



Effects of herbal medicine for xerostomia in head and neck cancer patients: an observational study in a tertiary cancer hospital

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Abstract

Purpose More than 80% head and neck cancer patients endured radiotherapy-induced xerostomia which impacts their quality of life (QoL). This observational study evaluated the effect of herbal treatment on head and neck cancer patients' xerostomia and QoL.

Methods Head and neck cancer patients were recruited from July 2016 till March 2017 at National Cancer Institute, Ministry of Health, Malaysia. All study participants continued their standard oncology surveillance. Treatment group participants additionally received Chinese herbal treatment. The assessments included unstimulated salivary flow rate (USFR), stimulated salivary flow rate (SSFR), and QoL questionnaire.

Results Of 42 recruited participants, 28 were in the treatment group and 14 were in the control group. Participants were mainly Chinese (71.4%), stage III cancer (40.5%), and had nasopharynx cancer (76.2%). The commonly used single herbs were Wu Mei, San Qi, and Tian Hua Fen. Sha Shen Mai Dong Tang, Liu Wei Di Huang Wan, and Gan Lu Yin were the frequently prescribed herbal formulas. The baseline characteristics, USFR, SSFR, and QoL between control and treatment groups were comparable ($p > 0.05$). USFR between control and treatment groups were similar throughout the 6-month study period. SSFR for the treatment group significantly improved from 0.15 ± 0.28 ml/min (baseline) to 0.32 ± 0.22 ml/min ($p = 0.04$; at the 3rd month) and subsequently achieved 0.46 ± 0.23 ml/min ($p = 0.001$; at the 6th month). The treatment group had better QoL in terms of speech ($p = 0.005$), eating ($p = 0.02$), and head and neck pain ($p = 0.04$) at the 6th month.

Conclusion Herbal treatment may improve xerostomia and QoL in post-radiotherapy head and neck cancer patients.

Keywords Chinese herbal drugs · Xerostomia · Radiotherapy · Head and neck neoplasms

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Abbreviations

Gy	Gray
<i>IQR</i>	Interquartile range
<i>M</i>	Mean
NCI	National Cancer Institute
QoL	Quality of life
<i>SD</i>	Standard deviation
SSFR	Stimulated salivary flow rate
T&CM	Traditional and complementary medicine
USFR	Unstimulated salivary flow rate

Introduction

Head and neck cancer has become the sixth leading cancer worldwide—approximately 630,000 new patients have been

diagnosed annually [1]. The principal treatment for head and neck cancer is radiotherapy, whether as a single treatment (stage I) or concurrent with chemotherapy (stage II, III, and IV) [2–4]. However, more than 80% head and neck cancer patients who have undergone radiotherapy endured xerostomia [5].

Xerostomia is progressive within 6 months post-radiotherapy [6], and may even be irreversible [7]. Xerostomia impacts the patients' quality of life (QoL) as it burdens chewing, speaking, and swallowing and also causes a higher incidence of oral candidiasis and dental caries [8]. Recommended pharmacologic treatments, such as pilocarpine and cevimeline [2], relieve xerostomia temporarily [9, 10]. However, pilocarpine causes intolerable adverse effects (such as sweating, headache, frequent urination) [10] and requires caution in patients with cardiovascular and respiratory conditions [11]. Similarly, non-pharmacological treatments (such as oral lubricants or saliva substitutes) offer transitory relief of xerostomia [10].

Traditional and complementary medicine (T&CM) units in four government hospitals in Malaysia (including the National Cancer Institute, NCI) offer Chinese herbal treatment as an adjunct to conventional cancer treatment [12]. Systematic reviews showed that Chinese herbal treatment may alleviate xerostomia [13, 14] and other sequelae of radiotherapy (e.g., oral mucositis, loss of appetite) [13]. Though previous systematic reviews and randomized controlled trials demonstrated the effectiveness of Chinese herbs in improving radiotherapy-induced xerostomia [15–18], only few studies had concurrently examined xerostomia improvement objectively and assessed QoL. Considering the paucity of herbal study on post-radiotherapy xerostomia (particularly in the local hospital setting), we conducted an observational study aimed to evaluate the effect of Chinese herbal treatment in relieving participants' xerostomia (i.e., salivary flow) and QoL.

Methods

This was a prospective observational study on post-radiotherapy head and neck cancer patients. Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia, approved the study protocol (NMRR-14-1925-22,407). All referred head and neck cancer patients to the T&CM unit, NCI, were screened for enrollment eligibility. The inclusion criteria were histopathologically confirmed diagnosis of head and neck cancer [19]; aged ≥ 18 ; received ≥ 52 Gy of radiotherapy on the head and neck area; and completed radiotherapy ≤ 6 months. We excluded patients with head and neck cancer stage IVC; thyroid cancer; medical history of xerostomia; history of taking medications which may affect saliva secretion (e.g., pilocarpine); pregnant or

breastfeeding; vulnerable patients; and patients who had recurrence, relapse, or metastases post-radiotherapy.

We recruited study participants from 1st July 2016 until 31st March 2017 and participants decided themselves to enroll either in the treatment or in the control group. Based on the primary outcome measure, i.e., salivary flow [15], the sample size was calculated using comparing 2 means formula [20]. Taking into account α of 0.05, desired power at 80% ($\beta = 0.2$) and an expected difference between the 2 means of 4.42, 12 participants were required for treatment and control group respectively. Allowing for 20% dropout, the calculated sample size was 14 participants for treatment and control groups respectively.

All study participants continued their standard oncology surveillance at the oncology clinic, NCI. In addition to the routine oncology care, participants of the treatment group received Chinese herbal treatment from the T&CM unit, NCI. The provided herbal treatment was plant-based Chinese herbal extract and in powder form. The participants of the treatment group were required to take the herbal treatment orally twice daily. Trained and qualified Chinese medicine practitioners tailored the herbal treatment monthly to address the participants' chief complaints, including their xerostomia complaints. Participants' de-identified demographic, clinical data and prescribed herbal treatment were extracted from the hospital electronic medical record. Study follow-up was 6 months and all participants were assessed at baseline, 1st month, 3rd month, and 6th month. The assessment for xerostomia progress included unstimulated salivary flow rate (USFR) and stimulated salivary flow rate (SSFR) [21] and administering the validated "Head and Neck Cancer-Specific Quality of Life Questionnaire" [22]. In assessing USFR, participants had a pre-weighed gauze under their tongue for 5 min. The soaked gauzes were then weighed [23]. The participants rinsed their mouth and rested for 3 min [21] before proceeding to SSFR whereby participants chewed another pre-weighed gauze over 5 min [23]. Flow rate was calculated as milliliters per minute. The QoL questionnaire comprised of 4 domains: speech, head and neck pain, eating, and emotion. The QoL score ranged from 0 to 100, which the higher score indicated a better outcome [22].

Data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics (frequency with percentage (%), mean and standard deviation ($M \pm SD$) and median and interquartile ranges (IQR)) were presented for participants' age and their radiotherapy details. The independent *t* test and Mann-Whitney *U* test (for non-normally distributed data) were used to compare the salivary flow rate and quality of life between control and treatment groups. Missing data were excluded from the analysis. Values of $p < 0.05$ indicated statistically significant.

Results

We examined 50 potential participants who met the inclusion criteria; however, only 42 participants were confirmed eligible for this study. Of the 42 recruited study participants, 28 participants chose to be in the treatment group and 14 participants enrolled in the control group. A total of 7 participants in the treatment group were unable to complete the study: passed away due to advanced disease ($n = 5$) and defaulted the last study visit because of disease progression during restaging ($n = 2$). By the end of the 6-month study period, 35 participants completed follow-up (21 in the treatment group, 14 in the control group). Data from 42 participants were included in the analysis.

Of the 42 participants included for analysis, they were largely male ($n = 26$, 61.9%), Chinese ($n = 30$, 71.4%), stage III cancer ($n = 17$, 40.5%), and had nasopharynx cancer ($n = 32$, 76.2%). Participants were mainly recruited within the first 3 months after completing radiotherapy for both the control group ($n = 9$, 64.3%) and the treatment group ($n = 20$, 71.4%). The baseline characteristics between the control and treatment groups were comparable ($p > 0.05$; Table 1).

Participants of the treatment group received a tailored combination of herbs. A total of 1469 prescriptions, 27 herbal

formula, and 88 single herbs were involved within 6 months of the study period. The top 3 commonly prescribed single herbs and herbal formulas are presented in Table 2.

Intergroup USFR and SSFR were not statistically different at baseline ($p > 0.05$; Table 3). USFR for both the control and treatment groups had no statistical changes throughout the study period. Contrarily, SSFR for the treatment group significantly improved from 0.15 ± 0.28 ml/min (baseline) to 0.32 ± 0.22 ml/min ($p = 0.04$; at the 3rd month) and subsequently achieved 0.46 ± 0.23 ml/min ($p = 0.001$; at the 6th month). The treatment group (0.46 ± 0.23 ml/min) had higher SSFR than the control group (0.28 ± 0.22 ml/min) at the 6th month, ($p = 0.03$; Table 3).

Higher QoL score suggested that participants had better QoL. The treatment group had better QoL in terms of speech ($p = 0.005$), eating ($p = 0.02$), and head and neck pain ($p = 0.04$) than the control group at the 6th month (Table 4).

Discussion

The median age of participants was more than 50 years old, which concurs with the increase in Malaysian incidence of head and neck cancer with age, especially after 50 years old

Table 1 Baseline characteristics of study participants ($N = 42$)

Variables	Control group ($n = 14$)	Treatment group ($n = 28$)	p value	
Age (years) ^a	55.00 (19.0)	54.00 (22.0)	0.63	
Gender ^b	Male	10 (71.4)	16 (57.1)	0.57
	Female	4 (28.6)	12 (42.9)	
Race ^c	Chinese	10 (71.4)	20 (71.4)	0.77
	Malay	3 (21.4)	4 (14.3)	
	Indian	1 (7.1)	4 (14.3)	
Stage of cancer ^c	I	0	4(14.3)	0.38
	II	3 (21.4)	4(14.3)	
	III	5 (35.7)	12(42.9)	
	IV	0	1(3.6)	
	IVa	3 (21.4)	5(17.9)	
	IVb	3 (21.4)	2(7.1)	
Tumor site ^c	Nasopharynx	12 (85.7)	20(71.4)	0.74
	Oropharynx	1 (7.1)	4(14.3)	
	Oral cavity	1 (7.1)	3(10.7)	
	Hypopharynx	0	1(3.6)	
Total tumor radiation dose (Gy) ^a	70.0 (0.01)	69.9 (4.0)	0.05	
Radiotherapy dose received by the parotid gland (Gy) ^d	39.7 (15.6)	37.0(17.9)	0.63	
Duration of post-radiotherapy (days) ^a	43.5 (99.0)	44.5 (92.0)	0.77	
	0–90 days	9 (64.3)		20 (71.4)
	91–180 days	3 (36.7)		8(28.6)

^a Median (interquartile range): Mann-Whitney U test

^b n (%): Chi-square test

^c n (%): Fisher's exact test

^d Mean (standard deviation): independent t test

Table 2 Common prescribed single herbs and herbal formula ($N = 1,469$ prescriptions)

Prescribed herbal	Frequency of prescriptions, n (%)
Single herbs	
Wu Mei (Fructus <i>Prunus mume</i>)	139 (9.5)
San Qi (Radix <i>notoginseng</i>)	59 (4.0)
Tian Hua Fen (Radix <i>Trichosanthis</i>)	48 (3.3)
Herbal formula	
Sha Shen Mai Dong Tang	114 (9.8)
Composed of Sha Shen (Radix <i>Glehnia littoralis</i>), Mai Men Dong (Radix <i>Ophiopogonis japonicus</i>), Yu Zhu (Rhizoma <i>Polygonati Odorati</i>), Tian Hua Fen (Radix <i>Trichosanthis</i>), Sang Ye (Folium <i>Mori</i>), Bai Bian Dou (<i>Lablab Album</i>), Gan Cao (Radix <i>Glycyrrhiza glabra</i> L.)	
Liu Wei Di Huang Wan	25 (1.7)
Composed of: Shou Di Huang (Radix <i>Rehmanniae praeparata</i>), Shan Yao (Rhizoma <i>Dioscoreae</i>), Mu Dan Pi (Cortex <i>Moutan</i>), Ze Xie (Rhizoma <i>Alismatis</i>), Fu Ling (Poria), Shan Zhu Yu (Fructus <i>Corni</i>)	
Gan Lu Yin	23 (1.6)
Composed of: Sheng Di Huang (raw Radix <i>Rehmannia glutinosa</i> Libosch.), Shou Di Huang (Radix <i>Rehmanniae praeparata</i>), Mai Men Dong (<i>Ophiopogon japonicus</i>), Tian Men Dong (<i>Asparagus cochinchinensis</i> (Lour.) Merr.), Yin Chen Hao (<i>Artemisia capillaris</i> Thunb.), Shi Hu (<i>Dendrobium chrysanthum</i> Wall.), Zhi Ke (<i>Citrus aurantium</i> L.), Huang Qin (<i>Scutellaria baicalensis</i> Georgi), Zhi Gan Cao (Radix <i>Glycyrrhizae praeparata</i>), Pi Pa Ye (<i>Eriobotrya japonica</i>)	

[24]. Aging is also a leading factor of increased prevalence of xerostomia [25, 26]. More than halves of study participants were Chinese male, consistent with the latest Malaysian cancer registry report that Chinese male had the highest incidence (age-standardized rate for Chinese male was 11.0, followed by Malay 3.3, Indian 1.1, and other race 9.9) [24]. The complex genetic background, epigenetic, diet, lifestyle, and environment of Chinese race population inherited from China mainland [27, 28] could be the main contributing factors suggesting the higher proportion of Chinese ethnic groups with head and neck cancer in the study. The study participants mainly had stage III and IV, which is a common presentation phase for most head and neck cancer patients. Most of the head and neck cancer patients were diagnosed with late stage (i.e., stage III and IV) on their first presentation [24] and generally with poor prognosis [29].

Head and neck cancer patients mainly received radiotherapy doses between 50 and 70 Gy [30] and irreversible xerostomia could occur with doses of over 60 Gy [31]. The parotid, submandibular, and sublingual glands secrete 90% of the total salivary secretion [32], and the parotid gland is more radiosensitive than the other salivary glands [5]. The study participants mainly had nasopharyngeal cancer and the parotid gland (function as one of the major salivary glands) [5] is located close to the radiation field. The Parotid gland secretes saliva largely under a stimulated condition; whereas the submandibular gland mostly secretes saliva under an unstimulated condition [33]. A mean radiotherapy dose of ≥ 26 Gy towards the parotid gland significantly reduced salivary

flow upon stimulation, which may lead to an irreversible xerostomia [34]. Participants of this study received > 26 Gy radiation at their parotid glands, suggestive of suffering severe xerostomia, which is more difficult to treat and recover over time [34]. Preliminary studies showed that some of the Chinese herbs may have increased salivary flow by acting specifically on the aquaporins (AQP) at the submandibular salivary glands; and this accounts for basal saliva secretion. However, our result did not show a positive result in USFR. The radiotherapy had lesser damage on the submandibular gland and could have resulted in the minimal alteration on the AQP, hence contributed to the non-significant changes in USFR. Since the parotid gland secretes most of the total saliva in stimulated conditions [32], improvement of SSFR at the 3rd month onwards (in the treatment group) may reflect the recovery of the parotid gland post-radiotherapy; hence, further studies can explore the possible mechanisms.

Chinese medicine perceived radiotherapy as a kind of heat toxin that attacks body constitution of the participants and injures body fluid and resulted symptoms of oral dryness, mucositis, poor appetite, lethargy, and insomnia [35]. Sha Shen Mai Dong Tang was one of the main herbal formulas prescribed for patients with above injuries and symptoms. Components in Sha Shen Mai Dong Tang improve the healing of dry mouth, mucositis, QoL, and immune system in post-radiotherapy patients [36]. The use of Gan Lu Yin in this study concurred with a study on post-radiotherapy nasopharyngeal cancer patients, beneficial in alleviating mucositis and dry mouth symptoms [37]. In addressing post-radiotherapy

Table 3 Intergroup comparison of salivary flow rate ($N = 42$)

Variable	Control group ($n = 14$)	Treatment group ($n = 28$)	p value
Unstimulated Salivary Flow Rate, USFR (ml/min)			
Baseline ^a	0.05 (0.07)	0.04 (0.06)	0.34
1st month ^a	0.06 (0.04)	0.03 (0.06)	0.23
3rd month ^a	0.06 (0.08)	0.04 (0.06) ^c	0.28
6th month ^a	0.08 (0.06)	0.08 (0.11) ^d	0.71
Stimulated salivary flow rate, SSFR (ml/min)			
Baseline ^a	0.20 (0.40)	0.15 (0.28)	0.36
1st month ^a	0.18 (0.27)	0.14 (0.25)	0.94
3rd month ^b	0.24 (0.23)	0.32 (0.22) ^c	0.33
6th month ^b	0.28 (0.22)	0.46 (0.23) ^d	0.03*
USFR (ml/min) changes compared to baseline			
1st month ^a	0.00 (0.05)	0.02 (0.04)	0.46
3rd month ^b	0.02 (0.05)	0.01 (0.06) ^c	0.38
6th month ^a	0.02 (0.07)	0.04 (0.11) ^d	0.39
SSFR (ml/min) changes compared to baseline			
1st month ^a	-0.02 (0.09)	-0.01 (0.10)	0.28
3rd month ^a	0.03 (0.08)	0.07 (0.17) ^c	0.04*
6th month ^a	0.05 (0.17)	0.24 (0.24) ^d	0.001*

^a Median (interquartile range): Mann-Whitney U test

^b Mean (standard deviation): independent t test

^c Missing ($n = 4$)

^d Missing ($n = 7$). Data analysis excludes missing values

xerostomia, the top 3 herbal formulas contain Mai Men Dong (*Radix Ophiopogonis japonicas*) and Sheng Di Huang (raw *Radix Rehmannia glutinosa* Libosch, in line with findings of a systematic review on Chinese herbal treatment for the same condition [13]. Among the commonly used single herbs and herbal formulas (Sha Shen Mai Dong Tang and Gan Lu Yin; Table 2), Sha Shen (*Radix Glehniae littoralis*), Mai Men Dong (*Radix Ophiopogonis japonicas*) and Wu Mei (*Fructus Prunus mume*) may continuously enhance the fluid secretion and thus directly promote salivary flow [38]. The proposed mechanism in promoting the salivary fluid secretion is through transcellular movement by activating receptors to increase cytosolic Ca^{2+} or stimulation of transporters for Cl^- entry [38]. Another single herb (and also a component of Sha Shen Mai Dong Tang) Tian Hua Fen (*Radix Trichosanthis*) clears heat and generates body fluid. It also elevates the anti-inflammatory effects and inhibits the nitric oxide activity [39] which probably helps in treating other mucositis inflammatory conditions due to radiotherapy.

Previous controlled trials [16–18, 40–42] had demonstrated the effects of herbs in improving radiotherapy-induced xerostomia. This study observed that participants in the treatment group had significant QoL improvement specifically speech ($p = 0.005$), eating ($p = 0.02$), and head and neck pain ($p = 0.04$) domains than the control group at the 6th month. We found significant SSFR improvement as early as the 3rd month (and lasted until the 6th month) of herbal treatment;

however, this was not reflected in the improvement of the QoL domain at the 3rd month. This finding was similar to other studies where no statistically significant correlation was observed between global health-related QoL scores and stimulated saliva production rates in the post-RT period [43]. The statistically significant improvement of SSFR at the 3rd-month follow-up may be clinically inadequate to improve the QoL in the treatment group. The improvement of SSFR, eating, speech, and head and neck pain of the QoL domain may require longer duration because the oral environment and functional recovery may need longer time (> 6 months of herbal treatment).

This study has several limitations. No randomization could be the confounding factors for an observational study, yet the results on the baseline characteristics affirmed that both control and treatment were comparable ($p > 0.05$). Using QoL questionnaires to assess xerostomia effect may not fully capture the changes in perceived oral dryness that may occur in acute- or late-phase post-radiotherapy [44]. The improvement in salivary flow may not correlate with QoL in post-radiotherapy head and neck cancer patients, as factors such as tumor site and surgery intervention largely affect patients' QoL [43].

Chinese herbal treatment has been used as an adjunct treatment for cancer patients in Malaysian government healthcare facilities for almost a decade. Thus, this study provided a method to assess the effect of herbal treatment that is close

Table 4 Intergroup comparison of Quality of Life (QoL) ($N = 42$)

QoL Domain	Control group ($n = 14$)	Treatment group ($n = 28$)	<i>p</i> value
Speech			
Baseline ^a	90.7 (23.5)	87.5 (29.7)	0.96
1st month ^a	100 (7.8)	100 (12.5)	0.39
3rd month ^a	96.9 (6.2)	100 (12.5) ^c	0.99
6th month ^a	90.7 (12.5)	100 (0) ^d	<i>0.005*</i>
Eating			
Baseline ^a	72.9 (26.1)	62.5 (32.3)	0.44
1st month ^a	83.3 (12.5)	81.3 (23.9)	0.84
3rd month ^a	83.3 (9.4)	85.4 (19.8) ^c	0.98
6th month ^a	83.3 (15.6)	95.8 (10.4) ^d	<i>0.02*</i>
Head and neck pain			
Baseline ^a	84.4 (14.1)	81.3 (25.0)	0.68
1st month ^a	93.8 (12.5)	93.8 (17.2)	0.44
3rd month ^a	90.6 (7.8)	100 (12.5) ^c	0.08
6th month ^a	87.5 (18.8)	95.8 (10.4) ^d	<i>0.04*</i>
Emotion			
Baseline ^a	85.4 (16.70)	83.3 (24.0)	0.63
1st month ^a	85.4 (11.46)	91.7 (21.9)	0.33
3rd month ^a	91.7 (13.53)	95.8 (15.7) ^c	0.45
6th month ^a	87.5 (18.72)	95.8 (8.3) ^d	0.13

^a Median (interquartile range): Mann-Whitney *U* test

^b Mean (standard deviation): independent *t* test

^c Missing ($n = 4$), ^d missing ($n = 7$). Data analysis excludes missing values

Statistically significant *p* values ($p < 0.05$) highlighted in italic and asterisk numbers

to the daily practice of T&CM units. Though the sample size is relatively small, the results are statistically significant. This study recruited post-radiotherapy head and neck cancer patients; whether the concurrent radiotherapy and Chinese medicine as radio-protective agents have a better outcome for head and neck cancer patients may be a potential area for future studies.

Conclusion

Evidence-based use of herbal treatment may improve xerostomia and QoL in post-radiotherapy head and cancer patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study (involving human participants) were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants in the study.

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