</td>
<td>-0.40(-0.88, -0.08)</td>
<td>0.110</td>
<td>-0.86(-1.72, 0.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>Week 2 vs Week 6</td>
<td>-1.10(-1.63, -0.57)</td>
<td>0.001</td>
<td>-1.71(-2.90, -0.53)</td>
<td>0.009</td>
</tr>
<tr>
<td>Week 4 vs Week 6</td>
<td>-0.70(-1.33, -0.07)</td>
<td>0.029</td>
<td>-0.86(-1.72, 0.00)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

^repeated measure ANOVA

Table III: Comparison of mucositis grading between the propolis mouthwash and normal saline mouthwash groups based on time (time–treatment interaction)

<table>
<thead>
<tr>
<th>Time</th>
<th>Comparison</th>
<th>Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>Normal saline – Propolis</td>
<td>1.043 (0.39, 1.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>Normal saline – Propolis</td>
<td>1.50 (0.93, 2.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 6</td>
<td>Normal saline - Propolis</td>
<td>1.657 (1.23, 2.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 1: Propolis mouthwash: Intraoral examination showed normal oral mucosa at the second and fourth weeks. Only a small tongue ulcer was seen at the sixth week (Grade 1: WHO Oral Toxicity Scale)
was not statistically significant (p=0.711). Comparison of the body weight over time between the propolis and normal saline groups (time–treatment interaction) at week 2 and week 6 did not reveal statistically significant differences (p=0.930 and p=0.508, respectively).

The types of feeding between the propolis and normal saline groups were analysed using Fisher's exact test. All ten patients (100%) in the propolis group were able to take food orally, while six patients (85.7%) in the normal saline group required Ryles tube feeding, and only 1 (14.3%) was able to take food orally. The difference in type of feeding between the propolis and normal saline groups was statistically significant (p=0.001).

None of the patients who used the propolis mouthwash developed any adverse side effects.

DISCUSSION
Oral mucositis is an inflammation of the oral mucosa that leads to sores and ulcerative lesions in the oral cavity. It is especially seen in cancer patients undergoing combined RT and chemotherapy. Recent studies have determined that the mechanisms involved in the pathogenesis of mucositis are more complex than simply direct injury to the epithelium. RT-induced mucositis and chemotherapy-induced mucositis are believed to be identical in their mechanisms. The initiation of tissue injury by RT induces cellular damage, resulting in epithelial cell death. This process is then followed by upregulation of inflammation via activation of pro-inflammatory cytokines, and this upregulation can lead to further cell death and tissue injury. Inflammatory cell infiltration is also associated with mucosal inflammation and ulceration. Epithelial cell proliferation and restoration of the integrity of epithelium eventually occurs in the healing process.4

Oral mucositis can be very painful and can lead to significant malnutrition and weight loss due to poor oral intake. This can affect the quality of life and disrupt the cancer treatment protocol. The majority of head and neck cancer patients receiving RT are unable to eat by mouth due to mucositis pain, and they usually require nasogastric or gastrostomy tubes for feeding.6

At present, no specific treatment exists that can prevent RT-induced mucositis; therefore, most treatments focus on symptom relief. Mouth rinses using salt water are believed to be the simplest and most economical method to help in oral hygiene. Rinsing can swipe and remove oral debris while also maintaining moisture in the oral cavity. However, the overall effect is not ideal, and the patient still suffers from this debilitating complication.
Recently, many studies have attempted to identify the best way to minimise and prevent the complications of RT-induced mucositis. Some studies have focused on the use of natural bee products, such as propolis, which is generally known as “bee glue” and is considered one of the most important bee products. Propolis contains numerous important organic compounds, vitamins, and minerals, and it shows antiseptic, anti-inflammatory, antibacterial, antioxidant, and anticancer properties. Its use has been approved based on numerous previous studies, making it very important and useful in treating various diseases. The healing properties of propolis are believed to arise due to the rich content of flavonoids, which are oxygen free radical scavenging compounds that can deactivate free radicals. This deactivation helps to reduce the severity of oral mucositis and to hasten the healing process.

A meta-analysis study by Kuo et al. on the efficacy of propolis mouthwash in cancer therapy-induced oral mucositis concluded that the severity of oral mucositis was significantly reduced by propolis mouthwash use (OR 0.35, p=0.003). However, in that meta-analysis, four studies involved patients who received chemotherapy only, and only one study administered RT. A study by Javadzadeh et al. on the therapeutic effects of propolis in RT-induced mucositis in head and neck cancer patients examined 20 patients who were randomly given either propolis mouthwash or a placebo. All the patients were instructed to gargle and swallow 15mL of the mouthwash three times a day for five weeks. A similar study led by Farzaneh et al. examined the efficacy and safety of propolis mouthwash in the management of RT-induced oral mucositis in 30 patients randomly assigned a propolis mouthwash or placebo; their patients were instructed to rinse their mouths with 20mL solution, three times a day, for four weeks. Both these studies used the National Cancer Institute Common Toxicity Criteria (NCI-CTC) to assess oral mucositis grading, and both reported that the propolis mouthwash was very effective at preventing RT-induced oral mucositis.

The present study is the first conducted in Malaysia to evaluate the effectiveness of propolis mouthwash in preventing RT-induced oral mucositis. It also differs from the previously mentioned studies in several ways. Our study focused on NPC patients, whereas the previous studies focused on patients with general head and neck cancer. All 17 NPC patients in our study received CCRT, hence we excluded stage 1 NPC to standardise the treatment protocol, as in stage 1 NPC, they only received RT. Our patients were given propolis mouthwash (10 patients) or a normal saline placebo (7 patients), and all were instructed to rinse their mouths three times daily with 7mL solution for 60 seconds and then spit it out, for a duration of seven weeks, corresponding to the cancer treatment duration. The incidence of oral mucositis is usually observed after the first week of CCRT treatment; therefore, we started to assess the patients in the second week. For the assessment of oral mucositis, we used the WHO Oral Toxicity Scale rather than the NCI-CTC. In our study, we used a propolis mouthwash with a concentration of 2.5%, whereas the previous studies used propolis at 3% and 80%. However despite our use of a lower propolis concentration, by the end of the study, we saw a significant difference in the severity of oral mucositis between the two groups (Figures 1 and 2), as 8 of the 10 patients in the propolis mouthwash group had only grade 1 mucositis at the sixth week, and two patients had grade 2. By contrast, in the normal saline group, 6 of the 7 patients had grade 3 mucositis and only one patient had grade 2 mucositis. All the patients using propolis mouthwash were also able to take food orally by the end of the CCRT treatment, whereas all 6 patients with grade 3 mucositis in the normal saline mouthwash group required nasogastric tube feeding. Despite less severity of mucositis and the ability to take orally in the propolis group, there were no statistical differences in weight loss pre and post treatment in both groups. In terms of safety using the propolis mouthwash, none of the patients in the propolis group experienced any side effect or complication from using it. The other studies mentioned before also reported zero side effect or complication from the usage of propolis mouthwash. Hence, we confirmed that propolis mouthwash is safe for use by the patients.

CONCLUSION
We found that a 2.5% propolis mouthwash was effective at reducing the severity of oral mucositis, and its use was proven safe. None of the patients who used the propolis mouthwash developed any adverse side effects. In future, we encourage the health practitioners to provide propolis mouthwash as an adjunct treatment to reduce the severity of RT-induced oral mucositis for the NPC patients undergoing cancer treatment.

ACKNOWLEDGEMENTS
This research was supported by research grant from Malaysian Society of Otorhinolaryngology and Head Neck Surgeons (MSOHNs).

DECLARATION OF CONFLICT OF INTEREST
Authors declared no conflict of interest in this study.

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