

An evaluation of the effect of acupuncture on salivary pH and the Xerostomia Inventory score in nasopharyngeal carcinoma patients with chemoradiation-induced xerostomia

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Abstract. Radiation-induced xerostomia is a distressing side-effect of radiation for nasopharyngeal carcinoma (NPC) treatment, commonly occurring in almost 100% of patients who undergo this procedure. It has been proposed that acupuncture can be used to treat radiation-induced xerostomia. To the best of our knowledge, the current study constitutes the first acupuncture research that has been conducted in Indonesia on xerostomia following chemo-irradiation in NPC patients. Twenty-five patients with xerostomia due to chemo-irradiation for NPC were divided randomly into three groups of auriculopuncture (group A), body acupuncture (group B), and combination acupuncture (group C). The subjects were evaluated according to Xerostomia Inventory scores before and after six and 12 acupuncture treatments. Salivary pH was determined before and after the 12th acupuncture treatment using a saliva check buffer kit. The success rate of acupuncture therapy in group A was 71–100%, 68–89% in group B, and 89–100% in group C ($p > 0.050$). The mean salivary pH increased after therapy from 6.18 ± 0.60 to 6.83 ± 4.48 in group A, from 6.16 ± 0.54 to 6.67 ± 2.26 in group B, and from 6.00 ± 0.40 to 6.60 ± 2.23 in group C ($p > 0.050$). After the 12th acupuncture therapy session, the mean Xerostomia Inventory score decreased from 35.70 ± 5.14 prior to acupuncture therapy to 22.89 ± 16.15 after it in group A, with corresponding decreases of 34.70 ± 7.77 to 20.89 ± 10.06 in group B, and of 36.70 ± 5.25 to 21.44 ± 8.97 in group C ($p > 0.050$). Auriculopuncture, body acupuncture, and combination acupuncture had the same effect of increasing salivary pH and decreasing the Xerostomia Inventory score in patients with xerostomia following chemo-irradiation for NPC.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy in the nasopharyngeal region (the area above the throat and behind the nose). It is predominantly found in males of reproductive age, with the ratio for male to female patients being 2–3: 1. The incidence of NPC peaks at ages 15–25 and 50–60 years. High incidence rates have been reported in east and south-east Asia. The highest global incidence, of 40–50 cases of NPC per 100,000 inhabitants, has been attributed to south-east China [1,2]. NPC is a common malignancy in Indonesia, ranking fourth after cervical, breast, and lung cancer. Two hundred and forty-three NPC patients were treated at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. Two hundred and fifty-eight cases were reported in 2010 [1,3]. Therapy includes radiation, chemotherapy, a combination of radiation and chemotherapy, and symptomatic therapy. External



radiation is the standard therapy for NPC. The recommended dose to administer is 180–200 cGy per fraction, five times a week, equating to total radiation of 66–70 cGy. Common side-effects usually occur at the onset of radiation and self-resolve, with or without treatment. However, the symptom of a dry mouth (xerostomia) persists as a further effect because the radiation dose received by the parotid glands is high; similar to that received by the nasopharynx [4].

Radiotherapy is often used as the treatment for NPC, but leads to xerostomia almost 100% of the time due to damage to the salivary gland tissues that are exposed to radiation [5]. The latter alters the volume and consistency of the salivary secretions, as well as the salivary pH. Thus, the salivary secretions change from a liquid consistency, with a neutral pH, to thick secretions with increased acidity. Salivary flow decreases by 50–60% during the first week of therapy, and by up to 80% by the seventh week. It was demonstrated in a long-term observation study that 64% of patients experienced moderate to severe xerostomia three years after conventional radiation therapy. The management of xerostomia is rarely effective [6–10]. Although a reduction in the incidence of post-radiotherapy xerostomia has been reported, numerous side-effects were experienced by patients on pilocarpine, including excessive sweating, dizziness, rhinitis, nausea, frequent urination, tachycardia, and visual impairment [11–13].

Blom *et al.* [14], conducted a randomized clinical trial (RCT) on 38 patients with radiation-induced xerostomia. Acupuncture was performed on the therapy (study) group ($n=20$) twice weekly for 20 minutes (a total of 24 times). The selected acupuncture points were 5–8 local and distal points, and 2–4 ear points. Placebo puncture was carried out in the control group ($n=18$). Superficial intradermal placement of the acupuncture needle for the latter was carried out at a distance of 1 cm from the classical acupuncture point. The result was a significant increase in saliva flow in both groups (68% in the study group and 50% in the control group). However, a statistically significant difference was not found between the groups. Johnstone *et al.* [5] conducted study on 18 patients with post-radiotherapy xerostomia who were resistant to pilocarpine therapy to establish the benefit of palliative acupuncture in these patients. Acupuncture was performed at one point on the radial side of the right and left index fingers, and at three points in each ear. If salivation did not occur 20 minutes after performing the manual acupuncture, electroacupuncture was carried out on the ear points. Acupuncture was performed twice weekly during the first week and 3–4 times a week during the next week. The result was an average decrease in the Xerostomia Inventory score by ≥ 10 points in nine patients (50%).

Garcia *et al.* [15], conducted a study on 19 patients with radiotherapy-induced xerostomia. They evaluated the impact of acupuncture on the Xerostomia Inventory score using a Patient Benefit Questionnaire (PBQ) and the effect of acupuncture on salivary flow and quality of life using a Functional Assessment of Cancer Therapy-Head and Neck scale. Acupuncture was performed twice weekly for four weeks at the CV-24, ST-36, LI-1, and LU-7 Shen Men ear points, the Zero Point, and at saliva gland # 2 for 20 minutes. The result was a significant decrease in the initial and final Xerostomia Inventory acupuncture scores at weeks 4 and 8, with a reduction in the mean score from 36.3 to 31.6 ($p = 0.000$) and 29.9 ($p = 0.000$), respectively. The PBQ score increased from an average of 43.94 at baseline to 56.85 ($p = 0.000$) at week 4 and to 56.10 ($p = 0.001$) at week 8. Significant quality-of-life differences relating to head and neck cancer were identified at weeks 4 and 8 weeks ($p = 0.040$ and $p = 0.006$, respectively). A significant difference in the initial and final salivary flow measurements was not found at 4 and 8 weeks in this study. Johnstone *et al.* [16], carried out a study on 50 xerostomia patients with various etiologies. Acupuncture was administered at one point on the radial side of the index finger and at three points in each ear. The result was that the condition of 70% of the patients ($n=35$) improved by $\geq 10\%$. In addition, a decrease was observed in the median Xerostomia Inventory score, recorded as 40 prior to acupuncture and as only 9 after it. The improvement in the condition of 13 patients (26%) was maintained up to three months after completion of the treatment.

It is believed that acupuncture enhances the release of neuropeptides and stimulates the autonomic nervous system, improving salivary secretion in both healthy and xerostomia patients. Radioimmunoassay analysis was used in two studies on xerostomia patients and it was determined that acupuncture

significantly improved the action of vasoactive intestinal polypeptides (VIPs) and calcitonin gene-related peptides (CGRPs) in the respondents' saliva [16,17]. With the use of Doppler laser flowmetry, it was established that blood flow to the skin that protects the parotid glands increased significantly during and after acupuncture in the acupuncture therapy group [16]. Deng *et al.* [18], performed a sham-controlled, crossover RCT, in which blood oxygen level-dependent functional magnetic resonance imaging technology was employed to examine the neuronal substrate involved at acupuncture point, LI-2 (a point used in clinical practice to treat xerostomia through the stimulation of salivary production). For this purpose, 20 healthy subjects were randomly divided into two acupuncture groups; a true acupuncture group involving acupuncture point LI-2 in the non-dominant arm and a sham acupuncture group in which a non-point and a Streitberger® needle were used. The results were activation of the parietal operculum, the Rolandi operculum, and the frontal and insula operculum (which play a role in salivary production) in the true acupuncture group, and an absence of activation in the sham acupuncture group.

It has been demonstrated in preliminary studies that acupuncture is relatively effective in relieving cancer-related symptoms and complaints, such as xerostomia, without any side-effects. There is also evidence that it is a safe and beneficial therapy for cancer patients. According to various cellular immunologic and molecular biology theories, it is hypothesized that acupuncture-specific mechanisms include enhancement of the cytotoxic activity of natural killer cells through neurotransmitters, as well as the immune system, nitric oxide, and β -endorphins and cytokines, thereby improving the anticancer-resistant immune function which plays an essential role in cancer prevention and management [19]. The Xerostomia Inventory questionnaire contains 11 questions and was developed to evaluate patients' subjective perceptions of a dry mouth. It is widely used in clinical research and has been validated in various cohorts. A high score (a maximum score of 55) represents worsening toxicity. A score of ≤ 14 is considered to be normal [7,13,15,20]. To the best of our knowledge, the determination of salivary pH in post-radiotherapy xerostomia has not been explored in previous acupuncture studies. Thus, the objective of the current study was to address this. The advantages of performing an assessment of saliva pH is that it is relatively easy to do, is non-invasive and the results can be obtained rapidly. A secondary objective of the study was to identify any differences between the efficacy of auricular acupuncture and body acupuncture, and whether or not the results improved with the simultaneous use of both acupuncture methods, i.e., combination acupuncture.

2. Materials and Methods

The selected study design was a RCT. The study subjects were patients who had been clinically diagnosed with NPC from imaging and histopathological analysis, without metastasis, and who had completed radiotherapy for at least three months and for a maximum of 1.5 years. Inclusion criteria in the were men and women aged 18–70 years and who were willing to provide signed informed consent and adhere to the research schedule. The subjects were divided into three groups (Table 2). Group A received bilateral ear acupuncture (auriculopuncture) at the MA-TF1 (Shen Men) and MA-AT (parotid gland) points. Group B received acupuncture at the CV-24 (Chengjiang), LI-2 (Erjian), LI-4 (Hegu), ST-6 (Jiache), and ST-36 (Zusanli) points. Group C received acupuncture at the CV-24 (Chengjiang), LI-2 (Erjian), LI-4 (Hegu), ST-6 (Jiache) and ST-36 (Zusanli) points, and auriculopuncture at the MA-TF1 (Shen Men) and MA-AT (parotidgland) points [39–42].

Injections were performed until a needling sensation was felt. The needle remained in position for 30 minutes and was then withdrawn. Acupuncture was performed twice weekly, for 12 times therapy sessions. The subjects were excluded from the study if they did not undergo ≥ 2 acupuncture sessions for six weeks and if they were using other therapies to treat xerostomia while participating in the study. As this was preliminary research, the sample size for each group comprised 10 people (a total of 30). An objective salivary pH examination was performed using Saliva-Check BUFFER® (GC America, Alsip, USA), consisting of a pH test strip, saliva collection cup, and testing chart, and executed prior to and after 12 acupuncture sessions. The subjective assessment comprised a Xerostomia Inventory questionnaire, administered after six and 12 acupuncture sessions. In terms of achieving a reduction in

the Xerostomia Inventory score, the following definitions applied in relation to a difference found between the initial and final score [15], (1) Success: ≥ 6 points; (2) An improvement: 3–5 points; (3) Failure: 3 points. The acupuncture was considered to have been effective if the results were either success or an improvement. In terms of achieving a reduction in salivary acidity (salivary pH), the following definitions applied in relation to difference between the initial and final score [12]: (1) Success: A pH ≥ 0.4 ; (2) Failure: A pH < 0.4 . The current study was conducted after ethical approval had been obtained from the Ethics Committee. The participants provided signed informed consent. They were guaranteed confidentiality and their participation was voluntary.

3. Results and Discussion

3.1 Results

Thirty participants were eligible for inclusion in the study, 25 of whom successfully completed it. Five subjects dropped out for reasons unrelated to the research. One experienced an improvement in his or her medical condition, another was admitted to intensive care for a respiratory infection, another received home treatment, and two of them did not provide a reason (Table 1).

Table 1. The subject characteristics according to gender, education level, and employment status

Variables	Group A <i>n</i> (%)	Group B <i>n</i> (%)	Group C <i>n</i> (%)	Total <i>n</i> (%)
Gender				
Males	7 (70)	8 (80)	8 (80)	23 (77)
Females	3 (30)	2 (20)	2 (20)	7 (23)
Educational level				
Elementary school	2 (20)	2 (20)	2 (20)	6 (20)
Junior high school	1 (10)	0 (0)	2 (20)	3 (10)
Senior high school	2 (20)	2 (20)	2 (20)	6 (20)
Bachelor's degree/diploma	4 (40)	5 (50)	4 (40)	13 (43)
Master's/Doctorate degree	1 (10)	1 (10)	0 (0)	2 (6)
Employment status				
Corporate employee	2 (20)	3 (30)	1 (10)	6 (20)
Housewife	2 (20)	1 (10)	1 (10)	4 (13)
Government employee	3 (30)	1 (10)	2 (20)	6 (20)
Entrepreneur	2 (20)	2 (20)	4 (40)	8 (27)
College student	0 (0)	0 (0)	1 (10)	1 (3)
Jobless	1 (10)	3 (30)	1 (10)	5 (17)

Table 2. The subject characteristics according to age, time interval between post-chemotherapy and acupuncture, radiotherapy dose, salivary pH, and Xerostomia Inventory

Variables	Group A Mean (SD)	Group B Mean (SD)	Group C Mean (SD)	p-value*
Age (years)	47.90 (12.42)	50.80 (11.62)	41.80 (12.66)	0.300
Post-chemotherapy (months)	6.10 (3.59)	8.50 (4.27)	4.90 (2.91)	0.110
Radiotherapy dose (Gy)	72.20 (9.78)	70.00 (6.99)	74.00 (10.81)	0.520
Initial salivary pH	6.18 (0.60)	6.16 (0.54)	6.00 (0.49)	0.660
Initial Xerostomia Inventory score	35.70 (5.14)	34.70 (7.77)	36.70 (5.25)	0.670

SD: standard deviation; *: Kruskal-Wallis test

A statistically significant difference was not observed between the mean salivary pH obtained for the three groups after 12 acupuncture sessions, as determined by the Kruskal-Wallis test (Table 2). A

statistically significant difference was not found between the mean Xerostomia Inventory score obtained for the three groups after six and 12 acupuncture sessions, as determined by the Kruskal-Wallis test (Figure 1). When the three groups were compared in terms of any improvement in the salivary pH following acupuncture using Fisher's exact test, a statistically significant ($p>0.050$) difference was not found (Figure 2). This was also the finding when Fisher's exact test was applied to compare the efficacy of acupuncture in decreasing the Xerostomia Inventory score following six (Figure 3) and 12 (Figure 4) acupuncture sessions.

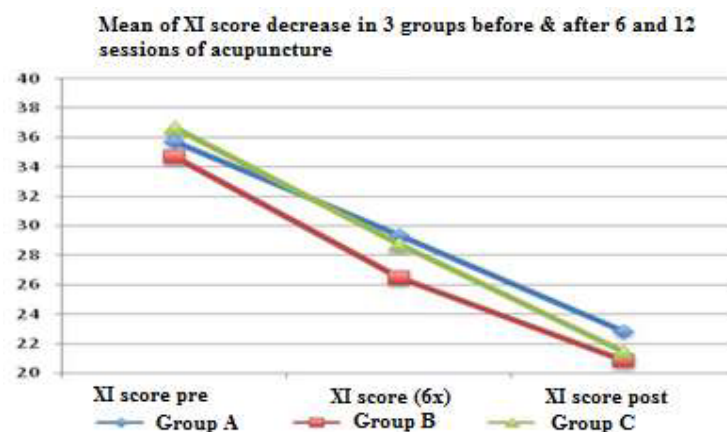


Figure 1. The mean Xerostomia Inventory score at baseline and a reduction therein after six and 12 acupuncture sessions

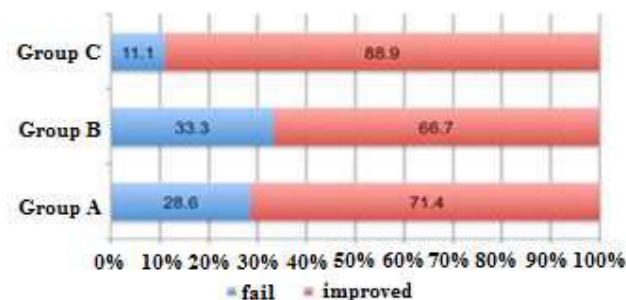


Figure 2. The efficacy of acupuncture in improving salivary pH



Figure 3. The efficacy of acupuncture in reducing the Xerostomia Inventory score after six acupuncture sessions



Figure 4. The efficacy of acupuncture in reducing the Xerostomia Inventory score after 12 acupuncture sessions

The side-effects of acupuncture, such as mild pain or stiffness in the area in which the needle was inserted and hematoma, were not found in the current study. Two of the subjects experienced mild pain or stiffness after three acupuncture sessions. Hematoma was reported in two subjects after two such sessions. None of the patients dropped out due to side-effects or received additional medication to treat them. All the patients were educated on oral hygiene maintenance and which foods and beverages affect moisture content in the mouth.

3.2 Discussion

Post-radiation xerostomia patients who met the inclusion criteria were randomly selected for participation in the current study. The selected subjects were randomly divided into three groups. Optimal results were achieved using this method of subject selection and randomized placement, as evidenced by the statistical analysis where it was found that a statistically significant difference was not found between the three age groups with respect to age, time interval between post-chemoradiation and the start of acupuncture, radiotherapy dose, initial salivary pH, and initial Xerostomia Inventory scores. Minimal side-effects were experienced by a small number of subjects as a result of the acupuncture, such as mild pain and hematoma at some of the acupuncture points. It was demonstrated in the current study that auriculopuncture, body acupuncture, and combination acupuncture were all effective in increasing the salivary pH of NPC patients experiencing post-chemoradiation xerostomia. A decrease in saliva pH was also shown in three of the patients after 12 acupuncture sessions, while a pH change was not recorded in two of the subjects until the 12th assessment. The reason for this is unknown, but it may pertain to technical imperfections in the salivary sampling, which was mixed with stool water, and could have resulted in the initial salivary pH being more alkaline than the actual salivary pH. Another possibility is that drinking certain liquids could have caused the salivary pH to become more acidic. Lastly, it is likely that the force exerted during the acupuncture administration process increased sympathetic nervous system activity.

The difference in the mean Xerostomia Inventory score before and after 12 acupuncture sessions was 14.29 ± 10.11 in group A, 13.00 ± 7.71 in group B, and 15.79 ± 7.00 in group C ($p > 0.050$). The findings of the current study matched those of the study conducted by Johnstone *et al.* [5] in which combination acupuncture was used and where a reduction in the Xerostomia Inventory score of ≥ 10 points in 50% of the patients was reported. The mean Xerostomia Inventory score prior to acupuncture was 35.70 ± 5.14 in group A, reducing to 29.38 ± 15.81 after six acupuncture sessions and to 22.86 ± 16.15 after 12 sessions. Similarly, the mean Xerostomia Inventory score before acupuncture was 34.70 ± 7.77 in group B, with recorded figures of 26.50 ± 8.92 and 20.89 ± 10.06 after six and 12 acupuncture sessions, respectively. In group C, the mean Xerostomia Inventory score before acupuncture was 36.70 ± 5.25 , which reduced to 28.78 ± 11.72 and to 21.44 ± 8.97 after six and 12 acupuncture sessions, respectively. The relatively modest reduction in the mean Xerostomia Inventory score for group C in the current study was slightly different to the results obtained in the study by

Garcia *et al.* [15] in which combination acupuncture was used and where a significant decrease in the Xerostomia Inventory score was demonstrated in the initial and final acupuncture sessions (week 4), and at the one-month follow-up (week 8). The mean initial Xerostomia Inventory score in the study by Garcia *et al.* [5] was 36.3, which reduced to 31.6 ($p = 0.000$) in week 4 and to 29.9 ($p = 0.000$) in week 8. The difference in the results between the two studies may have occurred due to differences regarding the intervention time and selected acupuncture points.

After acupuncture, an improvement in salivary pH was experienced by 89% of the subjects in group C, 71% of the subjects in group A, and 67% of the subjects in group B. However, the difference was not statistically significant when analyzed using Fisher's exact test. In other words, similar effects resulted from the use of the three types of acupuncture therapy with respect to improving salivary acidity in NPC patients with post-radiation xerostomia. The acupuncture success rate in reducing the Xerostomia Inventory score in group A was 100% compared to 78% in group B, and 89% in group A. However, according to Fisher's exact test, a statistically significant difference was not found between the groups. Thus, the different types of acupuncture therapy were equally effective in managing the patients' subjective symptoms. The results obtained for group C in the current study were better than those reported in the study by Johnstone *et al.* [16] in which combination acupuncture was used. Some degree of improvement was found in their study in 70% of the subjects ($n=35$), while $\geq 10\%$ achieved healing, demonstrated by a reduction in the initial median Xerostomia Inventory score from 40 to 9.

Possible acupuncture therapy mechanisms include central, peripheral, and autonomic nerve pathway activation, and the release of neurochemicals [15,17]. A significant increase in blood flux in the skin protecting the parotid glands in Sjögren's syndrome patients was demonstrated during and after acupuncture at the points commonly used to treat xerostomia when measured by Doppler laser flowmetry. Increased blood flow can affect salivary gland metabolism and result in increased salivary secretion [15]. Manual acupuncture affects the autonomic nervous system by increasing parasympathetic system activity and the restriction of sympathetic tone [21,22] through the release of several neuropeptides, including vasoactive intestinal peptide (VIP), neuropeptide-Y (NPY), substance-P (SP), calcitonin gene-related peptide (CGRP), and neurokinin A (NKA) in the acini, ductus, and blood vessels of the salivary glands, thereby increasing salivary production. The neuropeptides that affect the salivary glands include SP, NKA, and CGRP, causing an increase in salivary secretion. Neuropeptides that impact upon blood flow in the saliva glands include SP, CGRP and VIP; causing vasodilation. NPY has the effect of inhibiting noradrenaline secretion. In addition to causing vasodilation, VIP also strengthens the effect of acetylcholine, a classical neurotransmitter substance that regulates the salivation process [23]. Furthermore, SP, NKA, CGRP, and VIP serve as growth factors in wound healing, atherosclerosis, and in angiogenesis and immune responses, and support the post-radiotherapy atrophic salivary glands, while managing dysfunctional changes in the blood vessels and supporting tissue [24].

In the current study, the researcher used the Shen Men ear point located in the triangular fossa and innervated by the third branch of Nervus trigeminus (the fifth cranial nerve) which has a sensory and motor function. The motor function of N. trigeminus is to innervate the mastication muscles. The ear point in the parotid gland is located at the antitragus peak and innervated by N. glossopharyngeal. It is also used in acupuncture therapy as it has a sensory and motor function. The ninth cranial nerve plays a role in the ability to taste, and in the sensation of the tongue mucosa, oropharynx, and Eustachian tubes. The motor function of this cranial nerve affects the pharyngeal and palatum muscles, and salivation [25]. In our study, the acupuncture therapy lasted three months and the final follow-up took place 1.5 years later to allow the patient to complete radiotherapy and for the xerostomia symptoms to subside. Placebo acupuncture was not used because any needle in the skin produces a sensory stimulation that can be strong enough to stimulate the release of neuropeptides [14,24]. Electroacupuncture was not used in the current study because it was not found to significantly increase salivary flow and was even found to reduce it in the study by Dawidson *et al.* [21]. A weakness of this study was the high number of dropouts. Reference was made to the issue of drop outs in an earlier study conducted by Meidell *et al.* conducted to determine the effect of acupuncture and its possible

application in terminally ill cancer patients with xerostomia receiving home care. It was concluded that difficulty recruiting and maintaining patients and in ensuring their compliance with the study protocol was caused by the gravity of their condition [26].

Limitations of this study included difficulty fulfilling the inclusion criteria when recruiting subjects, one of which was the exclusion of patients living outside the city or having another condition that prevented them from undergoing recurrent acupuncture therapy. Ensuring patient compliance was also challenging owing to the lengthy study duration. Greater efficacy was achieved with acupuncture in our study compared to that accomplished with pilocarpine, commonly used to treat post-radiation xerostomia patients with head and neck cancer, including nasopharyngeal cancer [11]. In our study, success rates of 71–100%, 67–89%, and 89–100% were realized in groups A, B, and C, respectively, compared to a figure of 31–54% elsewhere [11]. Minimal side-effects were experienced following acupuncture in our study and long-term therapeutic effects were achieved when compared to those attained with the use of drugs and salivary stimulants, including pilocarpine; indicative that acupuncture is important as supportive therapy for post-chemoradiated NPC patients with xerostomia. Acupuncture also effectively reduces patient symptoms, ultimately improving the quality of life of patients with potential to heal [26,27].

4. Conclusion

Auriculopuncture, bodyacupuncture, and combination acupuncture increased salivary pH and decreased the Xerostomia Inventory score in NPC patients with xerostomia due to chemoradiation, but the differences reported between the three groups were not statistically significant. The success rate of acupuncture in increasing salivary pH after 12 acupuncture sessions was 76%, and in decreasing the Xerostomia Inventory score after six acupuncture and 12 acupuncture sessions, 89% and 96%, respectively. Thus, acupuncture is effective for the management of xerostomia experienced by NPC patients after chemoradiation.

References

- [1] Gondhowiardjo S, *et al.* 2010 *Cancer Management Guidelines*. 1 ed. (Jakarta: FKUI Publisher Agency) p 27-38.
- [2] Parkin D M, Bray F, Ferlay J and Pisani P 2005 Global cancer statistics 2002. *CA. Cancer. J. Clin.* **55** 101-3.
- [3] Department of Radiotherapy RSUPN 2011 Cipto Mangunkusumo Jakarta.
- [4] Susworo R 2006 Radiotherapy in various cases. In: *Radiotherapy*. (Jakarta: Universitas Indonesia) p 64-72.
- [5] Johnstone P A S, Peng P, May B C, Inouye W S and Niemtzow R C 2001 Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int. J. Radiat. Oncol. Biol. Phys.* **50** 353-7.
- [6] Scarpace S L, Brodzik F A, Mehdi S and Belgam R 2009 Treatment of head and neck cancers: Issues for clinical pharmacists. *Pharmacother.* **29** 578-92.
- [7] Dirix P, Nuyts S and Bogaert W V 2006 Radiation-induced xerostomia in patients with head and neck cancer. *Cancer.* **107** 2525-34.
- [8] Morganstein W M 2005 Auricular acupuncture in the treatment of xerostomia. *J. Chinese. Med.* **79** 5-8.
- [9] Berk L B, Shivnani A T and Small W 2005 Pathophysiology and management of radiation-induced xerostomia. *J. Support. Oncol.* **3** 191-200.
- [10] Wada A, Uchida N, Yokokawa M, Yoshizako T and Kitagaki H 2009 Radiation-induced xerostomia: objective evaluation of salivary gland injury using MR sialography. *Am. J. Neuroradiol.* **2009** 1-8.
- [11] Chitapanarux I, Kamnerdsupaphon P, Tharavichitkul E, Sumitsawan Y, Sittitrai P, Pattarasakulchai T, Lorvidhaya V, Sukthomya V, Pukanhaphan N, Traisatit 2008 Effect of

- oral pilocarpine on post-irradiation xerostomia in head and neck cancer patients: a single-center, single-blind clinical trial *J Med Assoc Thai* **91** 1410-5.
- [12] Rode M, Smid L, Budihna M, *et.al.* 2001 The influence of pilocarpine and biperiden on pH value and calcium, phosphate and bicarbonate concentrations in saliva during and after radiotherapy for head and neck cancer. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.* **92** 509-14.
- [13] Gornitsky M, Tsang C S P, Shenouda G, Sultanem K, *et.al.* 2004 Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral. Oral. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.* **98** 45-52.
- [14] Blom M, Dawidson I, Fernberg J O, Johnson G and Angmar-Manson B 1996 Acupuncture treatment of patients with radiation-induced xerostomia. *Oral. Oncol. Eur. J. Cancer.* **32** 182-90.
- [15] Garcia M K, Chiang J S, Cohen L, *et.al.* 2009 Acupuncture for radiation-induced xerostomia in patients with cancer: a pilot study. *Head. Neck.* **31** 1360-8.
- [16] Johnstone P A S, Niemtzow R C and Riffenburgh R H 2002 Acupuncture for xerostomia: clinical update. *Cancer.* **94** 1151-6.
- [17] Kiswojo, Widya D K and Srilestari A 2009 *Medical Acupuncture and its development.* (Jakarta: Kolegium Akupunktur Indonesia).
- [18] Deng G, Hou B L, Holodny A I and Cassileth B R 2008 Functional magnetic resonance imaging (fMRI) changes and saliva production is associated with acupuncture at LI-2 acupuncture point: a randomized controlled study. *BMC Complement. Altern. Med.* **8** 1-7.
- [19] Johnston M F, Sanchez E O, Vujanovic N L and Li W 2010 Acupuncture May stimulate anticancer immunity via activation of natural killer cells. *Evid. Based Complement Altern. Med.* **2010** 1-14.
- [20] Thomson W M and Williams S M 2000 Further testing of the xerostomia inventory. *Oral. Surg. Oral. Med. Pathol. Oral. Radiol. Endol.* **89** 46-50.
- [21] Haker E, Egekvist H, Bjerring P 2000 Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects *Journal of the Autonomic Nervous System* **79** 52-59.
- [22] Suzuki Y, Itoh H, Amada K, Yamamura R, Sato Y, Takeyama M 2013 Significant Increase in Salivary Substance P Level after a Single Oral Dose of Cevimeline in Humans. *International Journal of Peptides* **2013** 284765.
- [23] Dawidson I, Angmar-Mansson B, Blom M, Theodorsson E and Lundeberg T 1998 The influence of sensory stimulation (acupuncture) on the release of neuropeptides in the saliva of healthy subjects. *Life. Sci.* **63** 659-74.
- [24] Blom M and Lundeberg T 2000 Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral. Disease.* **6** 15-24.
- [25] Frank B L and Soliman N E 2005 *Auricular therapy: a comprehensive text.* 1st ed. (Bloomington: Acupuncture Arts & Press LLC) p 11-314.
- [26] Meidell L and Rasmussen B H 2009 Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study. *Int. J. Palliat. Nurs.* **15** 560-8.
- [27] Omi S 2009 WHO standard acupuncture point locations in the western pacific region. (Manila Philippines: WHO western Pacific Region).