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Research Report

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*

ABSTRAK

***Latar belakang**: Karsinoma nasofaring (KNF) merupakan tumor ganas terbanyak di daerah kepala-leher. Radioterapi merupakan terapi pilihan utama KNF yang belum mempunyai metastasis jauh. Komplikasi akibat radioterapi dalam rongga mulut yang terbanyak adalah mukositis (± 80%). Salah satu obat untuk pencegahan mukositis akibat radioterapi adalah benzydamine hydrochloride (HCl) 0,15%.* ***Tujuan**: Tujuan penelitian ini adalah untuk mempelajari efektivitas penggunaan obat kumur benzydamine HCl 0,15% sebagai pencegah mukositis akibat radioterapi pada karsinoma nasofaring.* ***Metode**: Sampel dibagi ke dalam 2 kelompok. Kelompok A yang menggunakan obat kumur benzydamine HCl selama 10 hari. Kelompok B menggunakan obat kumur plasebo selama 10 hari. Evaluasi dilakukan pada tahap awal, hari ke-5 radioterapi dan hari ke-10 radioterapi. Alat ukur adalah skor mukositis α Spijkervet.* ***Hasil**: Analisis Independent t-test menunjukkan awal terjadinya mukositis antara kedua kelompok tersebut tidak berbeda bermakna. Hasil uji t berpasangan antara skor mukositis α awal dengan skor mukositis α evaluasi II pada masing-masing kelompok tersebut menunjukkan perbedaan yang bermakna. Berdasarkan uji t, skor mukositis α evaluasi II antara kelompok A dengan B tersebut tidak berbeda bermakna.* ***Kesimpulan**: Disimpulkan bahwa obat kumur benzydamine HCl 0,15% tidak efektif sebagai pencegah mukositis akibat radioterapi pada penderita KNF.*

***Kata kunci**: Obat kumur benzydamine hydrochloride 0,15%, pencegahan, oral mukositis akibat radiasi, karsinoma nasofaring*

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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.[9,11] 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 effectivity 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 ($1 \leq 1$ cm, 2 = 1.0–2.0 cm, 3 = 2.1–4.0 cm, $4 \geq 4$ 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

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

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 α score and mucositis α score in tenth day in each group (Table 3 & 4). Independent t test analysis showed no significant difference in mucositis α 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 α 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

	Group	N	Rate	SD	p
Initial occurence of oral mucositis	A	10	7.20	1.14	0.504**
	B	9	7.56	1.13	

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

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

Group A	N	Rate	SD	p
Mucositis α score (1st day)	10	0.00	0.00	- ***
Mucositis α score (5th day)	10	0.00	0.00	
Mucositis α score (1st day)	10	0.00	0.00	0.00*
Mucositis α score (10th day)	10	1.37	0.79	

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

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

Group B	N	Rate	SD	p
Mucositis α score (1st day)	9	0.00	0.00	- ***
Mucositis α score (5th day)	9	0.00	0.00	
Mucositis α score (1st day)	9	0.00	0.00	0.00*
Mucositis α score (10th day)	9	1.86	0.96	

Notes: *: significant difference ($p < 0,05$); ***: could not be analyzed

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

	Group	N	Rate	SD	p
Mucositis α score (1st day)	A	10	0.00	0.00	- ***
	B	9	0.00	0.00	
Mucositis α score (5th day)	A	10	0.00	0.00	- ***
	B	9	0.00	0.00	
Mucositis α score (10th day)	A	10	1.37	0.79	0.245**
	B	9	1.86	0.96	

Notes: **: no 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.*[13] and Worthington *et al*.,[16] stated the opposite things. These differences because the method to assess oral mucositis was different. Epstein *et al.,*[13] used mucositis score based on subjective and clinical manifestation of oral mucositis (erythema, ulceration and pain). Worthington *et al*.[16] 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.[6] Besides that, the differences might be caused by initial occurence 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 occurence of oral mucositis. This was similar with Köstler *et al*.,[12] Berger & Kilroy,[17] Cheng *et al*.,[18] 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.[4]

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[8], Hancock *et al*.[11] 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*.[4] and Beck,[19] said that disintegrity of lining mucosa was port d'entry of microorganism and caused local infection which potentially disseminated through blood stream. According to Stokman *et al*.,[7] Epstein *et al*.[13] and Kazemian *et al*.,[20] 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 antiinflamation 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 occurence 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.

REFERENCES

1. Kentjono WA. Penatalaksanaan karsinoma nasofaring masa kini. Simposium Kanker Nasofaring dan Demo Biopsi dengan Tehnik Aspirasi Jarum Halus, 2003; p. 24–6.
2. Mulyarjo. Epidemiologi dan gambaran klinik karsinoma nasofaring. Simposium Kanker Nasofaring dan Demo Biopsi dengan Tehnik Aspirasi Jarum Halus, 2003; p. 1–3.
3. Mulyarjo. Diagnosis dan penatalaksanaan karsinoma nasofaring. Pendidikan Kedokteran Berkelanjutan III Ilmu Penyakit THT-KL. Perkembangan Terkini Diagnosis dan Penatalaksanaan Tumor Ganas THT-KL, 2002; p. 38–48.
4. Kartabrata M, Hendarti HT, Ayu S. Prevalensi kandidiasis mulut pada penderita yang mendapat terapi radioterapi kanker kepala dan leher. Maj Ked Gigi (Dent J) 2001; 34(3a): 376–9.

5. Roopashri G, Jayanthi K. Radiotherapy and chemotherapy induced oral mucositis-prevention and current therapeutic modalities. IJDA 2010; 2(2): 174–9.
6. Schubert MM. Measurement of oral tissue damage and mucositis pain. 2004. Available at http://painresearch.utah.edu/cancerpain/ch.15.html. Accessed April 26, 2004.
7. Stokman MA, Spijkervet FKL, Boezen HM, Schouten JP, Roodenburg JLN, de Vries EGE. Preventive intervention possibilities in radiotherapy and chemotherapy-induced oral mucositis: Results of meta-analyses. J Dent Res 2006; 85(8): 690–700.
8. Rosenthal DI, Trotti A. Strategies for managing radiation-induced mucositis in head and neck cancer. Semin Radiat Oncol 2009; 19: 29–34.
9. Wardhany II, Subita GS. Meningkatkan kualitas hidup pasien kanker kepala dan leher yang menjalani radioterapi melalui pengendalian mukositis. Maj Ked Gigi (Dent J) 2001; 34(3a): 582–5.
10. Harrison JS, Dale RA, Haveman CW, Redding SW. Oral complications in radiation therapy. Oral Medicine, Oral Diagnosis 2003 November-December; 552-60. Available at http://www.acd.org. Accessed July 30, 2004.
11. Hancock PJ, Epstein JB, Sadler GR. Oral and dental management related to radiation therapy for head and neck cancer. J Can Dent Assoc 2003; 69(9): 585–90.
12. Köstler WJ, Hejna M, Wenzel C, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. CA Cancer J Clin 2001; 51: 290–315.
13. Epstein JB, Silverman S Jr, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, Lockhart PB, Gallagher MJ, Peterson De, Leveque FG. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer 2001; 92: 875–85.
14. Harun SR, Putra ST, Wiharta AS, Chair I. Uji klinis. In: Sastroasmoro S, Ismael S, eds. In: Dasar-dasar metodologi penelitian klinis. Jakarta: Sagung Seto; 2002. p. 145–65.
15. Putwatana P, Sanmanowong P, Oonprasertpong L, Junda T, Pitiporn S, Narkwong L. Relief of radiation-induced oral mucositis in head and neck cancer. Cancer Nurs 2009; 32(1): 82–7.
16. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2006 .Apr; 19(2): CD000978. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625538. Accessed August 16, 2011.
17. Berger AM, Kilroy TJ. Oral complications. In: DeVita Jr. VT, Hellman S, Rosenberg SA, eds. In: Cancer principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2881–93.
18. Cheng KK, Chang AM, Yuen MP. Prevention of oral mucositis in paediatric patients treated with chemotherapy; a randomised crossover trial comparing two protocols of oral care. Eur J Cancer 2004; 40: 1208–16.
19. Beck S. Mucositis in cancer. 2000. Available at http://www.cancersource.com/ Nursing/CE/CECourse.cfm?courseid=56&contentid=19481. Accessed June 21, 2004.
20. Kazemian A, Kamian S, Aghili M, Hashemi FA, Haddad P. Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: a double-blind placebo-controlled randomized clinical trial. Eur J Cancer Care (Engl) 2009; 18(2): 174–8.