A Comparative Study of Carboxymethylcellulose and Enzyme-Containing Saliva Substitute on Quality of Life in Head and Neck Cancer Patients with Self-Reported Postradiation-Xerostomia

นิพนธ์ต้นฉบับ

ฐิรายุ บุญเรือง[1], ธนิตา ณรงค์เดช[1] และ สมฤทัย วัชราวิวัฒน์[2*]

[1] ฝ่ายทันตกรรม โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย กรุงเทพมหานคร
[2] ภาควิชาเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

* **ติดต่อผู้นิพนธ์:** Somratai.r@chula.ac.th

วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2554;6(1):17-24

Original Article

Thirayu Boonroung[1], Tanita Narongdej[1] and Somratai Vadcharavivad[2*]

[1] Dental Department, King Chulalongkorn Memorial Hospital, Bangkok Thailand
[2] Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

* **Corresponding author:** Somratai.r@chula.ac.th

Thai Pharmaceutical and Health Science Journal 2011;6(1):17-24

บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบผลระยะสั้นต่อคุณภาพชีวิตที่สัมพันธ์กับภาวะน้ำลายแห้งในผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับรังสีรักษา ระหว่างผลิตภัณฑ์น้ำลายเทียม 2 ชนิด คือ 1) ชนิดที่มีคาร์บอกซีเมทิลเซลลูโลส (CMC) กับ 2) ชนิดที่มีเอนไซม์ (Enzyme) **วิธีการศึกษา:** ตัวอย่างเป็นผู้ป่วยมะเร็งศีรษะและลำคอ 50 คน ที่ประเมินตนว่ามีคะแนนภาวะน้ำลายแห้งโดยมีvisual analog scale score ≥ 50 มม. แบ่งเป็น 2 กลุ่ม (1:1) โดยการสุ่ม แล้วใช้ผลิตภัณฑ์น้ำลายเทียมชนิด CMC หรือ Enzyme นาน 2 สัปดาห์ ประเมินคุณภาพชีวิตที่สัมพันธ์กับภาวะน้ำลายแห้งก่อนและหลังใช้น้ำลายเทียมด้วยแบบประเมินด้วยตนเองทดสอบความต่างของคุณภาพชีวิตที่สัมพันธ์กับภาวะภาวะน้ำลายแห้งระหว่างกลุ่มโดยพิจารณาความต่างก่อนการทดลองร่วมด้วย โดยสถิติ ANCOVA และทดสอบความต่างของตัวแปรไม่ต่อเนื่องโดย chi-square ที่ระดับนัยสำคัญทางสถิติ 0.05 **ผลการศึกษา**: เมื่อครบ 2 สัปดาห์ พบว่าค่าเฉลี่ยความรุนแรงของภาวะน้ำลายแห้งในกลุ่ม CMC และกลุ่ม Enzyme เท่ากับ 50.1 และ 52.1 มม. ตามลำดับ (*P*–value = 0.87) สัดส่วนตัวอย่างที่ระบุว่าตอบสนองหรือมีคุณภาพชีวิตเพิ่มขึ้นอย่างมากเมื่อเทียบกับค่าตั้งต้นของคะแนนทั้งในมิติด้านหน้าที่ทางกายและความเจ็บปวด/ไม่สบาย รวมถึงความยอมรับทางคลินิกด้านอื่น ๆ ของทั้งสองกลุ่มไม่ต่างกัน **สรุป:** ไม่พบความแตกต่างทางสถิติระหว่างการใช้น้ำลายเทียมที่มีคาร์บอกซีเมทิลเซลลูโลสกับที่มีเอนไซม์เป็นส่วนประกอบต่อคุณภาพชีวิตที่สัมพันธ์กับภาวะน้ำลายแห้ง ในผู้ป่วยมะเร็งศีรษะและลำคอที่มีภาวะน้ำลายแห้ง

คำสำคัญ: ภาวะน้ำลายแห้ง, รังสี, คาร์บอกซีเมทิลเซลลูโลส, สารทดแทนน้ำลาย, คุณภาพชีวิต

Abstract

Objective: To compare short-term effects of two commercially available saliva substitutes, carboxymethylcellulose (CMC) based preparation and enzyme-containing saliva substitute, on xerostomia-related quality of life (QoL) in postradiation head and neck cancer (HNC) patients. **Method:** Fifty HNC patients with xerostomia whose self-rated xerostmia VAS score of ≥ 50 mm were blinded and randomly assigned (1:1) to receive either CMC based (CMC group) or enzyme-containing saliva substitute (ENZ group), each for 14 days. A xerostomia questionnaire was used to evaluate self-rated xerostomia-related QoL. ANCOVA was used to compare response differences adjusting for baseline differences. Chi-square statistics were used to test categorical parameters between groups. *P*-value of < 0.05 was considered significant. **Results:** After treatment, mean VAS scores of xerostomia severity in CMC and ENZ groups were 50.1 and 52.1 mm, respectively (*P*–value = 0.87). Proportions of patients reporting a “response” or “major improvement” from baseline in each of all individual QoL questions, and in other clinical acceptance were comparable between groups. **Conclusion:** No significant difference on xerostomia-related QoL was observed between CMC based and enzyme-containing saliva substitute usage in HNC patients with xerostomia.

Keywords: xerostomia, radiation, carboxymethylcellulose, saliva substitute, quality of life

Introduction

Radiation therapy (RT) is a very effective treatment of head and neck cancer (HNC); however, it generally causes acute and long-term unwanted effects. One of the most common complications is xerostomia, a subjective complaint of dry mouth due to a lack of saliva. Xerostomia can cause difficulty in speech, chewing and swallowing. It also causes altered taste and burning sensation, affects the use of oral prosthesis, and increases risk of dental caries and oral infections.[1,2] These problems may lead to severe and long term oral diseases, and impaired quality of life (QoL) of potentially cured cancer patients.[3,4]

Since it is not possible to correct the cause, treatment of radiation related xerostomia focuses on relieving symptoms. Wetting the oral tissue alleviates the symptoms of xerostomia. There are various preparations of saliva substitutes developed and available for selection. Among

commercial saliva substitute products, carboxymethylcellulose (CMC)-based saliva substitutes have been used and evaluated extensively.[5-7] CMC however does not completely resemble many properties of saliva such as viscosity, wetting, sheeting, stringing, and elasticity.[5] It also does not contain specific antibacterial components and enzymes found in human saliva.

Various kinds of saliva substitute have been developed to help maintain a healthy balance in the mouth and encourage healthy oral flora. These new preparations contain either immunologic components such as immunoglobulins or enzymatic components such as lysozyme, lactoferrin, and lactoperioxidase.[5] It has been reported that the soothing effects of enzyme-engineered saliva substitutes are superior to the effects of CMC based saliva substitutes.[5]

Aside from better soothing effect, enzyme-containing saliva substitutes had no effect on colonization of candida species and cariogenic oral microflora and it did not promote infection in different groups of patients.[5,8,9] Nagy et al[10] also found that enzyme-engineered products assist in controlling oral microbial flora. Furthermore, there were also researches indicating that enzyme-engineered saliva substitute products alleviate the symptoms of radiation-induced xerostomia.[11.12] Self-evaluated QoL represents the individual's sense of well-being which is potentially affected by an illness and its treatment.[13] Performance of contemporary saliva substitutes has been summarized.[14] Previous studies reported effects of saliva substitute in treatment of radiation-induced xerostomia evaluated by either laboratory results or dentist-assessment of clinical performance of patients. Whether enzyme-containing saliva substitute or CMC-based saliva substitute is better in improving patient's self-assessed QoL has not been tested.

The purpose of this present study was to compare the clinical effects of commercially available carboxymethyl-cellulose based saliva substitute with enzyme-containing saliva substitute by using the comprehensive questionnaire related to the Xerostomia-related Quality of Life Scale (XeQoLS). This would guide the selection of the commercially available saliva substitutes for alleviating the distress symptoms of xerostomia in HNC patients.

Materials and Method

Patient selection

This study was a prospective, open-label, comparative study in which two saliva substitute preparations were randomly assigned to patients previously treated with RT for HNC and came in for their regular follow-up visits at the multidisciplinary outpatient clinic at King Chulalongkorn Memorial Hospital. The Institutional Review Board of the Medical School of Chulalongkorn University, Thailand granted approval for this study on August 27, 2009 (IRB Number 200.1/52). The examiner explained the study to each participant who read, agreed, and provided written informed consent before enrollment.

Patients eligible to participate in this study were 18 years or older and had subjective complaints of xerostomia with self-evaluated xerostomia VAS score of ≥ 50mm. All patients had completed either parotid-sparing radiation technique or conventional radiotherapy of 66-70cGy/33-35F with the fields of radiation encompassing the major and minor salivary glands for at least 1 month before enrollment into this study. Those who received bilateral Intensity 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 took nutrition orally and had at least one tenth of their natural teeth remaining. Patients with evidence of a persisting or recurring malignant disease or terminal cancer, and those with Sjögren's syndrome or with medical conditions that cause xerostomia were not included.

The VAS xerostomia scores were translated into a four-grade xerostomia scale[4,15,16], 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), and grade 3 = VAS score between 75 and 100 (completely dry, disturbing).

Patients were instructed to refrain from using any other treatment for xerostomia (e.g., saliva stimulant or other saliva substitutes) two weeks before and during the trial period, but were permitted to take frequent sips of water for their comfort. They were also 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 using the study products if any problems.

Treatment Protocol

Fifty patients were blinded and randomly assigned (1:1) to receive either the commercially available gel formulation of CMC saliva substitutes (GC Dry Mouth Gel®, CMC group), or the gel formula of saliva substitute containing lysozyme, lactoferrin, and lactoperioxidase (Biotene®, ENZ group) for home application for 2 weeks. The containers of the saliva substitutes were weighed prior to dispensing and immediately after the patients returned them to the examiner at the end of the treatment period.

Each patient was instructed to apply a sufficient amount of the saliva substitute on their tongue, gum, and any soft tissue with their fingertip, cotton swab or with their own tongue for at least 4 times a day (before and after meals, and at bedtime) and re-applied between meals as needed whenever they had a dry mouth.

Xerostomia-related Quality of Life Questionnaire

Items of our Xerostomia-related Quality of Life Scale (XeQoLS) were modified from xerostomia questionnaires of Shahdad et al [11], Meirovitz et al[15], and Henson et al.[1] The XeQoLS was translated into Thai language by a dentist and tested in 20 patients before it was adjusted and approved by another two senior dentists. Four major domains of the XeQoLS included physical functioning, personal/psychological functioning, social functioning and pain/discomfort. In addition, the XeQoLS included other aspects of clinical acceptance (Table 2).

The XeQoLS had two parts. Part 1 contained 8 questions with continuous response score derived from a 100 mm. visual analogue scale (VAS) where positive response was placed on the left and negative response on the right (for example, 0 = not dry at all and 100 = the worst imaginable dryness). These 8 questions were asked before and after treatment (questions shown in Table 2). The main VAS question for xerostomia severity asked "How dry is your mouth?" Part 2 contained Yes/No type questions where 12 questions were applicable for pre-treatment, and their accompanying questions for post-treatment. For example, "Do you have difficulty chewing because of your dry mouth?" was accompanied with "Did the product make chewing easier?" In addition, there were 4 additional questions applicable only for post-treatment (Table 2).

Internal consistency of the XeQoLS's VAS scoring questions dichotomous scoring questions was acceptable with Cronbach alpha of 0.84 and KR-20 coefficient of 0.76, respectively. All participating patients completed the pre-treatment questionnaires before randomization (day 0) and the post-treatment questionnaire at the end of treatment period (day 14). The same dentist read the XeQoLS to each patient in Thai language. All patients completed the XeQoLS by themselves without any help or interruption.

Outcome measures

Xerostomia severity level and xerostomia-related quality of life based on 100 mm. VAS, before and after 14 days of treatment were assessed in each group. At the end of the 2-week treatment period, patients with a decrease of 10 – 24 mm. score from baseline were classified as "having a response"; while those with a decrease of $\geq$ 25 mm. from baseline as "having a major improvement" in their symptoms. However, patients with a decrease of <10 mm. from baseline were classified as non-responders.[12,13]

Statistic Analysis

For 1-β = 0.8, and α =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 should be recruited into each group of this study.

Data were analyzed using SPSS for Windows version 17.0. Means and standard deviations of continuous variables were calculated. Patient and tumor characteristics between two groups were compared using t-test or chi-square test when applicable. Analysis of covariance (ANCOVA) was used to compare mean response differences between groups after accounting for pre-existing 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

Fifty patients, 25 in each group, were enrolled into this study. All patients reported grade 2 - 3 xerostomia after receiving conventional RT or bilateral IMRT for HNC with field of irradiation encompassing the major and minor salivary glands. The radiation dose range was about 66 – 70 Gy. Patients who received bilateral IMRT had completed their RT within 12 months before enrollment. Patient and tumor characteristics were comparable between groups (Table 1).

Table 1 Patient and tumor characteristics.

	CMC group (n = 25)	ENZ group (n = 25)
Age (years)		
Mean ± SD	48.6 ± 10.27	50.84 ± 11.88
Median	51	50
Gender, n (%)		
Men	12 (48)	15 (60)
Women	13 (52)	10 (40)
Primary cancer site, n (%)		
Nasopharynx	19 (76)	19 (76)
Base of tongue	0	1 (4)
Floor of mouth	1 (4)	2 (8)
Maxillary sinus	1 (4)	0
Parotid	2 (8)	1 (4)
Tonsil	2 (8)	1 (4)
Floor of nose	0	1 (4)
Clinical stage of cancer, n (%)		
I	4 (16)	2 (8)
II	4 (16)	7 (28)
III	8 (32)	11 (44)
IV	9 (36)	5 (20)
Radiation technique, n (%)		
Conventional RT	13 (52)	11 (44)
IMRT	11 (44)	14 (56)
3-D CRT	1 (4)	0
Duration after radiation (months)		
Mean ± SD	32.76 ± 46.92	31.63 ± 41.83
Median	14.40	12.72
Concomitant chemotherapy (%)	96	96

Note: IMRT = intensity modulated radiation therapy; 3-D CRT = three dimensional conformal radiotherapy. No significant differences between groups (t-test for mean and chi-square test for frequency.

Most patients found that both saliva substitute products were easy to use. The mean quantity of saliva substitute usage in CMC and ENZ groups were 30.44 ± 15.95 g and 39.40 ± 22.93 g, respectively (*P*-value = 0.23, t-test).

At baseline (day 0), mean VAS scores of the main xerostomia severity (How dry is your mouth?) in CMC and ENZ groups were 81.2 and 85.6 mm, respectively. At day 14, such xerostomia severity was alleviated in both groups (mean VAS scores of 50.1 and 52.1 mm, respectively) with no statistical significance (*P*-value = 0.87). At day 14, there were no differences between groups in all other XeQoLS questions and clinical aspects (Table 2).

The proportion of patients who responded to the treatment and those who had a major improvement from baseline in various domains of XeQoLs are shown in Table 3. In both groups, 8 patients (32%) reported a response to the treatment as their severity of xerostomia score improved (i.e., an increase of ≥ 10 mm.) from their baseline and 17 (68%) patients reported a major improvement (i.e., ≥ 25 mm.) of their severity of xerostomia score.

No statistically significant difference in all variables of the four major domains and other aspects of clinical acceptance was found between groups. In addition, no adverse event related to any studied products was reported.

Table 2 Xerostomia related quality of life and other clinical acceptance between the two groups at day 0 and 14 of treatment.

Parameters	**Response by groups**		***P*-value**
	CMC group (n = 25)	**ENZ group (n = 25)**	
1. Physical functioning			
VAS score, mean (SD)			
1.1 Do you have difficulty chewing because of your dry mouth?			
Before treatment	84.0 (10.11)	80.9 (15.58)	< 0.001*
After treatment	57.6 (21.73)	55.4 (22.04)	0.96†
1.2 Do you have difficulty swallowing because of your dry mouth?			
Before treatment	84.7 (17.16)	78.6 (15.50)	< 0.001*
After treatment	61.5 (21.75)	56.1 (22.17)	0.81†
1.3 Is speech difficult because of your dry mouth?			
Before treatment	69.2 (21.09)	56.3 (25.77)	< 0.001*
After treatment	45.8 (20.98)	38.9 (22.48)	0.60†
1.4 Is taste affected by your dry mouth?			
Before treatment	78.0 (21.34)	65.6 (26.26)	< 0.001*
After treatment	61.8 (22.61)	51.1 (23.70)	0.80†
			Contd.

Note: The scale was set up with positive responses on the left and negative responses on the right (e.g., 0 = not dry at all, 100 = the worst imaginable dryness).

* t-test; † ANCOVA adjusting for baseline (before treatment) difference.

Table 2 (contd.) Xerostomia related quality of life and other clinical acceptance between the two groups at day 0 and 14 of treatment.

Parameters	Response by groups		*P*-value
	CMC group (n = 25)	ENZ group (n = 25)	
Dichotomous responses variables, n (%)			
1.5 (before treatment) Do you have difficulty chewing because of your dry mouth?	22 (88%)	23 (92%)	1.00‡
(after treatment) Did the product make chewing easier?	18 (72%)	18 (72%)	1.00‡
1.6 (before treatment) Do you have difficulty swallowing because of your dry mouth?	25 (100%)	25 (100%)	1.00‡
(after treatment) Did the product make swallowing easier?	17 (68%)	18 (72%)	1.00‡
1.7 (before treatment) Do you have speech difficult because of your dry mouth?	21 (84%)	17 (68%)	0.32‡
(after treatment) Did the product make talking easier?	21 (84%)	18 (72%)	0.50‡
1.8 (before treatment) Is taste affected by your dry mouth?	24 (96%)	21 (84%)	0.35‡
(after treatment) Did the product improve your sensation of taste?	16 (64%)	13 (52%)	0.39‡
2. Pain/Discomfort			
VAS score, mean (SD)			
2.1 How dry is your mouth?			
Before treatment	81.2 (8.84)	85.6 (11.30)	< 0.01*
After treatment	50.1 (17.80)	52.1 (16.41)	0.87†
2.2 Do you have a burning sensation in your mouth?			
Before treatment	64.0 (34.95)	66.8 (34.32)	< 0.001*
After treatment	47.8 (32.94)	56.5 (32.41)	0.14†
Dichotomous responses variables, n (%)			
2.3 (before treatment) Do you suffer from a dry mouth?	25 (100%)	25 (100%)	1.00‡
(after treatment) Did the product make your dry mouth better?	25 (100%)	25 (100%)	1.00‡
2.4 (before treatment) Do you have a burning sensation in your mouth?	18 (72%)	19 (76%)	0.59‡
(after treatment) If you had a burning mouth, did the product improve the burning sensation?	9 (36%)	11 (44%)	1.00‡
2.5 (before treatment) Do you suffer from a dry mouth in the daytime?	23 (92%)	23 (92%)	1.00‡
(after treatment) Was the product most useful in the daytime?	22 (88%)	22 (88%)	1.00‡
3. Personal / psychological functioning			
Dichotomous responses variables, n (%)			
3.1 (before treatment) Do you visit people less frequently because of your dry mouth?	13 (52%)	13 (52%)	1.00‡
(after treatment) Did you visit people more than you used to?	12 (48%)	8 (32%)	0.39‡
4. Social functioning			
Dichotomous responses variables, n (%)			
4.1 (before treatment) Do you avoid speaking to people because of your dry mouth?	14 (56%)	10 (40%)	0.40‡
(after treatment) Did you speak to people more than you used to? (at day 14)	15 (60%)	13 (52%)	0.78‡
4.2 (before treatment) Do you stay at home more because of your dry mouth?	14 (56%)	12 (48%)	0.78‡
(after treatment) Do you get out the house more than you used to?	9 (36%)	11 (44%)	0.77‡
5. Other clinical acceptance			
VAS score, mean (SD)			
5.1 Do you have difficulty with sleeping caused by your dry mouth?			
Before treatment	69.56 (25.58)	57.16 (26.71)	< 0.001*
After treatment	41.52 (25.36)	39.12 (23.82)	0.41†
5.2 How often do you sipping liquids for oral comfort when not eating?			
Before treatment	71.08 (23.08)	69.36 (23.19)	< 0.001*
After treatment	45.12 (20.13)	46.92 (20.07)	0.43†
Dichotomous responses variables, n (%)			
5.3 (before treatment) Do you suffer from a dry mouth in the night time?	19 (76%)	20 (80%)	1.00‡
(after treatment) Did the product stop you waking in the night?	17 (68%)	16 (64%)	1.00‡
5.4 (before treatment) If you wear dentures, does your dry mouth affect the retention of the dentures?	3 of 7 (42.9%)	3 of 6 (50%)	1.00‡
(after treatment) If you wear dentures, did the product help with the retention of the dentures?	2 of 7 (28.6%)	1 of 6 (16.7%)	1.00‡
5.5 (after treatment) Did the product improve your quality of life?	22 (88%)	22 (88%)	1.00‡
5.6 (after treatment) Was the product easy to use?	22 (88%)	24 (96%)	0.60‡
5.7 (after treatment) Did you feel better when using this product?	22 (88%)	23 (92%)	1.00‡
5.8 (after treatment) Would you like to continue using this product?	20 (80%)	23 (92%)	0.42‡

Note: The scale was set up with positive responses on the left and negative responses on the right (e.g., 0 = not dry at all, 100 = the worst imaginable dryness).

* t-test; † ANCOVA adjusting for baseline (before treatment) difference; ‡ chi-squared test.

Table 3 Number of patients who had a response (a VAS score decrease of 10 - 24 mm.) and major improvement (a VAS score decrease of ≥ 25 mm.) from baseline.

Parameters	Response by groups		*P*-value*
	CMC group (n = 25)	ENZ group (n = 25)	
1. Physical functioning			
1.1 Do you have difficulty chewing because of your dry mouth?			0.69
number of patients with a VAS score decrease of <10 mm.	3 (12%)	4 (16%)	
number of patients with a response	9 (36%)	11 (44%)	
number of patients with a major improvement	13 (52%)	10 (40%)	
1.2 Do you have difficulty swallowing because of your dry mouth?			0.74
number of patients with a VAS score decrease of <10 mm.	4 (16%)	6 (24%)	
number of patients with a response	11 (44%)	9 (36%)	
number of patients with a major improvement	10 (40%)	10 (40%)	
1.3 Is speech difficult because of your dry mouth?			0.10
number of patients with a VAS score decrease of <10 mm.	3 (12%)	5 (20%)	
number of patients with a response	11 (44%)	16 (64%)	
number of patients with a major improvement	11 (44%)	4 (16%)	
1.4 Is taste affected by your dry mouth?			0.48
number of patients with a VAS score decrease of <10 mm.	6 (24%)	10 (40%)	
number of patients with a response	13 (52%)	10 (40%)	
number of patients with a major improvement	6 (24%)	5 (20%)	
2. Pain/Discomfort			
2.1 How dry is your mouth?			1.00
number of patients with a VAS score decrease of <10 mm.	0	0	
number of patients with a response	8 (32%)	8 (32%)	
number of patients with a major improvement	17 (68%)	17 (68%)	
2.2 Do you have a burning sensation in your mouth?			0.47
number of patients with a VAS score decrease of <10 mm.	9 (36%)	11 (44%)	
number of patients with a response	11 (44%)	12 (48%)	
number of patients with a major improvement	5 (20%)	2 (8%)	
3. Other clinical acceptance			
3.1 Do you have difficulty with sleeping caused by your dry mouth?			0.33
number of patients with a VAS score decrease of <10 mm.	5 (20%)	6 (24%)	
number of patients with a response	8 (32%)	12 (48%)	
number of patients with a major improvement	12 (48%)	7 (28%)	
3.2 How often do you sip liquid for oral comfort when not eating?			0.31
number of patients with a VAS score decrease of <10 mm.	2 (8%)	2 (8%)	
number of patients with a response	12 (48%)	17 (68%)	
number of patients with a major improvement	11 (44%)	6 (24%)	

Note: * Chi-squared statistics.

Discussions and Conclusion

In this randomized study, we examined the efficacy of CMC-based and enzyme containing saliva substitutes on QoL. We used the Xerostomia-related Quality of Life Scale (XeQoLS) which were questions on xerostomia severity we had modified from various studies.[1,11,15] The use of xerostomia severity questionnaire in our study was in accordance with previous studies where they reported the effects of saliva substitute evaluated by the xerostomia questionnaire (XQ).[5-7,11-13] Our study was successful in determining subjective measure of oral dryness and evaluating effects of treatments in patients with xerostomia. After 2 weeks of treatment, we found no statistically significant difference between groups, in each issue in all four major domains of XeQoLS and other aspects of clinical acceptance that related to QoL.

Even though no differences between groups, each of the two saliva substitutes appeared to offer a major improvement in xerostomia severity (representing discomfort issue) and difficulty chewing (representing physical functioning). The results further showed that both products improved physical functioning problems which included difficulty chewing (major improvement) and difficulty swallowing; however, patients still needed to drink while eating. Patients with eating problems which limited their nutritional intake and risked jeopardizing the continuation of therapeutic radiation and chemotherapy, found that saliva substitutes would be an alternative therapy

to improve their ability to eat normally. Also both products were able to help patients with speech difficulty (representing physical functioning). Saliva substitutes can benefit patients with simple activities such as telephone conversation or participation in meetings, and patients who need extensive speaking in their jobs (e.g., teachers, sale persons, and priests).[7,12] Therefore, this means the improvement of the social and personal functioning aspects of quality of life.

Both saliva substitutes also alleviated problem with taste alteration (representing physical functioning). Such improvement was crucial since impaired taste is associated with weight loss through reduced appetite and altered food intake patterns, further profoundly reducing patients' QoL.[14] While Temmel et al[15] reported that these "simple" lubricants containing CMC have little or no effect on whole-mouth gustatory function, our study suggested that in patients whose taste alteration problem affects their nutritional intake, both saliva substitutes seemed to be preferable.

Regarding improvement of burning sensation (intolerance to spicy foods, representing pain/discomfort issue), both saliva substitutes helped patients not to suffer from eating especially spicy foods. Similarly, both products improved quality of sleep in a majority of patients, especially in CMC groups where 48% showed a major improvement. This could be partly due to the effect duration of both saliva substitutes was long enough to reduce the need to awaken to moisten their mouth or to pass urine (as a result of decreased need for fluid ingestion).[12] Some patients gained weight and felt healthier from the improvement in nocturnal sleep pattern (data not shown). A large number of patients in CMC group (44%) also had a major improvement regarding frequency of sipping water.

Enduring effect of saliva substitute may not be a sole reason for continuing use as Momm et al[7] reported that the reason could also be patients' appreciation including the product's good taste and easy usage. Since patients may have very different opinions about taste of the product, the best treatment of xerostomia seems to highly depend on personal preference. Every patient should therefore be encouraged to test different artificial saliva products to find the best individual way to cope with their xerostomia. Cost of different saliva substitutes should also be considered when assisting individual patients to select a preferred agent.

Among patients wearing denture, both products can improve the retention of the denture in 28.6% of patients in CMC group and 16.7% in ENZ group. This is probably because the formulation of both products is gel which usually can improve denture retention and lubrication. However, this benefit is yet questionable since only few patients with denture problems were included in the study.

Four methodological issues in our study should be addressed. First, with recurring outcome characteristics, a relatively short duration of symptom alleviation, and a relatively small sample size, a cross-over study design could have lessened inter-patient variability between the two groups. This however should not be a significant design drawback since the characteristics of our patients were comparable between groups in all aspects.

The second issue is that the correlations between subjective patient-reported scores and objective measures of salivary functions were not determined in this study. Our outcome measures however are still valid and reliable since there has been an advocate for validity of patient self-report of symptom severity during xerostomia treatment. Meirovitz and colleagues[16] reported that patient self-reporting, rather than physician-assessed scores should be the main end point in evaluating xerostomia. Patient self-reported xerostomia related to QoL was consistently significant determinant of treatment intervention throughout post-RT study period. XQ was used in studies evaluating the efficacy of saliva substitutes.[5-7,11-13]

Third, the extent of radiation-induced salivary dysfunction can be influenced by several factors, for instance, radiation dose, the pre-treatment function of salivary gland, radiation technique, the extent of radiation field (especially the volume of the salivary gland receiving full-dose RT). In the patient-self reported study, the inclusion criteria are very important. The homogeneous tumor sites and stage, operation performed (radiation technique and dose, and surgery) should be similar between study groups. Jabbari[19] reviewed that after initial post xerostomia, QoL was improved overtime after IMRT but not after standard RT. Chronic xerostomia is still a considerable problem for QoL in HNC patients after RT. QoL was influenced by the time since RT.[4] In this study, we identified time interval since RT completion so that we could include xerostomic patients as much homogeneous as possible.

The fourth methodological issue is that no placebo-control group was included in our study and it was accepted that the improvement could be partly due to a placebo effect.

It is also not clear that to what extent QoL scores are susceptible to a placebo effect. However, CMC saliva substitute could be considered a controller as in the study of Epstein et al (1999).[5]

In conclusion, we observed no significant difference in all four major domains of xerostomia related quality of life and other aspects of clinical acceptance between CMC based saliva substitute and enzyme-containing saliva substitute usage. Comparing between groups, proportions of patients who reported a response and a major improvement from baseline scores on xerostomia were not different in physical functioning and pain/discomfort domains of xerostomia-related quality of life, and other aspects of clinical acceptance.

Acknowledgements

This study was supported by grants from Chula Quality Improvement Fund, King Chulalongkorn Memorial Hospital.

References

1. Henson BS, Inglehart MR, Eisbrusch A, Ship JA. Preserved salivary output and xerostomia –related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol* 2001;37(1): 84-93.
2. Ship JA, Hu K. Radiotherapy-induced salivary dysfunction. *Sem Oncol* 2004;(suppl 18):29-36.
3. Dirix P, Nuyts S, Van den Boqaert N. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. *Cancer* 2006; 107(11):2525-2534.
4. Dirix P, Nuyts S, Poorten V, Delaere P, van den Boqaert W. The influence of xerostomia after radiotherapy on quality of life. *Support Care Cancer* 2008;16(2):171-179.
5. Epstein JB, Emerton S, Le ND, Stevenson-Moore P. A double-blind cross-over trial of Oral Balance gel and Biotene® toothpaste versus placebo in patients with xerostomia following radiation therapy. *Oral Oncol* 1999;35(2):132-137.
6. Oh DJ, Lee JY, Kim YK, Kho HS. Effects of carboxymethylcellulose (CMC)-based artificial saliva in patients with xerostomia. *Int J Oral Maxillofac Surg* 2008;37:1027-1031.
7. Momm F, Voleqova-Neher NJ, Schulte-Mönting J, Guttenberger R. Different saliva substitutes for treatment of xerostomia following radiotherapy: a prospective crossover study. *Strahlenther Onkol* 2005; 181(4):231-236.
8. Suguira Y, Soga Y, Tanimoto I, et al. Antimicrobial effects of the saliva substitutes, Oralbalance®, against microorganism from oral mucosa in the hematopoietic cell transplantation period. *Support Care Cancer* 2008;16(4):421-424.
9. Suguira Y, Soga Y, Yamabe K, et al. Total bacterial counts on oral mucosa after using a commercial saliva substitute in patients undergoing hematopoietic cell transplantation. *Support Care Cancer* 2010; 18(3):395-398.
10. Nagy K, Urban E, Fazekas O, Thurzo L, Nagy E. Controlled study of lactoperioxidase gel on oral flora and saliva in irradiated patients with oral cancer. *J Craniofac Surg* 2007;18(5):1157-1164.
11. Shahdad SA, Taylor C, Barclay SC, Steen IN, Preshaw PM. A double-blind cross-over study of Biotene Oralbalance and Bioxtra systems as salivary substitutes in patients with post-radiotherapy xerostomia. *Eur J Cancer Care* 2005;14(4):319-326.
12. Warde P, Kroll B, O'Sullivan B, et al. A phase II study of Biotene in the treatment of postradiation xerostomia in patients with head and neck cancer. *Support Care Cancer* 2000;8(3): 203-208.
13. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. *Int J Radiat Oncol Biol Phys* 2003;57(1):61-70.
14. Hahnel S, Behr M, Handel G, Bürgers R. Saliva substitutes for the treatment of radiation-induced xerostomia--a review. *Support Care Cancer* 2009;17(11):1331-1343.
15. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006;66(2):445-453.
16. Dirix P, Nuyts S, Vander Poorten V, Dalaere P, Van den Boquaert W. Efficacy of the Bioxtra dry mouth care system in the treatment of radiotherapy-induced xerostomia. *Support Care Cancer* 2007;15(12): 1429-1436.
17. Ruo Reddar MG, Allis S. Radiotherapy-induced taste impairment. *Cancer Treat Rev* 2006;32(7):541-547.
18. Temmel AF, Quint C, Schickinger-Fischer B, Hummel T. Taste function in xerostomia before and after treatment with saliva substitute containing carboxymethylcellulose. *J Otolaryngol* 2005;34(2):116-120.
19. Jabbari S, Kim HM, Feng M, at al. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. *Int J Radiat Oncol Biol Phys* 2005;63(3):725-731.

Editorial note
Manuscript received in original form on March 4, 2011;
accepted in final form on September 27, 2011