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Original article

Effects of two carboxymethylcellulose-containing saliva substitutes on post-radiation xerostomia in head and neck cancer patients related to quality of life

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Background: Post-radiotherapy xerostomia affects a patients' quality of life (QoL). Carboxymethylcellulose (CCMC)-based saliva substitute products have been widely used to relieve symptoms of xerostomia.
Objective: We compared subjective short-term clinical effectiveness between commercially available CCMC-based saliva substitutes (GC Dry Mouth Gel) and King Chulalongkorn Memorial Hospital (KCMH) saliva substitutes on post-radiation xerostomia related QoL.
Methods: Fifty head and neck cancer patients with post-radiation xerostomia were randomly assigned (1:1) to receive either CCMC-based saliva substitutes (CCMC group) or KCMH saliva substitutes (KCMH group) in a blinded manner. Patients returned to our clinic 14 days after treatment for follow-up assessment. Comprehensive xerostomia questionnaires were used to evaluate the clinical effectiveness of the two CCMC-based saliva substitutes. Xerostomia severity level and four major domains of xerostomia-related quality of life, before and after treatments were assessed. Primary outcomes of QoL were analyzed using an ANCOVA, adjusting for baseline differences and chi-square statistics.
Results: After the completion of 14 days treatment, mean self-rated VAS scores of xerostomia severity in the CCMC group and KCMH group were 50.1 and 59.0 mm., respectively ($p = 0.04$). Mean scores of the CCMC group were significantly different from the KCMH group in three continuous outcome variables, namely speech difficulty, taste alteration, and frequency of sipping water. Additionally, there was one dichotomous outcome variable, taste alteration ($p < 0.05$). No other significant difference was found between the groups. The proportion of patients reporting a "response" or "major improvement" from baseline in xerostomia severity and speech difficulty were significantly different between groups ($p = 0.03$ and 0.04, respectively).
Conclusion: Commercially available CMC-based saliva substitute showed better outcomes in improving severity of xerostomia, speech difficulty, taste alteration, and frequency of sipping water compared with KCMH saliva substitute.

Keywords: Carboxymethylcellulose, head and neck cancer, quality of life, radiation, saliva substitute, xerostomia

Radiotherapy (RT) is a primary modality of treatment in head and neck cancer (HNC). Xerostomia is a very common complication found after RT for HNC [1]. Patients with post-radiation xerostomia may suffer from various symptoms such as oral discomfort or pain, taste alteration, nocturnal oral discomfort, intolerance to spicy food, and difficulty in speaking, chewing, and swallowing [2-4]. Xerostomia can also cause problems with dentures and increase risk of dental caries and oral infections [2-4].This may lead to a decrease in nutritional intake and weight loss [3].

Symptomatic management of xerostomia is required when saliva production cannot be stimulated effectively. Saliva substitutes have been considered as treatment alternatives. In Thailand, most commercially available saliva substitutes are based on carboxymethlycellulose (CMC). CMC is a polymer derived from natural cellulose. It is used in saliva substitute formulation as a thickening agent, although CMC does not completely resemble properties of human saliva such as viscosity, sheeting, stringing, and elasticity [5, 6]. Nevertheless, CMC based saliva

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substitutes have been commonly used and evaluated extensively [5-10]. CMC based saliva substitutes have moderate effects on the reduction of dry mouth related symptoms [8]. It has been shown that CMC based saliva substitutes can decrease the severity of symptoms associated with xerostomia and have few side effects [11].

King Chulalongkorn Memorial Hospital (KCMH) artificial saliva is a liquid CMC based preparation that has been compounded and dispensed at KCMH for over 20 years. The preparation is formulated to provide prolonged oral wetness in xerostomia patients. It does not contain immunologic or enzymatic ingredients. While it has been used for a long time, we still know relatively little about its effects on quality of life (QoL).

In our previous report [12], we evaluated short-term effects of the two commercially available gel formulations of saliva substitute on xerostomia-related QoL by using a xerostomia-related quality of life questionnaire. No significant difference was found between the CMC based preparation (GC Dry Mouth Gel) and enzyme-containing saliva substitute (Biotene) usage in HNC patients with post-radiation xerostomia [12]. This study was designed to compare the clinical effectiveness of the in-hospital prepared liquid formulation (KCMH saliva substitute) with the commercially available CMC-based saliva substitute (gel formula with fruit flavor, GC Dry Mouth Gel) on xerostomia-related QoL in post-radiation HNC patients.

Material and method

Participants

Men and women over the age of 18 with persisting xerostomia who came for their regular follow-up visits at our multidisciplinary outpatient clinic and self rated their VAS score of xerostomia. These patients had completed radiotherapy of 66–70 cGy/33–35 F with the fields of radiation encompassing the major and minor salivary glands for at least 1 month before enrollment. Those who received bilateral intensified modulated RT (IMRT) were included if they completed the RT within 12 months before enrollment. Patients who received unilateral or bilateral conventional RT were also included. All patients received nutrition orally and had at least one tenth of their natural teeth remaining. Participants were excluded if they were taking antidepressants, pilocarpine, or other medications associated with anticholinergic effects. Patients with evidence of a persisting or recurring malignant disease or terminal cancer and those with Sjoegren syndrome or with medical conditions that cause xerostomia were also excluded.

Visual analog scale (VAS) xerostomia scores were transposed into a four grade xerostomia scale [1, 3, 13], where grade 0 = VAS score of 24 or less (no xerostomia), grade 1 = VAS score between 25 and 49 (now and then, partially dry), grade 2 = VAS score between 50 and 74 (always, partially dry), grade 3 = VAS score between 75 and 100 (completely dry, disturbing).

All patients were instructed to refrain from using any other products for the treatment of xerostomia (e.g. saliva stimulants or other saliva substitutes) two weeks before and during the study period, but were permitted frequent sips of water as needed for their comfort. They were allowed to use other mouth care products (for treating oral disease) which did not affect xerostomia symptoms if indicated (e.g., topical analgesics, topical antiseptics, and antifungals). They were also advised to stop if they developed new problems.

Prior to study enrollment, the coordinator read and explained details of the study to each patients. Written informed consent was agreed and obtained. This study obtained ethical clearance by the Institutional Review Board of the Medical School of Chulalongkorn University.

Treatment protocol

Fifty patients were blinded and randomly assigned (1:1) to receive either the in-hospital prepared liquid formulation (KCMH) or the commercially available CMC based saliva substitute (gel formula with fruit flavor, GC Dry Mouth Gel, GC Dental Products Corp, Japan) for home application for 2 weeks. The containers were weighed prior to dispensing and immediately after the patients returned them at the end of the treatment period.

Each patient was asked to apply a sufficient amount of saliva substitute on the tongue, gum, and any soft tissue with their fingertip, cotton swab or with their own tongue for at least four times a day (before and after meals, and at bedtime) and reapply between meals as often as needed for dry mouth. A spray bottle was allowed for liquid KCMH application.

Xerostomia questionnaire (XQ)

Most items of our xerotomia-related quality of life scale (XeQoLS) were modified from xerostomia questionnaires of Shahdad et al. [14]. Only questions no. 3.1 and 3.2 in XQ part 1 were modified from Meirovitz et al. [13], and Henson et al. [15]. The XeQoLS was translated into Thai by a dentist and tested in 20 patients before it was adjusted and approved by two other senior dentists. XeQoLS contained four major domains (physical functioning, personal/psychological functioning, social functioning, and pain/discomfort). In addition, the XeQoLS included other aspects of clinical acceptance.

The XQ has two parts. Part 1 contained eight questions with continuous response score derived from a 100 mm VAS where the positive response was placed on the left and negative response on the right. The highest possible scores on each questions are 100, representing perfect functioning, e.g., 0 = not dry at all and 100 = the worst imaginable dryness. These questions were asked before (day 0) and after treatment (day 14). The main VAS question for xerostomia severity asked, "How dry is your mouth?"(questions shown in **Table 2**). Part 2 contained 12 yes/no type questions for pretreatment (day 0) and their accompanying questions for posttreatment (day 14). For example, "Is taste affected by your dry mouth?" was accompanied with "Did the product improve your sensation of taste?" (questions shown in **Table 3).**

Internal consistency of the XeQoLS VAS scoring questions was acceptable with Cronbach alpha and KR-20 coefficients of 0.84 and 0.81, respectively. All participants completed the pretreatment questionnaire before randomization and the posttreatment questionnaire at the end of 14 days of treatment. The same dentist read the XQ to each participant in Thai. All patients completed the XeQoLS by themselves without any help or interruption.

Outcome measures

The severity level of xerostomia and xerostomia-related quality of life were evaluated before and after 14 days of treatment. Other aspects of clinical acceptance were also assessed.

At the end of the treatment period, patients with a decrease of ≥25 mm score from baseline were classified as "having a major improvement"; while those with a decrease of 10–24 mm. from baseline were classified as "having a response". Patients with a decrease of <10 mm from baseline were classified as nonresponders [3, 16].

Statistical analysis

For $1–\beta = 0.8$, and $\alpha = 0.05$, a sample size of 17 was required to demonstrate an effect size of 0.5. Allowing for a dropout rate of approximately 10%, at least 21 patients were recruited into each group of this study.

Data was analyzed using SPSS (Statistical Package for Social Sciences) software for MS Windows (version 17.0). Means and standard deviations of continuous variables were calculated. Patient and tumor characteristics between the two groups were compared using *t* or chi-square tests where applicable. An analysis of covariance (ANCOVA) was used to examine mean response differences between groups after accounting for preexisting differences at baseline. Chi-square statistics were calculated to assess categorical parameters between groups. A *p*-value of less than 0.05 was considered significant.

Results

Table 1 shows the characteristics of the participants. Fifty patients who self-reported grade 2 or 3 xerostomia (VAS score of xerostomia ≥50 mm.) were enrolled in this study. The study population consisted of 27 (54%) men and 23 (46%) women. Mean age and mean duration after radiation were 50.6 and 2.6 years, respectively. The majority of patients had the nasopharynx as their primary site of cancer. All had received RT treatment for HNC with field of irradiation encompassing the major and minor salivary glands and had completed their RT at least one month before enrollment into this study. The radiation dose range was between 66 and 70 Gy. Patient and tumor characteristics were comparable between the groups.

The mean quantity of saliva substitute used during treatment in CCMC group was lower than KCMH group (30.4±15.9 and 271.7±153.6 g., respectively) with statistical significance ($p < 0.001$). All patients completed the questionnaires before randomization and at the end of 14-day treatment period.

Table 2 presents the means of XeQoLS's VAS scores of difference domains before and after treatment by groups. At baseline, mean VAS scores of xerostomia severity in CCMC and KCMH group were 81.2 mm and 80.3 mm, respectively. At the end

of the 2-week treatment period, mean VAS scores of xerostomia severity in CCMC and KCMH group were decreased in both group (50.1 and 59.0 mm, respectively) with statistical significance ($p = 0.04$).

At day 14, there were statistically significant differences between groups in mean VAS scores of four variables namely the xerostomia severity (in pain/discomfort domain), speech difficulty, and taste alteration (in physical functioning domain), and frequency of sipping water (an aspect of clinical acceptance). No statistically significant differences in the other variables of the four major domains and the other aspects of clinical acceptance were found between groups. There was no statistically significant difference between groups in any yes/no response variable, but taste alteration (in the physical functioning domain) as shown in **Table 3**.

Table 4 includes the proportion of patients who responded to the treatment and had a major improvement from baseline in various VAS parameters. In both groups, eight patients (32%) reported a response to the treatment as their severity of xerostomia score decreased ≥10 mm. from baseline. However, the proportion of patients who had a major improvement from baseline in CCMC group was higher than KCMH group (17 patients (68%) vs. 11 patients (44%), respectively). The two statistically significant differences between groups were xerostomia severity and speech difficulty ($p = 0.026$ and 0.042, respectively). No statistically significant difference in the proportion of patients who responded or had a major improvement was found between the two groups in the other VAS parameters. No adverse reaction related to both study products was reported.

Table 1. Characteristics of patients, tumors, and treatments

		CCMC group n = 25	**KCMH group n = 25**
Age, years	Mean±SD	48.6±10.27	52.56±12.33
	Median	51	54
Gender, n (%)	Male: Female	12 (48): 13 (52)	15 (60): 10 (40)
Primary cancer site, n (%)	Nasopharynx	19 (76)	16 (64)
	Base of tongue	0	5 (20)
	Floor of mouth	1 (4)	1 (4)
	Maxillary sinus	1 (4)	1 (4)
	Parotid	2 (8)	1 (4)
	Tonsil	2 (8)	1 (4)
Clinical stage, n (%)	Stage I	4 (16)	3 (12)
	Stage II	4 (16)	8 (32)
	Stage III	8 (32)	7 (28)
	Stage IV	9 (36)	7 (28)
Radiation technique, n (%)	Conventional	13 (52)	14 (56)
	IMRT	11 (44)	11 (44)
	3-D CRT	1 (4)	0
Duration after radiation, months	Mean±SD	32.76±46.92	29.83±37.54
	Median	14.40	15.52
Concomitant chemotherapy, %		96	100

IMRT = intensity modulated radiation therapy, 3-D CRT = three-dimensional conformal radiotherapy
No significant differences were found between groups (*t* test for mean and chi-square test for frequency).

Table 2. Responses to Part 1 Xerostomia Questionnaires at day 0 (before) and day 14 (after) of treatment

Parameters	VAS score, mean (SD)		*p*
	CCMC group (n = 25)	KCMH group (n = 25)	
1. Physical functioning			
1.1 Do you have difficulty chewing because of your dry mouth?			
Before treatment	84.0 (10.11)	81.08 (15.16)	<0.001*
After treatment	57.6 (21.73)[a]	59.96 (24.53)[b]	0.33[#]
1.2 Do you have difficulty swallowing because of your dry mouth?			
Before treatment	84.7 (17.16)	82.84 (12.79)	<0.001*
After treatment	61.5 (21.75)[b]	62.16 (25.44)[b]	0.69[#]
1.3 Is speech difficult because of your dry mouth?			
Before treatment	69.2 (21.09)	57.44 (25.23)	<0.001*
After treatment	45.8 (20.98)[b]	45.48 (21.46)[b]	0.03[#]
1.4 Is taste affected by your dry mouth?			
Before treatment	78.0 (21.34)	65.4 (27.78)	<0.001*
After treatment	61.8 (22.61)[b]	57.4 (25.45)[c]	0.04[#]
2. Pain/ Discomfort			
2.1 How dry is your mouth?			
Before treatment	81.2 (8.84)	80.32 (14.69)	<0.001*
After treatment	50.1 (17.8)[a]	58.96 (22.67)[b]	0.04[#]
2.2 Do you have a burning sensation in your mouth?			
Before treatment	64.0 (34.95)	63.88 (33.37)	<0.001*
After treatment	47.8 (32.94)[a]	54.96 (32.13)[c]	0.09[#]
3. Other clinical acceptances			
3.1 Do you have difficulty with sleeping caused by your dry mouth?			
Before treatment	69.56 (25.58)	65.76 (31.58)	<0.001*
After treatment	41.52 (25.36)[a]	44.6 (27.43)[b]	0.38[#]
3.2 How often do you sipping liquids for oral comfort when not eating?			
Before treatment	71.08 (23.08)	67.92 (20.81)	<0.001*
After treatment	45.12 (20.13)[a]	50.88 (22.49)[b]	0.04[#]

The VAS was set up with positive responses on the left and negative responses on the right (for example: 0 = not dry at all, 100 = the worst imaginable dryness).
**t* test, [#]ANCOVA adjusting for baseline difference, [a]The change of mean VAS score was ≥25 mm., [b]The change of mean VAS score was 10-24 mm., [c]The change of mean VAS score was <10 mm.

Table 3. Responses to Part 2 Xerostomia Questionnaires at day 0 (before) and day 14 (after) of treatment

Parameters	Response yes, n (%)		*p*[$]
	CCMC group (n = 25)	KCMH group (n = 25)	
1. Physical functioning			
1.1 Do you have difficulty chewing because of your dry mouth?[a]	22 (88%)	24 (96%)	0.61
Did the product make chewing easier?[b]	18 (72%)	19 (76%)	1.00
1.2 Do you have difficulty swallowing because of your dry mouth?[a]	25 (100%)	25 (100%)	1.00
Did the product make swallowing easier?[b]	17 (68%)	17 (68%)	1.00
1.3 Do you have speech difficulty because of your dry mouth?[a]	21 (84%)	17 (68%)	0.32
Did the product make talking easier?[b]	21 (84%)	16 (64%)	0.20
1.4 Is taste affected by your dry mouth?[a]	24 (96%)	20 (80%)	0.19
Did the product improve your sensation of taste?[b]	16 (64%)	8 (32%)	0.05

Table 3. Responses to Part 2 Xerostomia Questionnaires at day 0 (before) and day 14 (after) of treatment

Parameters	Response yes, n (%)		$p^{\$}$
	CCMC group (n = 25)	KCMH group (n = 25)	
2. Pain/Discomfort			
2.1 Do you suffer from a dry mouth?[a]	25 (100%)	25 (100%)	1.00
Did the product make your dry mouth better?[b]	25 (100%)	22 (88%)	0.24
2.2 Do you have a burning sensation in your mouth?[a]	18 (72%)	18 (72%)	1.00
If you have a burning mouth, did the product improve the burning sensation[b]	9 (36%)	6 (24%)	0.54
2.3 Do you suffer from a dry mouth in the daytime?[a]	23 (92%)	22 (88%)	1.00
Was the product most useful in the daytime?[b]	22 (88%)	20 (80%)	0.70
3. Personal/psychological functioning			
3.1 Do you visit people less frequently because of your dry mouth?[a]	13 (52%)	10 (40%)	0.57
Did you visit people more than you used to?[b]	12 (48%)	5 (20%)	0.07
4. Social functioning			
4.1 Do you avoid speaking to people because of your dry mouth? [a]	14 (56%)	10 (40%)	0.40
Did you speak to people more than you used to?[b]	15 (60%)	8 (32%)	0.09
4.2 Do you stay at home more because of your dry mouth?[a]	14 (56%)	10 (40%)	0.40
Do you get out the house more than you used to?[b]	9 (36%)	4 (16%)	0.20
5. Other clinical acceptances			
5.1 Do you suffer from a dry mouth in the night time?[a]	19 (76%)	18 (72%)	1.00
Did the product stop you waking in the night?[b]	17 (68%)	14 (56%)	0.56
5.2 If you wear dentures, does your dry mouth affect the retention of the dentures?[a]	3 (42.9%)	5 (62.5%)	0.62
If you wear dentures, did the product help with the retention of the dentures? [b]	2 (33.3%)	2 (28.6%)	1.00

[$]Chi-square test, [a]before treatment, [b]after treatment

Table 4. Number of patients who had a response (a decrease of 10 to 24 mm VAS score from baseline) and a major improvement (a decrease of at least 25 mm. VAS score) at the end of treatment.

Parameters	Type of artificial saliva		p^{*}
	CCMC group (n = 25)	KCMH group (n = 25)	
1. Physical functioning			
1.1 Do you have difficulty chewing because of your dry mouth?			0.30
Non-responded	3 (12%)	6 (24%)	
Response	9 (36%)	11 (44%)	
Major improvement	13 (52%)	8 (32%)	
1.2 Do you have difficulty swallowing because of your dry mouth?			0.27
No responded	4 (16%)	9 (36%)	
Response	11 (44%)	8 (32%)	
Major improvement	10 (40%)	8 (32%)	
1.3 Is speech difficult because of your dry mouth?			0.04
No responded	3 (12%)	11 (44%)	
Response	11 (44%)	7 (28%)	
Major improvement	11 (44%)	7 (28%)	
1.4 Is taste affected by your dry mouth?			0.12
No responded	6 (24%)	12 (48%)	
Response	13 (52%)	11 (44%)	
Major improvement	6 (24%)	2 (8%)	

Table 4. Number of patients who had a response (a decrease of 10 to 24 mm VAS score from baseline) and a major improvement (a decrease of at least 25 mm. VAS score) at the end of treatment.

Parameters	Type of artificial saliva		*p**
	CCMC group (n = 25)	KCMH group (n = 25)	
2. Pain/Discomfort			
2.1 How dry is your mouth?			0.03
No responded	0	6 (24%)	
Response	8 (32%)	8 (32%)	
Major improvement	17 (68%)	11 (44%)	
2.2 Do you have a burning sensation in your mouth?			0.18
No responded	9 (36%)	13 (52%)	
Response	11 (44%)	11 (44%)	
Major improvement	5 (20%)	1 (4%)	
3. Other clinical acceptance			
3.1 Do you have difficulty with sleeping caused by your dry mouth?			0.33
No responded	5 (20%)	8 (32%)	
Response	8 (32%)	10 (40%)	
Major improvement	12 (48%)	7 (28%)	
3.2 How often do you sipping liquids for oral comfort when not eating?			0.18
No responded	2 (8%)	4 (16%)	
Response	12 (48%)	16 (64%)	
Major improvement	11 (44%)	5 (20%)	

*Chi-squared statistics

Discussion

RT for HNC causes salivary dysfunction and diminished xerostomia-related QoL [15]. Although, the most effective intervention for reduced salivary function is its prevention such as the advent of parotid-sparing RT technique that has enhanced cytocidal efficiency while reducing damage to healthy tissues [17]. After initial IMRT, direct consequences of xerostomia are still found and improved overtime [18]. While standard RT, xerostomia can cause a lifetime of oral and pharyngeal disorders and multiple oral complaints. Xerostomia has been implicated as factor affecting the QoL [19].

This study demonstrated correlation between patient-reported xerostomia and four major domains of QoL. Xerostomia questionnaires, used in many previous studies [3, 6-8, 14, 16, 20], are an effective method for determining subjective measures of dry mouth and for assessing the results of treatments in patients with xerostomia. CCMC-based saliva substitute was significantly superior to KCMH artificial saliva for four outcome variables with regard to the severity of xerostomia (represented pain/discomfort), difficulty speaking, taste alteration (represented physical functioning), and frequency of sipping water (represented other aspects of clinical acceptance). The same proportion of patients who reported improvement from baseline in CCMC, were better than those with KCMH with regard to severity of xerostomia and difficulty speaking.

Most patients with xerostomia experience difficulty with physical function, such as eating dry or solid foods [19]. In our study, most patients found that both products improved difficulty in chewing and swallowing. This is because the saliva substitute increases moisture in the oral cavity and pharynx, thus oral manipulation and swallowing of food becomes less painful and easier [3]. However, patients still need to drink while eating. This limits their ability to eat normally. Problems with eating can impair oral nutritional intake and may jeopardize continuation of therapeutic radiation and chemotherapy [15]. In cases with speech impairment, CCMC-based saliva substitute achieve a better result than KCMH artificial saliva. However, both saliva substitutes can assist patients with simple speech activities, and especially

those patients who have to do a lot of speaking in their careers (e.g. teachers, salespersonsman, and priests) [7]. Treating xerostomia results in improvement of social and personal functioning and QoL [3].

CCMC-based saliva substitute achieved better results than KCMH for improvement of taste perception. Taste alteration is associated with weight loss and has a profound effect on QoL. Taste impairment alters patterns of food intake and reduces appetite [21]. Temmel et al. [22] reported that "simple" lubricants based on carboxymethylcellulose have little or no effect on whole-mouth gustatory function. However, in patients with taste alteration problems that affect nutritional intake, CCMC-based saliva substitute seemed to be preferable.

The improvement in burning sensation (intolerance to spicy foods) allows patients to eat spicy foods, which are favored by Thais. Thus, both saliva substitutes seem to be effective in helping patients.

Most patients were found somewhat improved personal and social functioning. For other aspects of clinical acceptance, both products improve quality of sleep, although there is no statistically significant difference. However, the CCMC-based saliva substitute showed major improvements in this area. Saliva substitutes minimize interruption of sleep from symptoms of oral dryness by reducing the need to awaken and moisten their mouth [16]. A number of patients were able to gain weight, which made them feel healthier.

CCMC produced a major improvement in the frequency of sipping water (representing other aspects of clinical acceptance), and this was statistically significantly different from KCMH. CCMC had a longer duration of effect than KCMH. This effect can be explained by the different viscosity between these products. CCMC isformulated as a gel, while KCMH artificial saliva is formulated as a liquid. Hahnel et al. [23] reported that for patients with severe xerostomia, high viscosity products such as gels might be preferable to saliva substitutes with lower viscosity. Regelink et al. [24] argued that there is a correlation between the viscosity of saliva substitutes and their clinical efficacy. Momm et al. [7] also reported that the continued use of the product could be explained by the patients as an enduring effect, but also because of its good taste and its easy usage. Treatment of xerostomia appears to be very individualistic and patients might need to try different saliva substitutes to find the most suitable. Patients who find their favorites can choose to combine them. For example a spray (a liquid formula) at daytime and a gel at night [7]. Silvestre et al. [25] reported that the application of a spray is simple and effective, affording immediate relief and with reasonable acceptance among patients with dry mouths.

Epstein et al. [6] found that patients' continued use of an agent depended upon lubrication, duration of action, taste, and delivery system used for the product. The cost of the product may also be an important factor in deciding continued usage on a regular basis during the day. In this study, the cost per volume of KCMH artificial saliva was cheaper than CCMC-based saliva substitute. Cost-effectiveness comparing between these two CMC-based saliva substitutes needs to be evaluated further.

For improvement of retention of dentures, the sample size in our study is too small to determine the overall benefit of saliva substitutes affecting retention of denture.

Five potential factors may have affected our study findings. First, our study was not a crossover design. Each patient received one treatment regimen and the profile of the patients and tumor characteristics between groups in this study were not significantly different. Thus, our study was not concerned about carry-over effect between both products and adequate time for a washout period. Second, we did not correlate the subjective patient-reported symptom scoring with objective measurements. This may have explained the relationship between lack of saliva production and subjective xerostomia [13]. Patient self-reported scores seem to be more reliable in evaluating consequences of severity of xerostomia compared with physician-based assessment. The XQ has been used in many studies evaluating the efficacy of other saliva substitutes [3, 6-8, 14, 16, 20]. In this study, we related our XQ to the fifteen-item XeQoLS [15] that includes four major domains representing QoL. Third, in the patient self-reported study, the inclusion criteria for the similarity of patients in tumor site and stage, radiation dose, field, and technique should be considered. Several factors influenced degree of radiation-induced xerostomia. There was consistent improvement of xerostomia-related symptoms over time. QoL was influenced by the interval since RT and the radiation technique. IMRT may improve QoL over time by reducing the dose to the salivary glands and the volume of other nontargets receiving a high dose, while standard RT does not [18]. In our study,

the correlation between the time interval since RT to radiation techniques was considered for inclusion criteria to provide as homogeneous a population of xerostomia patients as possible. Fourth, it can be considered that a proportion of the observed response may be due in part to a placebo effect. We did not use a placebo in our study for two reasons. Some studies, for example the study of Epstein [6], used a CMC-based saliva substitute as a placebo. Additionally, we believe that it would be inappropriate not to provide any treatment for our patients. Fifth, it is difficult to blind completely because the two preparations are in different dosage forms; one is a gel formulation, the other is a liquid preparation.

Conclusion

Commercially available CMC-based saliva substitutes showed better results in improving severity of xerostomia, speech difficulty, taste alteration, and frequency of sipping water. However, cost-effectiveness comparing these two CMC-based saliva substitutes needs to be considered.

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