The Effectiveness and Satisfaction of Carboxymethylcellulose Oral Spray on Xerostomia-Related Quality of Life in Post-Radiation Head and Neck Cancer Patients

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Abstract

Radiotherapy is the standard treatment of head and neck cancer (HNC). The radiation may affect surrounding normal tissue and the salivary gland, resulting in xerostomia. The treatment of post-radiation-related xerostomia focuses on relieving symptoms by using saliva substitutes or saliva stimulants. Since salivary stimulants have significant side effects such as sweating, dizziness, or increased urge to urinate, saliva substitutes are preferable. Saliva substitute has been suggested to improve moisture in a dry mouth condition. The form of saliva substitutes may be in oral gel or oral rinse. However, patients complained of the thick consistency of the solution. The purpose of this study is to evaluate the effectiveness and patient satisfaction of carboxymethylcellulose (CMC) oral spray to improve dry mouth condition and quality of life (QoL) in post-radiotherapy patients. Thirty-five post-radiotherapy patients diagnosed with HNC were included to use CMC oral spray. The patients were interviewed with a Xerostomia-related Quality of Life score (XeQoLs) questionnaire and collected saliva, then instructed to use spray for two pumps (approximately 0.4 ml.), 4 times a day, after 3 meals and before bedtime. After 14 days of use, all participants were interviewed with the questionnaire and collected saliva again. The patients had significantly better XeQoLs scores after the use of CMC oral spray in the aspect of physical, pain/discomfort, and psychological dimensions ($P<0.05$) but not in the social dimension ($P>0.05$). Salivary pH and saliva volume were increased after use, but not statistically significant. The results suggested that CMC oral spray can effectively relieve a subjective symptom of oral dryness with adequate patient satisfaction, leading to improve QoL in the post-radiated period for HNC patients.

Keywords: *Head and neck cancer, Post-radiotherapy, Quality of life, Xerostomia, CMC oral spray*

1. Introduction

Xerostomia is a subjective symptom of feeling of dry mouth associated with salivary gland hypofunction. Xerostomia is common in head and neck cancer (HNC) patients treated with radiotherapy. Radiotherapy is a standard treatment for HNC; however, it also has an effect on surrounding normal tissues and causes other functional disorders such as sore throat, altered taste, dental caries due to low pH condition, changes in voice quality effected to speaking, impaired chewing and swallowing function (Plemons, Al-Hashimi, & Marek, 2014). These factors may cause reduced nutritional intake and weight loss and significantly affect general health and quality of life (QoL). Salivary glands are often involved causing reduced salivation and pH of secreted saliva (Dirix, Nuyts, & Van den Bogaert, 2006; Lastrucci et al., 2018)

Currently, the treatment approach for radiation-related xerostomia focuses on relieving symptoms. The symptomatic management of xerostomia includes the use of saliva substitutes and saliva stimulants. However, the saliva stimulants have significant side effects such as increased sweating, dizziness, flushing of the face and neck, chills, or increased urge to urinate. Therefore, saliva substitutes are preferable (Ota et al., 2012; Silvestre-Donat, Miralles-Jorda, & Martınez-Mihi, 2004). The artificial saliva substitutes are in various forms such as moisturizing gel (Boonroung, Narongdej, & Vadcharavivad, 2011), oral rinse, and oral spray (Davies, 1997; Ota et al., 2012). Several products have been reported to physically coat oral tissues for

moisture retention (Ota et al., 2012; Plemons et al., 2014). Most products available in the market contain carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxymethylcellulose, linseed oil, or polyethylene oxide (Hahnel, Behr, Handel, & Burgers, 2009).

The previous study compared two CMC-containing saliva substitutes (oral gel and oral rinse) in HNC patients with dry mouth (Vadcharavivad & Boonroung, 2013). The results demonstrated that an oral gel was more preferable to relieve oral dryness. The patients reported that pain/discomfort, difficulty in speaking, and frequency in sipping water after the use of an oral gel were better than an oral rinse, which may be because the gel formed and stayed longer in oral condition with good flavor. Nonetheless, the oral rinse has been prepared in-house at an affordable cost, therefore, the form of oral rinse is prescribed more often. Because previous studies showed that the oral spray was quick and simple to use (Mardani, Ghannadi, Rashnavadi, & Kamali, 2017; Murakami et al., 2016; Plemons et al., 2014), it may be possible to use as an alternative approach in patients with dry mouth. Therefore, this study will examine the use of an in-house saliva substitute solution in the form of an oral spray, instead of an oral rinse, to relieve oral dryness in HNC patients.

2. Objective

This study aims to examine the effect of CMC saliva substitutes in the form of an oral spray to relieve post-radiation oral dryness after use. The outcomes to be measured are Xerostomia-related Quality of life score (XeQoLs), salivary pH, and saliva volume in HNC patients.

3. Materials and Methods

This clinical study was conducted at the Head and Neck Cancer Unit at King Chulalongkorn Memorial Hospital from January to September 2020. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No.534/62). Thirty-five participants matched with the following inclusion and exclusion criteria were recruited with informed consent. Criteria for inclusion were patients aged over 18 years and previously completed radiotherapy (51-70 Gy) with the fields of radiation encompassing the major and minor salivary glands for at least 1 month. Exclusion criteria were patients with Sjögren's syndrome or other salivary gland diseases, being uncooperative, and on a feeding tube.

The in-house CMC oral spray was prepared by the Pharmacy Department at King Chulalongkorn Memorial Hospital and then refilled in unlabeled 15-ml spray bottles. There was no label on any of the bottles.

Before intervention (Day 0), the participants were interviewed for collection of demographic data, and a baseline Xerostomia-related Quality of Life score (XeQoLs), and then saliva was collected. During the interview, the participants were asked questions from the quality-of-life questionnaire modified from XeQoLs (Henson, Inglehart, Eisbruch, & Ship, 2001) and King Chulalongkorn Memorial Hospital questionnaire in Thai language (Boonroung et al., 2011). The questionnaire consisted of 14 questions and divided into 4 dimensions: physical, pain/discomfort, psychological and social. The subjects were asked to reply in the Visual Analogue Scale (VAS). The VAS was scaled from 0 to 10, in which "0" was the most positive response and "10" was the most negative response; for example, "0" for not dry at all and "10" for the worst imaginable dryness. Index of item objective congruence (IOC) was adjusted to ≥0.5 in every question and was tested in the same subjects for reliability measurement. Internal consistency of the questionnaire was acceptable with Cronbach's alpha of 0.81 (Taber, 2018). For saliva collection, the participants were asked to collect saliva by spitting it out into the tube for 5 mins without stimulation. Salivary pH was measured after the collection by using a pH tester (HI 98100 Checker Plus, HANNA Instruments, Thailand). In the concern of contamination and disease transmission, saliva volume was measured after centrifugation in the biosafety tissue culture hood.

For the intervention, the participants used the given solution spray 4 times a day, after 3 meals, and before bedtime. The patients were instructed to use two pumps (approximately 0.4 ml) each time. After 14 days of use (Day 14), all participants were appointed to the clinic for an interview using the same questionnaire as the baseline time point, and VAS scores were recorded. Saliva collection was performed as

described above, and salivary pH and saliva volume were recorded to analyze the effect of CMC oral spray after use.

All statistical analyses were performed using SPSS software v25.0 (SPSS Inc. New York, NY, USA). Description of the subjects was carried out by descriptive statistics. Shapiro-Wilk test was used for the normality test. Wilcoxon Signed Ranks was used to compare the median before-after intervention differences of XeQoLs scores. Paired T-test was used to compare the mean of salivary pH and saliva volume. The significance level was defined at 0.05.

4. Results and Discussion

4.1 Results

The characteristics of HNC subjects with post-radiation xerostomia were shown (Table 1). The mean age of the patients was 54.1 ± 13.9 years (range: 36-75 years) with 65.7% males and 34.3% females. The two most primary cancer sites were the nasopharynx (71.3%) and oral cavity (20.0%). Other primary cancer sites including the salivary gland, nasal cavity, paranasal sinus, and larynx were about 3%. Most participants were first diagnosed at stage III (48.6%) and stage IV (40%). More than 90% received IMRT/VMAT radiation. Duration after the radiation was 7.1 ± 3.9 months, and about 91% concomitantly received chemotherapy.

Table 1 Characteristics of HNC subjects with post-radiation xerostomia

Characteristics	**n=35**
Age, years	
Mean±SD	54.1±13.9
Range	36-75
Gender, n (%)	
Male	23 (65.7)
Female	12 (34.3)
Primary cancer site, n (%)	
Nasopharynx	25 (71.3)
Oral cavity	7 (20.0)
Salivary gland	1 (2.9)
Nasal cavity and paranasal sinus	1 (2.9)
Larynx	1 (2.9)
Thyroid	-
Stage of cancer, n (%)	
Stage I	1 (2.9)
Stage II	3 (8.6)
Stage III	17 (48.6)
Stage IV	14 (40.0)
Radiation technique, n (%)	
IMRT/VMAT	33 (94.3)
3D	2 (5.7)
Duration after radiation, months	
Mean±SD	7.1±3.9
Range	1-12
Concomitant, n (%)	
Chemotherapy	32 (91.4)

Table2 Comparison of XeQoLs scores before and after treatment with CMC oral spray

Questionnaire	XeQoLs score)Median±IQR(		
	Before	**After**	**ρ-value**
Part 1: Physical			
Q1: Rate your difficulty in chewing due to dryness	4.0 ± 7.0	3.0 ± 5.0	P = 0.002**
Q2: Rate your difficulty in swallowing food due to dryness	5.0 ± 4.0	3.0 ± 4.0	P = 0.000***
Q3: Rate your difficulty in talking due to dryness	3.0 ± 5.0	2.0 ± 4.0	P = 0.003**
Q4: Rate your taste alteration	5.0 ± 4.0	5.0 ± 4.0	P = 0.000***
Part 2: Pain / Discomfort			
Q5: Rate your feeling dry mouth	6.0 ± 3.0	4.0 ± 3.0	P = 0.000***
Q6: Rate the frequency of sipping water (nocturnal)	4.0 ± 5.0	3.0 ± 5.0	P = 0.047*
Q7: Rate the frequency of sipping water (Daytime)	8.0 ± 2.0	6.0 ± 4.0	P = 0.001**
Q8: Rate your pain and discomfort	0.0 ± 2.0	0.0 ± 2.0	P = 0.768
Part 3: Psychological			
Q9: My mouth/throat dryness interferes with my daily activity	2.0 ± 5.0	0. 0 ± 4.0	P = 0.011*
Q10: My mouth/throat dryness makes me nervous	2.0 ± 5.0	0.0 ± 5.0	P = 0.006**
Q11: My mouth/throat dryness reduces my general happiness	0.0 ± 5.0	0.0 ± 4.0	P = 0.019*
Part 4: Social			
Q12: My mouth/throat dryness makes me uncomfortable speaking in front of other people	0.0 ± 2.0	0.0 ± 2.0	P = 0.103
Q13: My mouth/throat dryness makes me uncomfortable when eating in front of other people	0.0 ± 4.0	0.0 ± 4.0	P = 0.169
Q14: My mouth/throat dryness makes me from socializing (going out)	0.0 ± 2.0	0.0 ± 2.0	P = 0.211

*P<0.05; **P<0.01; ***P<0.001
*Wilcoxon Signed Ranks (Median±IQR)

Table 3 Comparison of salivary pH and saliva volume before and after treatment with CMC oral spray

Measurement	**Before (n=25)**	**After (n=25)**	**ρ-value**
Salivary pH	6.8 ± 0.6	7.0 ± 0.7	P = 0.202
Saliva volume (ml)	0.9 ± 0.8	1.0 ± 1.0	P = 0.146

*10 participants drop out.
*Paired T-test)Mean ± SD(

Because of the COVID-19 pandemic, the XeQoLs questionnaire after treatment was performed by phone. The XeQoLs score after treatment with CMC oral spray from 4 categories was presented (Table 2). XeQoLs scores significantly improved after the use of the oral spray in the physical part from Q1 to Q4 about chewing (P=0.002), swallowing (P=0.000), talking (P=0.003), and taste alteration (P=0.000). It was also significantly better in some of the pain/discomfort parts, Q5 (P=0.000), Q6 (P=0.047), Q7 (P=0.001), and psychological part, Q9 (P=0.011), Q10 (P=0.006), and Q11(P=0.019), about oral dryness that could disturb daily activities, and causing nervousness. However, the individual question relating to the social part, including Q12 (P=0.103), Q13 (P=0.169), and Q14 (P=0.211), showed improved scores but not statistically significant.

Ten participants dropped out and denied commuting to the hospital for a collection of salivary pH and saliva volume due to the COVID-19 pandemic and inconvenience. Therefore, 25 of 35 samples were collected after Day 14. Consistent with the improved comfort feeling, salivary pH and saliva volume were increased after the use of CMC oral spray. Mean salivary pH increased from 6.8 ± 0.6 before use to 7.0 ± 0.7 after use (P = 0.202), and mean saliva volume increased from 0.9 ± 0.8 ml to 1.0 ± 1.0 ml (P = 0.146). However, the increases in the salivary pH and saliva volume were not statistically significant (Table 3).

4.2 Discussion

To relieve xerostomia, saliva substitutes contained CMC have been commonly used (Epstein, Emerton, Le, & Stevenson-Moore, 1999; Oh, Lee, Kim, & Kho, 2008). The CMC oral rinse was developed and prepared in-house to be prescribed in HNC patients who experienced oral dryness during and after radiotherapy. The in-house CMC preparation is at affordable cost, but the previous study showed that it had less efficacy to improve oral dryness comparing to other imported products, and less patient satisfaction because of its taste (Vadcharavivad & Boonroung, 2013).

This study demonstrated that CMC oral spray can significantly improve the HNC patients' QoL in many aspects. The comparison of XeQoLs scores before and after the use of CMC oral spray demonstrated better patients' satisfaction. The patients perceived significant improvement when responding to questions relating to oral functions such as chewing, swallowing, talking, and taste perception, relieving pain/discomfort, and having the ability for daily activities, happiness, and well-being. For the questions relating to the social part, the participants were asked about confidence when having socializing activities with friends and families. The scores rating for each question of the social part were not significant. This may be caused by large variations that may dampen the positive effect of the oral spray. The application approach by using an oral spray may favor patients' satisfaction with the in-house CMC products, and therefore increase the efficacy of the in-house CMC preparation to expand its use in the HNC patients.

Time duration of post-radiotherapy seems to influence oral dryness. Salivary flow rate decreased steeply in the first month and gradually increased between 3-6 months after radiotherapy. However, the salivary flow rate could not be recovered to a healthy level as pretreatment (Deasy et al., 2010; Möller, Perrier, Ozsahin, & Monnier, 2004). Similarly, salivary pH declined steeply at 1 month and also later recovered back until 6 months after radiotherapy (Lin et al., 2015). In this study, the average post-radiation duration in CMC oral spray was 7 months, as compared with approximately 30 months in the previous study (Vadcharavivad & Boonroung, 2013). Thus, participants' strong feelings on oral dryness could affect how participants responded to XeQoLs questionnaires and the subjectiveness of oral dryness and pain/discomfort (Tessier, Blanchin, & Sébille, 2017). Similar to salivary pH and saliva volume after using the spray, there were increased but not significant, which may be because the salivary flow rate and pH were still constant or slightly changed after 6 months of post-radiation.

It was clear that CMC oral spray effectively improved subjective symptoms of oral dryness but the advantage of oral spray application over the CMC oral rinse application needs further studies in the larger population.

5. Conclusion

CMC oral spray, which is prepared in-house at an affordable cost, can effectively improve QoL in HNC patients who experienced oral dryness in post-radiation therapy. After use, the patients reported improvement of oral functions, pain and discomfort, nervousness, and confidence in social activities. Thus, the CMC oral spray can be prescribed as a treatment to relieve oral dryness, apart from conventional imported products.

6. Acknowledgements

I would like to express my deeply thankful to my thesis advisors and really thank you Associate Professor Dr. Jeerus Sucharitakul, Department of Biochemistry, Faculty of Dentistry, Chulalongkorn University for help and support in the laboratory process. Moreover, I sincerely thank you Dr. Anussara Prayongrat, Professor Chawalit Lertbutsayanuku, and all staff at King Chulalongkorn Memorial Hospital for their supports. This study was supported by CU Graduate School Thesis Grant.

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