EFFECT OF TREHALOSE SOLUTION SPRAY ON POST-RADIATION XEROSTOMIA RELATED QUALITY OF LIFE IN HEAD AND NECK CANCER PATIENTS

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ผลของสเปรย์สารละลายทรีฮาโลสต่อคุณภาพชีวิตที่เกี่ยวข้องกับภาวะปากแห้งหลังได้รับรังสีรักษาในผู้ป่วยมะเร็งศีรษะและลำคอ

น.ส.กุลปริยา ประวีณวงศ์วุฒิ

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กุลปริยา ประวีณวงศ์วุฒิ : ผลของสเปรย์สารละลายทรีฮาโลสต่อคุณภาพชีวิตที่เกี่ยวข้องกับภาวะปากแห้งหลังได้รับรังสีรักษาในผู้ป่วยมะเร็งศีรษะและลำคอ. (EFFECT OF TREHALOSE SOLUTION SPRAY ON POST-RADIATION XEROSTOMIA RELATED QUALITY OF LIFE IN HEAD AND NECK CANCER PATIENTS) อ.ที่ปรึกษาหลัก : ผศ. ทญ. ดร.อัญชลี วัชรักษะ, อ.ที่ปรึกษาร่วม : รศ. ทญ. ดร.พรพรรณ พิบูลย์รัตนกิจ

รังสีรักษาเป็นการรักษาที่เป็นมาตรฐานในการรักษามะเร็งบริเวณศีรษะและลำคอ โดยการรักษาด้วยรังสีนั้นจะส่งผลต่อเนื้อเยื่อปกติที่อยู่รอบๆบริเวณที่ฉายแสงให้ได้รับผลกระทบไปด้วย ซึ่งจะส่งผลต่อต่อมน้ำลายและนำไปสู่การเกิดภาวะปากแห้ง การรักษาเพื่อบรรเทาภาวะปากแห้ง/น้ำลายน้อยหลังได้รับรังสีรักษาจะใช้น้ำลายเทียมหรือสารกระตุ้นการหลั่งน้ำลาย เนื่องจากกลุ่มสารกระตุ้นการหลั่งน้ำลายมักมีผลข้างเคียงตามมา เช่น ภาวะเหงื่อออกมากผิดปกติ มีนงงสับสน หรือปัสสาวะมากเกินปกติ ดังนั้นกลุ่มน้ำลายเทียมจึงเป็นที่นิยมใช้มากกว่า สารละลายทรีฮาโลสมีคุณสมบัติที่ช่วยในเรื่องของการเก็บกักความชุ่มชื้นจึงถูกนำมาพัฒนาใช้ในการผลิตน้ำลายเทียม วัตถุประสงค์ของการศึกษานี้เพื่อประเมินประสิทธิผลของสารละลายทรีฮาโลสที่ความเข้มข้นร้อยละ10 ในการช่วยให้สภาวะปากแห้ง และคุณภาพชีวิตของผู้ป่วยมะเร็งศีรษะและลำคอหลังได้รับรังสีรักษาดีขึ้นโดยเปรียบเทียบกับสารละลายคาร์บอกซีเมทิลเซลลูโลส ซึ่งเป็นน้ำลายเทียมที่ใช้บ่อยสำหรับผู้ป่วยที่ปากแห้ง ผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับรังสีรักษาเรียบร้อยแล้วจำนวน 70 คน ถูกแบ่งเป็นสองกลุ่มแบบสุ่ม คือ กลุ่มที่ใช้สารละลายคาร์บอกซีเมทิลเซลลูโลสในรูปแบบสเปรย์และกลุ่มที่ใช้สารละลายทรีฮาโลสที่ความเข้มข้นร้อยละ10 ในรูปแบบสเปรย์ ผู้ป่วยจะได้รับการสัมภาษณ์ด้วยแบบสอบถามคุณภาพชีวิต Xerostomia-related Quality of Life scale (XeQoLs) และได้รับคำแนะนำให้สเปรย์ 2 ปั๊ม (ประมาณ 0.4 มล.) วันละ 4 ครั้ง หลังมื้ออาหารสามเวลาและก่อนนอน ผู้ป่วยจะได้รับการสัมภาษณ์ด้วยแบบสอบถามคุณภาพชีวิตหลังใช้สเปรย์ 14 วัน และถูกเก็บตัวอย่างน้ำลายก่อนและหลังใช้สเปรย์ เพื่อวัดปริมาณน้ำลายและค่าความเป็นกรดด่างของน้ำลาย ผลการศึกษาหลังใช้สารละลายทั้ง 2 กลุ่ม ผู้ป่วยมีคะแนนคุณภาพชีวิตที่ดีขึ้นอย่างมีนัยสำคัญทางสถิติในด้านกายภาพ ด้านความเจ็บปวด/ระคายเคือง และด้านจิตใจ ($P<0.05$) ยกเว้นในด้านสังคม ($P>0.05$) เมื่อเปรียบเทียบค่าความต่างของคะแนนคุณภาพชีวิตก่อน-หลังใช้สารละลายคาร์บอกซีเมทิลเซลลูโลสและสารละลายทรีฮาโลสไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($P>0.05$) ค่าความเป็นกรดด่างและปริมาณน้ำลายเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติในกลุ่มที่ใช้สารละลายทรีฮาโลส ($P<0.05$) แต่เพิ่มขึ้นอย่างไม่มีนัยสำคัญทางสถิติในกลุ่มที่ใช้สารละลายคาร์บอกซีเมทิลเซลลูโลส ($P>0.05$) โดยสรุปอาจกล่าวได้ว่าสารละลายทรีฮาโลสในรูปแบบสเปรย์มีประสิทธิผลในการบรรเทาภาวะปากแห้งหลังได้รับรังสีรักษา ซึ่งนำมาสู่คุณภาพชีวิตที่ดีขึ้นของผู้ป่วยมะเร็งศีรษะและลำคอเทียบเท่ากับสารละลายคาร์บอกซีเมทิลเซลลูโลสในรูปแบบสเปรย์

สาขาวิชา	ทันตกรรมผู้สูงอายุและการดูแลผู้ป่วยพิเศษ	ลายมือชื่อนิสิต .....
ปีการศึกษา	2563	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
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Kulpriya Pravinvongvuthi : EFFECT OF TREHALOSE SOLUTION SPRAY ON POST-RADIATION XEROSTOMIA RELATED QUALITY OF LIFE IN HEAD AND NECK CANCER PATIENTS. Advisor: Asst. Prof. ANJALEE VACHARAKSA, D.D.S., Ph.D Co-advisor: Assoc. Prof. PORNPAN PIBOONRATANAKIT, D.D.S., M.Sc., Ph.D

Radiotherapy is the standard treatment of head and neck cancer (HNC). The radiation may affect on normal tissue and surrounding salivary gland resulting to xerostomia. Treatment of radiation-related xerostomia focuses on relieving symptoms by using saliva substitutes or saliva stimulants. Because the salivary stimulants have significant side effects, such as sweating, dizziness or increasing urge to urinate, saliva substitutes are preferable. Trehalose solution has been suggested for improve moisture in dry mouth condition and can be used as saliva substitute. The purpose of this study is to evaluate the effectiveness of 10% Trehalose solution spray to improve dry mouth condition and quality of life (QoL) in post-radiotherapy HNC patients compared with carboxymethylcellulose (CMC) solution spray, which is commonly prescribed for dry mouth patients. Seventy post-radiotherapy patients diagnosed with HNC were included and randomly divided into two groups; to use CMC or Trehalose solution spray. Patients were interviewed with a Xerostomia-related Quality of Life scale (XeQoLs) questionnaire, and 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 again. Saliva was collected before and after use interventions 14 days for measurement of saliva volume and salivary pH. Patients significantly had better XeQoLs scores after use of either CMC or Trehalose solution spray in the aspect of physical, pain/discomfort, and psychological dimensions ($P<0.05$) but not social dimension ($P>0.05$). When compared between CMC and Treholose solution spray, the before-after intervention differences of XeQoLs scores were not significantly different ($P>0.05$). Salivary pH and saliva volume were significantly increased after use Trehalose solution spray ($P<0.05$), but not statistically significant increased after use CMC solution spray ($P>0.05$). In conclusion, Trehalose solution spray can effectively relieve post-radiation xerostomia leading to improve QoL of HNC patients comparable with CMC solution spray.

Field of Study:	Geriatric Dentistry and Special Patients Care	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....
		Co-advisor's Signature .....

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Kulpriya Pravinvongvuthi

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

Chapter I INTRODUCTION

Background and Rationale

Xerostomia is a subjective symptom of feeling of dry mouth that is associated with salivary gland hypofunction.[1] Xerostomia is frequently found in the head and neck cancer (HNC) patients treated with radiotherapy. Radiotherapy is a standard treatment for HNC; however, it also has effect on surrounding normal tissues and causes other functional disorders such as sore throat, altered taste, dental caries, changes in voice quality effecting to speaking, impaired chewing and swallowing function. 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.[2, 3]

Currently, treatment approach for radiation-related xerostomia focuses on relieving symptoms. The symptomatic management of xerostomia includes the use of saliva substitutes or 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.[4, 5] The artificial saliva substitutes are in various forms such as moisturizing gel, oral rinse and oral spray.[4, 6] The form of oral rinse is often prescribed; however, previous studies showed that the oral spray was quick and simple to use in patients with dry mouth.[1, 7, 8] Several products have been reported to physically coat oral tissues for moisture retention.[1, 4] Most products available in the market contain carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxymethylcellulose, linseed oil, or polyethylene oxide.[9]

Trehalose is a nonreducing disaccharide with two glucose units (1,1-glycosidic linkage). This sugar is reported in many organisms, including bacteria, yeast, fungi, insects, invertebrates, and lower and higher plants.[10] Trehalose is safe for using as a dietary ingredient approved by U.S. Food and Drug Administration (FDA).[11] Due to moistening property of Trehalose, a previous study showed that Trehalose protected corneal epithelial cells from dehydration and protected cells and cellular protein from oxygen radical damage.[12] Previous study, using 3% Trehalose as an adjuvant treatment of dry eyes after Laser In-Situ Keratomileusis (LASIK) showed an

improvement in the objective and subjective parameters of tear quality compared to treatment with hyaluronic acid (HA) solution (conventional treatment).[13] To be used in the oral cavity, Trehalose is not only a low cariogenic, but also an anti-cariogenic substance. Although Trehalose is sugar, it is not a substrate for glucosyltransferase and can inhibit synthesis of water-insoluble glucan that is the major factor to promote dental caries.[14]

The moisturizing oral spray containing 10% Trehalose solution has been first time reported in the study by Mori et al.[15] Ten healthy patients were under a high power-vacuum inducing drying condition when the Trehalose oral spray was applied. The results showed that Trehalose solution reversed the oral moisture based on reduction in the percent shrinkage of fungiform papillae.[15] Consistently, Ota et al[4] showed significantly improved symptoms of dry mouth in cancer patients after using micro-gel spray for one week. Furthermore, our previous preliminary study revealed that the subjective oral moistening feeling in healthy adults were increased but not significantly different among the various concentrations of Trehalose solution spray (5, 10, 15 and 20% in gram per 100 ml) (unpublished data). However, there is still no study using Trehalose solution spray in xerostomia patients with HNC after radiotherapy.

Research questions

Can Trehalose solution spray improve QoL on post-radiation xerostomia in HNC patients?

Research objectives

1. To assess QoL score, saliva volume and salivary pH before and after treatment with Trehalose solution spray.

2. To assess QoL score, saliva volume and salivary pH before and after treatment with CMC solution spray.

3. To compare QoL score, saliva volume and salivary pH between treatment with Trehalose solution spray and CMC solution spray.

Research hypothesis

Trehalose solution spray can improve QoL in the patients with xerostomia more than CMC solution spray.

Scope of research

This study focused on the efficacy of 10% Trehalose oral spray to reduce oral dryness symptoms and improve the QoL in patients with radiotherapy-induced xerostomia.

Limitation

The data collection in this study was restricted because of various factors. Patients had to participate in 2 visits; the first visit was the same appointment as the radiologist, but the second was after using oral spray 2 weeks. Due to the COVID-19 situation, some patients had difficulties to commute causing a delay in data collection, and loss of some patients.

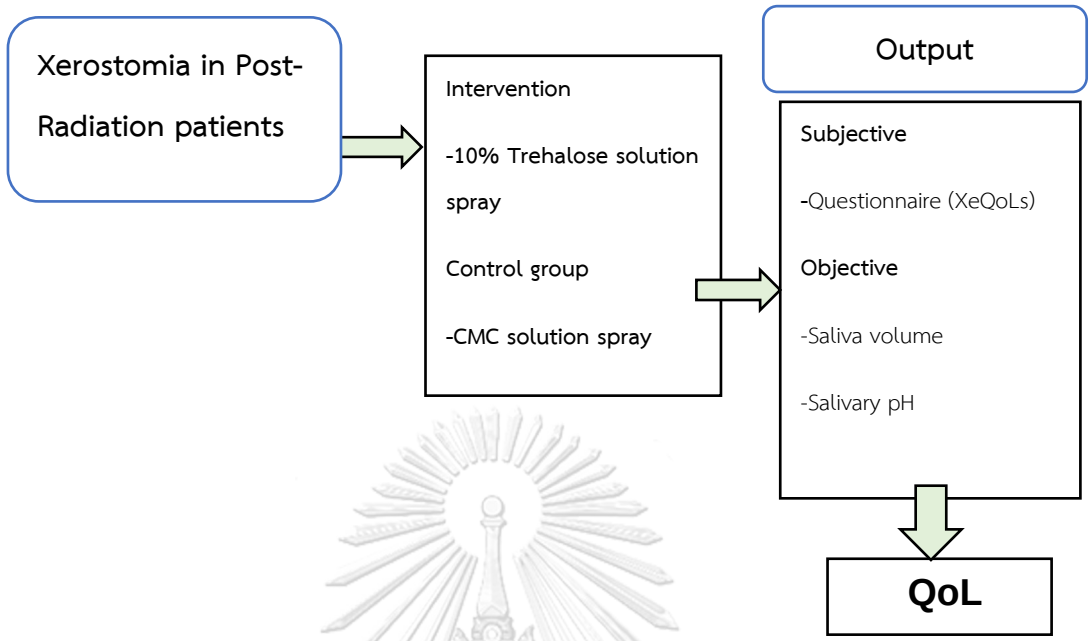
Keywords

head and neck cancer, moistening, post-radiotherapy, quality of life, Trehalose, xerostomia

Research design

Clinical and laboratory research

Conceptual framework



Chapter II LITERATURE REVIEW

Saliva and saliva flow stimuli

Saliva plays an important role in oral health monitoring, regulating and maintaining the integrity of the oral hard tissues and soft tissues.[16] Saliva functions are protection against bacteria and fungi, transportation of nutrients and digestive enzymes, lubrication of the oral cavity.[17] Furthermore, saliva components contribute to mucosal coating and provision of antimicrobial action and defense as well as digestive actions.[18] Eating can stimulate the secretion of saliva by the major salivary glands. Large volumes of saliva are secreted before, during, and after eating via the gustatory salivary reflex, masticatory-salivary reflex, olfactory-salivary reflex, and esophageal-salivary reflex.[19]

However, the detail of secretion mechanisms in the minor salivary glands is unclear due to difficulty in collecting and quantifying the volume from the minor salivary glands.

Shizuko et al, 2018[19] showed that the subjective feeling of dry mouth was more strongly related to a reduction in minor salivary gland flow than that in whole salivary flow. This finding suggested an important role of the minor salivary glands in xerostomia.[19, 20] Although the minor glands produce less than 10% of the total volume of saliva but they play an important role in lubricating the mucosa.[18]

Shizuko et al, 2018[19] studied the effects of five basic taste stimuli (sweet, salty, sour, bitter, and umami) on reflex salivation in the human labial minor salivary glands (LMSGs). The result indicated that basic tastes can induce the gustatory-salivary reflex in human LMSGs and that parasympathetic regulation is involved in this mechanism.[19]

Post-radiation effect of salivary flow rate and salivary pH

Salivary gland dysfunction is a common side effect of radiotherapy in HNC patients.[21, 22] The total dose for a course of radiotherapy for HNC is 50 Gy to 70 Gy. However, doses over 52 Gy cause severe salivary gland dysfunction.[23, 24]

Saliva hyposalivation can be prevented by restricting mean parotid gland

doses to 26-30 Gy. However, some patients received parotid gland doses more than 30 Gy but they did not have xerostomia. These depend on individual physical factors, age and care.[25]

Many articles have reported salivary flow rate decreasing steeply at 1 month after radiotherapy and recovered after the 3 months to the 6 months, but the flow rate could not return to the pretreatment level.[26, 27] Möller et al reported that salivary flow rate slowly recovered 4-months after radiotherapy but could not return to the original level.[28] Same as the salivary pH, Lin et al showed that salivary pH declined steeply at 1 month after radiotherapy and later recovered back at 6 months after radiotherapy.

Post-radiation xerostomia related quality of life in head and neck cancer patients

QOL is a subjective assessment of the impact of an illness or treatment on physical, functional, psychological, social, and general well-being.[29] Recently, QOL has been known as an important outcome parameter in HNC patients that received many side effects from treatment by radiotherapy.[30, 31]

Xerostomia is defined as the subjective perception of dry mouth associated with salivary gland hypofunction.[1, 32] Hyposalivation, a pathologic low saliva secretion, is commonly defined as a resting whole saliva flow rate of less than 0.1 ml/min and/or a stimulated whole saliva flow rate of less than 0.5 ml/min.[33]

Xerostomia is a predictable side effect of radiotherapy to the head and neck region, and is associated with a significant impairment of QoL by oral discomfort and impaired oral functions.[34]

Radiotherapy is regular current standard treatment modality in HNC.[30, 35] This method destroys tumor cells and effects on surrounding normal tissues. Salivary glands are often involved in causing reduced salivation.[36] Saliva is an important host defense component of the oral cavity. Reduction of saliva flow leads to functional oral disorders such as sore throat, altered taste, dental caries, changes in voice quality effecting speaking, impaired chewing and swallowing function. These factors

may cause reduced nutritional intake, weight loss and significantly affect oral health-related quality of life (OHRQoL).[37-39]

Xerostomia Quality of life scale (XeQoLs) questionnaire

QOL is known as an important outcome parameter in HNC patients. The questionnaires have been developed increasingly in recent years.

Heutte et al, 2014 showed the most frequently utilized questionnaire were: the EORTC QLQ-H&N35, University of Washington QOL questionnaire (UWQOL), the FACT-HN, and the University of Michigan Head and Neck QOL questionnaire (HNQoL) (table1).[40] Another frequently used questionnaire, Xerostomia-Related Quality of Life Scale questionnaire (XeQoLs), had been developed from University of Michigan Head and Neck QOL questionnaire (table1).[35, 38, 41] XeQoLs was used in many studies that related the QoL in xerostomia patients. It was translated in own languages by native speakers such as in Italian,[2] and French.[42] XeQoLs is a validated questionnaire to measure on 15 items, grouped into 4 domains (physical functioning, personal/psychological functioning, social functioning, pain/discomfort).[41]

In Thailand, there are few studies about xerostomia-related QOL especially in post-radiation HNC. Boonroung et al, in 2011 compared QOL between CMC and enzyme-containing saliva substitute in HNC patients with self-reported post radiation-xerostomia.[38] They used XeQoLs that were modified from xerostomia questionnaires of Shahdad et al[35], Meirovitz et al[43], and Henson et al[41] The XeQoLs was translated into Thai language by 4 dentists and tested for the internal consistency (Cronbach alpha=0.84 and KR-20 coefficient=0.76).[38]

Table 1 *The most frequently utilized HNC QOL questionnaires and Xerostomia-related Quality of Life scale (XeQoLs)*

Scale	Domain of measurement	Benefit and Limitation
1. EORTC QLQ-H&N35[44]	7 dimensions: pain, swallowing, taste/smell, speech, eating in public, social life, sexuality	**Benefit**: General assessment of health-related QoL in clinical studies of H&N cancer patients **Limitation:** Multiple dimensions, the scales were not specific to xerostomia
2.Fact-H&N[45]	4 dimensions: physical, social/family, emotional, functional well-being	**Benefit**: Suitable for measurement general performance status of patients between cancer treatment **Limitation** The scales were not specific to xerostomia
3.University of Washington Questionnaire (UW-QOL)[46]	12 items: pain, appearance, activity, leisure, swallowing, mastication, speech, shoulder dysfunction, taste, production of saliva, mood, anxiety	**Benefit:** Suitable tool for screening cases in the routine clinical checkup **Limitation** Multiple dimensions, the scales were not specific to xerostomia
4.University of Michigan Head and Neck QOL questionnaire (HNQoL)[47]	4 dimensions: pain, communication, feeding and emotion	**Benefit:** To general assess HNC related functional status and well-being **Limitation:** The scales were not specific to xerostomia
5.Xerostomia-related Quality of Life scale (XeQoLs) [40]	4 dimensions: physical, psychological, social, pain/discomfort	**Benefit:** Specific for HNC function due to salivary gland hypofunction **Limitation:** May not be suitable for measurement general performance status of patients

Saliva substitutes

Currently, treatment of radiation related xerostomia focuses on relieving symptoms. Increasing moistening of oral tissue can alleviate the symptoms of xerostomia.[38, 48]

The symptomatic management of xerostomia includes the use of both saliva substitutes and saliva stimulants. However, the salivary stimulants; Pilocarpine hydrochloride and cevimeline hydrochloride, which work as stimulators of muscarinic and cholinergic receptors have significant side effects. The side effects such as gastrointestinal dysfunction and sweating limit their use.[4, 5] The alternative therapy is given for dry mouth, with use of saliva substitutes in form of moisturizing gels, rinses and sprays.[49, 50]

Moreover, products for managing xerostomia include buccal patches, toothpastes, mouthwashes, tablets, aerosols, gels, and chewing gums containing xylitol.[51] In spite of the variety of formulations for treatment of xerostomia, there is no clear consensus as to which is the most effective agent for relief of symptom of dryness.[51] Among saliva substitutes, solutions containing sodium carboxymethylcellulose (CMC) or animal mucins have been used and evaluated extensively.[52] None of these has serious side effects and all have been investigated for a long time.[53] The major property of CMC is to coat oral mucosa and improve dry mouth but not simulate saliva.[54] However, the commercially available mucin-containing spray, was not superior than the placebo.[55]

The previous study compared two CMC containing saliva substitutes (oral gel and oral rinse) in HNC patients with dry mouth.[56] The results demonstrated that oral gel was more preferrable to relieve oral dryness. The patients reported that pain/discomfort, difficulty in speaking, and frequency in sipping water after the use of oral gel were superior than the oral rinse. This may be resulting from the fact that the gel formed and stayed longer in oral condition with good flavor. Nonetheless, the oral rinse has been prepared in-house at affordable cost, therefore the form of oral rinse is prescribed more often.[38] Because previous studies showed that the oral

spray was quick and simple to use,[1, 7, 8] it may be possible to use as alternative approach in patients with dry mouth.

A new method has recently been developed for evaluation of moisture retention based on the survival rate of dried oral mucosal cells as an objective marker for comparison of moisturizing ingredients which we referred to as a micro-gel spray.[4] The micro-gel spray contained glycerine, gellan gum and glycosyltrehalose. The micro-gel spray significantly improved symptoms of dry mouth at night time.[4]

Trehalose

Trehalose is safe for using as a dietary ingredient improved by U.S. Food and Drug Administration (FDA).[11] Trehalose is a nonreducing disaccharide containing two glucose units (1,1-glycosidic linkage). This sugar is present in many organisms, including bacteria, yeast, fungi, insects, invertebrates, and lower and higher plants.[57] It has been suggested that Trehalose is capable of preventing dental caries. Trehalose is not only a low cariogenic, but also an anti-cariogenic substance because it is not a substrate for glucosyltransferase and can inhibit synthesis of water-insoluble glucan that is the major factor to promote dental caries.[14] By moistening property of Trehalose, previous study showed that Trehalose protected corneal epithelial cells from dehydration and protected cells and cellular protein from damage by oxygen radicals.[12] Findings from clinical study by Emanuele et al in 2014, suggested that Trehalose could protect eyes from cellular damage induced by UVB rays and could reduce the chance of getting dry eyes.[58] Fariselli et al revealed that treatment with a Trehalose/hyaluronate tear substitute decreased ocular discomfort symptoms, surface damage, and tear cytokine levels in dry eye patients.[59] Previous study, using 3% Trehalose as an adjuvant treatment of dry eyes after LASIK showed an improvement in the objective and subjective parameters of tear quality compared to treatment with hyaluronic acid (HA) solution as conventional treatment.[13]

Trehalose plays a key role in stabilizing protein membranes. It can also inhibit protein denaturation from elimination of water at protein surface when cells are in hydrated state.[60] In the cosmetic industry, Trehalose is used as a moisturizing ingredient which effectively protects properties of liposomes contained in cosmetic

products same as lipids and proteins that presented in the skin.[61]

In dentistry, Mori et al used 10% Trehalose solution to reduce oral dryness. The result found that the 10% Trehalose solution prevented the shrinkage of fungiform papillae and atrophy of the tongue mucosa and maintained moisture under drying condition in healthy volunteers.[15]

Morito et al found that long-term treatment with glycosyltrehalose significantly inhibited epithelial cell death due to drying.[62] Ota et al developed a new moisturizing product (micro-gel spray). The micro-gel spray significantly improved symptoms of dry mouth at night and on awakening in cancer treatment patients.[4]

Our previous study used Trehalose solution spray with different concentration (5%, 10%, 15% and 20% in gram per 100 ml) to evaluate the subjective oral moistening feeling in healthy adults compared with using control glucose solution spray. The result found that Trehalose solution spray increased subjective oral moistening feeling but not statistically significant. No significant differences among each concentration of Trehalose solution spray in increasing unstimulated salivary flow rate. (unpublished data).

Chapter III RESEARCH METHODOLOGY

Sample size

Sample size was calculated by using n4studies application version1.4.1.

Sample size was calculated from the study of Gerardo Gomez-Moreno et al in 2014[63]: at alpha = 0.05 and beta = 0.2

Sample size was 29 subjects per group. Allowing for a dropout rate of approximately 10% so at least 32 subjects should be recruited into each group. In this study, 35 subjects were included in each group.

Study population

This study was conducted at 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). Seventy participants matched with the following inclusion and exclusion criteria were recruited with informed consent. Criteria for inclusion were patients who had previously completed radiotherapy (51–70 Gy) with the fields of radiation encompassing the major and minor salivary glands for at least 1 month and over 18 years of age. Exclusion criteria were patients with Sjögren's syndrome or other salivary gland diseases, being uncooperative and on feeding tube. Patients were randomly assigned for using interventions.

Pilot questionnaires

The study used the quality-of-life questionnaire for the main measurement. The questionnaire was modified from Xerostomia-related Quality of Life scale (XeQoLs) (table1) and King Chulalongkorn Memorial Hospital questionnaire.[35, 38, 41, 43] and translated into Thai language by 4 dentists.

The questionnaire consisted of 14 questions and divided into 4 dimensions:

1. Physical: 4 questions
2. Pain/discomfort: 4 questions
3. Psychological: 3 questions
4. Social: 3 questions

Index of item objective congruence (IOC) was adjusted to ≥0.5 in every question and was tested in the same subjects for reliability measurement with Cronbach's alpha of 0.81.[64] (The questionnaire tested in 18 patients).

The subjects were asked to reply in 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.

Test solution preparation

1. 10% Trehalose solution spray

Trehalose solution spray was prepared, sterilized and packaged in the unlabeled 15-ml spray bottles. Briefly, Trehalose powder (TREHA®, Nagase America LLC., USA) was weighed and dissolved in sterilized drinking water to produce 10% Trehalose solution (10 g in 100 mL). Potassium metabisulfite was added for a preservative to final concentration of 0.05%.[4, 62]

2. CMC solution spray

CMC solution spray was purchased from Pharmacy Department at King Chulalongkorn Memorial Hospital, and then refilled in unlabeled 15-ml spray bottles identical to CMC spray bottles.

Data collection

Before intervention (Day 0), the participants were interviewed for collection of demographic data. Then, the participants were asked to collect saliva by splitting out into the tube for 5 mins without stimulation in the private room.

Salivary pH was measured after the collection by using pH tester (HI 98100 CHECKER PLUS, HANNA INSTRUMENTS, THAILAND). Salivary pH was calibrated each day before measurement with 3 standard buffering solutions (pH 4, 7 and 10)

In the concern of contamination and disease transmission, saliva volume was measured after centrifugation in the biosafety tissue culture hood in the same day.

For the intervention, the participants used the given solution spray for 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 the intervention spray after use.

Statistical analysis

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 normality test. Wilcoxon Signed Ranks was used to compare the median before-after intervention differences of XeQoLs scores. Independent T-test was used to compare the means of parotid gland mean doses between ipsilateral and contralateral sides in each intervention group and between Trehalose and CMC solution spray groups, saliva volume and salivary pH between Trehalose and CMC solution spray groups. Paired T-test was used to compare saliva volume and salivary pH at baseline and after using intervention in each intervention group. The significance level was defined at 0.05.

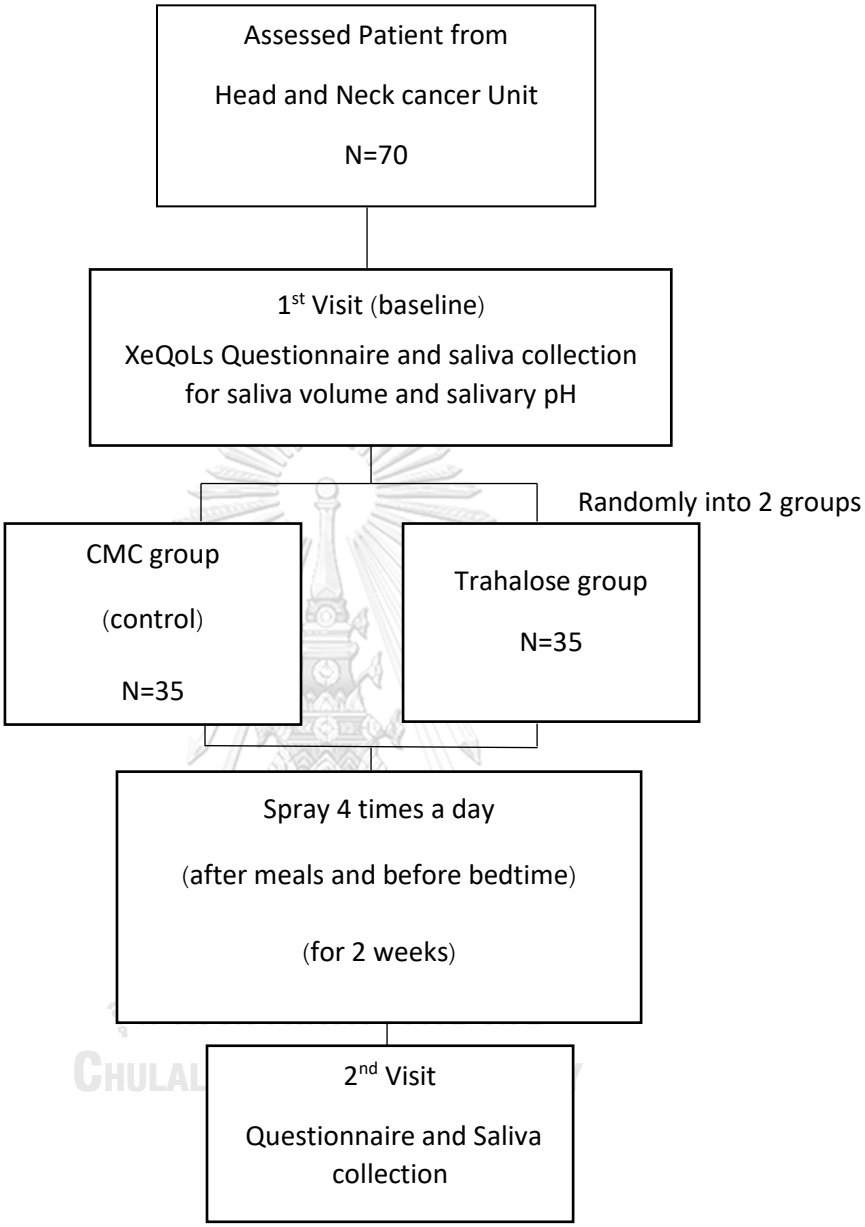


Figure 1 *Methods of this research*

Chapter IV RESULTS

Characteristics of subjects

Table 2 showed the characteristics of 70 HNC patients with post-radiation xerostomia. There were 35 patients in each of CMC and Trehalose solution spray group. The mean age of patients was 54.14±13.89 years (range: 36-75 years) and 58.29±14.75 (range: 22-85 years) in CMC and Trehalose groups, respectively. Numbers of male and female in both groups were relatively similar (male 65.71% and female 34.29% in CMC group; male 62.86% and female 37.14% in Trehalose group). The two most primary cancer sites in both groups were the nasopharynx (71.42% in CMC and 31.43% in Trehalose group) and the oral cavity (20% in CMC and 34.29% in Trehalose group). Other primary cancer sites including salivary gland, nasal cavity and paranasal sinus and larynx were about 3% in CMC group, but 10% in Trehalose group. The most common stage of cancer of the patients was stage III (48.56% in CMC and 37.14% in Trehalose group), followed by stage IV (40% in both groups). More than 90% in each group received Intensity Modulated Radiation Therapy/Volumetric Modulated Radiation Therapy (IMRT/VMAT). Duration after radiation in CMC group was 7.06±3.86 months and 4.71±3.41 months in Trehalose group. About 91% and 66% in CMC and Trehalose groups concomitantly received chemotherapy.

Table 2 *Characteristics of HNC subjects with post-radiation xerostomia*

Characteristics of subjects	Intervention group	
	CMC group (n=35)	Trehalose group (n=35)
Age (years)		
mean±SD	54.14±13.89	58.29±14.75
Range	36-75	22-85
Gender, n (%)		
Male	23 (65.71%)	22 (62.86%)
Female	12 (34.29%)	13 (37.14%)
Primary cancer site, n (%)		
Nasopharynx	25 (71.42%)	11 (31.43%)
Oral cavity	7 (20%)	12 (34.29%)
Salivary gland	1 (2.86%)	3 (8.58%)
Nasal cavity and paranasal sinus	1 (2.86%)	4 (11.42%)
Larynx	1 (2.86%)	4 (11.42%)
thyroid	-	1 (2.86%)
Stage of cancer, n (%)		
Stage I	1 (2.86%)	1 (2.86%)
Stage II	3 (8.58%)	7 (20%)
Stage III	17 (48.56%)	13 (37.14%)
Stage IV	14 (40%)	14 (40%)
Radiation technique, n (%)		
IMRT/VMAT	33 (94.29%)	32 (91.42%)
3D	2 (5.71%)	3 (8.58%)
Duration after radiation (months)		
Mean±SD	7.06±3.86	4.71±3.41
Range	1-12	1-11
Concomitant Chemotherapy, n (%)	32 (91.42%)	23 (65.71%)

Parotid glands mean dose (Gy) in HNC subjects with post-radiation xerostomia

Table 3 *Comparison both sides of parotid gland mean dose (Ipsilateral and Contralateral) between CMC and Trehalose group.*

	Parotid gland mean dose (Gy) Mean±SD		ρ-value
	CMC group (n=35)	Trehalose group (n=35)	
Ipsilateral (Gy) Mean±SD	28.59± 10.37	27.74±15.67	P=0.791
Contralateral (Gy) Mean±SD	23.70±6.38	21.71±12.17	P=0.396
ρ-value	P=0.000*	P=0.000*	

**P<0.001*

The result in table 3 showed comparison both sides of parotid gland mean dose. There were no significant differences of parotid gland mean doses in ipsilateral side (P=0.791) and contralateral side (P=0.396) between Trehalose and CMC solution spray groups. There were significant differences between ipsilateral and contralateral parotid gland mean doses in both CMC and Trehalose solution spray groups (P=0.000).

Because of the COVID19 pandemic and inconvenient transportation, XeQoLs questionnaire after treatment was performed by phone. Twenty participants dropped out and denied commuting to the hospital for a collection of salivary pH and saliva volume. Therefore, 50 of 70 samples were collected after Day 14.

Salivary pH and saliva volume in HNC subjects with post-radiation xerostomia

Table 4 *Comparison of salivary pH and saliva volume before and after treatment with CMC and Trehalose solution spray*

Intervention group	(mean±SD)		ρ-value
	Before (Day 0)	After (Day 14)	
CMC group (n=25)			
Salivary pH	6.78±0.64	6.96±0.7	P=0.202
Saliva volume (ml)	0.86±0.82	0.96±0.99	P=0.146
Trehalose group (n=25)			
Salivary pH	6.91±0.67	7.16±0.56	P=0.033*
Saliva volume (ml)	0.82±1.12	0.99±1.20	P=0.009**

**P<0.05; **P<0.01*

Table 5 *The mean difference of salivary pH and saliva volume before and after treatment between CMC and Trehalose group*

	Intervention group (mean±SD)		ρ-value
	CMC group (n=25)	Trehalose group (n=25)	
Salivary pH	0.19± 0.59	0.34±0.38	0.378
Saliva volume	0.10±0.32	0.17± 0.29	0.472

The result showed that salivary pH and saliva volume were increased after the use of the intervention spray. In Trehalose group, salivary pH significantly increased from 6.91±0.67 before use to 7.16±0.56 after use (P=0.033) and saliva volume significantly increased from 0.82 ±1.12 before use to 0.99±1.20 after use (P=0.009). In CMC group, salivary pH increased but not significantly from 6.78±0.64 before use to 6.96±0.7 after use (P=0.202) and saliva volume increased from 0.86±0.82 before use to 0.96±0.99 after use (P=0.146) (Table4). However, the differences of increases of salivary pH and saliva volume were not statistically significant comparing between both groups. (P=0.378 and P=0.472) (Table5).

Questionnaires

Table 6 *Comparison of XeQoLs scores before and after treatment with CMC or Trehalose solution spray*

Questionnaire	XeQoLs score (Median±IQR)					
	CMC group (n=35)			Trehalose group (n=35)		
	Before	After	ρ-value	Before	After	ρ-value
Part 1: Physical						
Q1: Rate your difficulty in chewing due to dryness	4.00±7.00	3.00±5.00	P=0.002**	0.00±5.00	0.00±4.00	P=0.015*
Q2: Rate your difficulty in swallowing food due to dryness	5.00±4.00	3.00±4.00	P=0.000***	5.00±5.00	4.00±4.00	P=0.000***
Q3: Rate your difficulty in talking due to dryness	3.00±5.00	2.00±4.00	P=0.003**	4.00±5.00	3.00±4.00	P=0.002**
Q4: Rate your taste alteration	5.00±4.00	5.00±4.00	P=0.000***	6.00±4.00	5.00±3.00	P=0.000***
Part 2: Pain / Discomfort						
Q5: Rate your feeling dry mouth	6.00±3.00	4.00±3.00	P=0.000***	6.00±3.00	4.00±2.00	P=0.000***
Q6: Rate the frequency of sipping water (nocturnal)	4.00±5.00	3.00±5.00	P=0.047*	4.00±5.00	3.00±3.00	P=0.003**
Q7: Rate the frequency of sipping water (Daytime)	8.00±2.00	6.00±4.00	P=0.001**	0.00±1.00	0.00±1.00	P=0.000***
Q8: Rate your pain and discomfort	0.00±2.00	0.00±2.00	P=0.768	0.00±1.00	0.00±1.00	P=0.066
Part 3: Psychological						
Q9: My mouth/throat dryness interferes with my daily activity	2.00±5.00	0.00±4.00	P=0.011*	0.00±5.00	0.00±4.00	P=0.005**
Q10: My mouth/throat dryness makes me nervous	2.00±5.00	0.00±5.00	P=0.006**	0.00±3.00	0.00±3.00	P=0.004**
Q11: My mouth/throat dryness reduces my general happiness	0.00±5.00	0.00±4.00	P=0.019*	0.00±0.00	0.0±4.00	P=0.046*
Part 4: Social						
Q12: My mouth/throat dryness makes me uncomfortable speaking in front of other people	0.00±2.00	0.00±2.00	P=0.103	0.00±0.00	0.00±0.00	P=0.180
Q13: My mouth/throat dryness makes me uncomfortable when eating in front of other people	0.00±4.00	0.00±4.00	P=0.169	0.00±0.00	0.00±0.00	P=0.157
Q14: My mouth/throat dryness makes me from socializing (going out)	0.00±2.00	0.00±2.00	P=0.211	0.00±0.00	0.00±0.00	P=0.109

**P<0.05; **P<0.01; ***P<0.001*

Table 7 *The difference of XeQoLs scores before and after treatment between CMC and Trehalose group*

Questionnaire	Difference XeQoL score (before-after) (Median±IQR)		ρ-value
	CMC group (n=35)	Trehalose group (n=35)	
Part1: Physical			
Q1: Rate your difficulty in chewing due to dryness	0.00±0.10	0.00±0.00	P=0.320
Q2: Rate your difficulty in swallowing food due to dryness	0.00±2.00	1.00±2.00	P=0.381
Q3: Rate your difficulty in talking due to dryness	0.00±1.00	0.00±1.00	P=0.744
Q4: Rate your taste alteration	0.00±2.00	0.00±1.00	P=0.628
Part2: Pain / Discomfort			
Q5: Rate your feeling dry mouth	2.00±2.00	2.00±2.00	P=0.841
Q6: Rate the frequency of sipping water (Nocturnal)	0.00±0.00	0.00±1.00	P=0.421
Q7: Rate the frequency of sipping water (Daytime)	0.00±2.00	0.00±2.00	P=0.781
Q8: Rate your pain and discomfort	0.00±0.00	0.00±0.00	P=0.685
Part3: Psychological			
Q9: My mouth/throat dryness interferes with my daily activity	0.00±0.00	0.00±1.00	P=0.749
Q10: My mouth/throat dryness makes me nervous	0.00±0.00	0.00±1.00	P=0.753
Q11: My mouth/throat dryness reduces my general happiness	0.00±0.00	0.00±0.00	P=0.451
Part4: Social			
Q12: My mouth/throat dryness makes me uncomfortable speaking in front of other people	0.00±0.00	0.00±0.00	P=0.655
Q13: My mouth/throat dryness makes me uncomfortable when eating in front of other people	0.00±0.00	0.00±0.00	P=0.977
Q14: My mouth/throat dryness makes me from socializing (going out)	0.00±0.00	0.00±0.00	P=0.645

Table 6 demonstrated XeQoLs scores after treatment with CMC or Trehalose solution sprays. In CMC solution spray group, XeQoLs scores significantly improved after the use of the CMC oral spray in 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 pain/discomfort part, 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.

Similarly, after use Trehalose solution spray XeQoLs scores significantly improved in physical part from Q1 to Q4 about chewing (P=0.015), swallowing (P=0.000), talking (P=0.002) and taste alteration (P=0.000). In pain/discomfort part, Q5 (P=0.000), Q6 (P=0.003), Q7 (P=0.000), and psychological part, Q9 (P=0.005), Q10 (P=0.004), and Q11(P=0.046). However, in both groups, the question relating to the social part Q12, Q13 and Q14 showed improved scores, but not statistically significant (P>0.05) (Table 6).

Comparing of difference of XeQoLs scores before-after treatment, there were no statistical differences of XeQoLs scores before-after treatment between 2 groups in each question and overall of each part (P>0.05) (Table 7).

Satisfaction

The satisfaction score after treatment with Trehalose solution spray (8.00±1.00) was significantly higher than that with CMC solution spray (7.00±2.00) (P=0.000) (Table 8).

Table 8 *The satisfaction scores after treatment between CMC and Trehalose group*

	Intervention group (Median±IQR)		ρ-value
	CMC group (n=35)	Trehalose group (n=35)	
Satisfaction score	7.00±2.00	8.00±1.00	0.000***

****P<0.001*

CHAPTER V DISCUSSION

To relieve xerostomia, saliva substitutes containing CMC had been commonly used.[52, 54] Recently, Trehalose had been developed as moistening eye drop.[13, 65] A few studies showed positive results of using Trehalose in oral spray to relieve xerostomia in patients with dry mouth.[4, 15] This study demonstrated that Trehalose solution spray improved QoL similar to CMC solution spray. Comparison of XeQoLs scores before and after treatment demonstrated that both CMC and Trehalose solution spray resulted in patients' positive responses and satisfaction. These findings suggested that Trehalose can be effectively used in oral spray to relieve oral dryness.

The patients responded to questions relating to their daily routine and well-being. Both CMC and Trehalose solution spray significantly improved their xerostomia related QoL in three dimensions, including physical pain/discomfort and psychological aspects. The major property of CMC is to coat and moisten oral mucosa to improve dry mouth.[54] Similarly, Trehalose solution maintained moisture, prevented atrophy of the tongue mucosa and relieved the discomfort in the mouth under drying condition in dental treatment.[15] However, the social dimension of xerostomia related QoL was not improved after using CMC or Trehalose solution sprays. The result of this part, which reflects the patients' social activities, may be affected by the COVID-19 pandemic. All social events were reduced during the lockdown, while patient's anxiety had been increased. Some denied visiting the hospital for the 2nd visit. Therefore, the dropout rate was about one-third of total participants. Thus, the unchanged XeQoLs scores in the social aspects may not depend on the intervention but affected by a lockdown policy during COVID pandemic.

Salivary gland dysfunction is a common side effect post radiation in HNC patients.[21, 22] The accumulating doses of radiotherapy for HNC patients is 50 Gy to 70 Gy. When the accumulating dose is over 52 Gy, the damage of severe salivary gland function is increased and causes dry mouth.[23, 24] Nevertheless, the previous studies showed slight reduction of salivary gland function when the average radiation doses

were less than 10–15 Gy. The salivary gland function could be gradually improved after the average radiation doses of 20–40 Gy. However, a strong effect occurred when the average radiation doses were more than 40 Gy.[66, 67] Hyposalivation therefore can be prevented by reducing the average doses on parotid glands to 26-30 Gy.[68, 69] Our results showed that the mean parotid gland doses between 24-28 Gy in our patients affected decrease of saliva volume in both groups.

Although the salivary flow rate could not be recovered to healthy level as pretreatment,[26-28] oral dryness seems to improve over time post-radiotherapy. Salivary flow rate steeply decreased during the first month, then gradually increased within 3-6 months after radiotherapy. Similarly, salivary pH declined steeply at 1 month and also later recovered back until 6 months after radiotherapy.[27] Jenson et al[70] showed that slight increase of unstimulated saliva flow rates was observed after 6 months; however, it was strongly higher increase up to 2 years after radiation. In the present study, an average of post-radiation duration in the CMC solution spray group was 7 months, thus the patients of CMC group might experience less dryness as compared with the Trehalose solution spray group (5 months in average). As a result, the patients might report less change in oral dryness regardless of the intervention. Nonetheless, patients' responses to questionnaires may be varied on a person's affective feelings because of the subjectiveness of oral dryness.[71]

Regarding salivary pH, the previous study observed anionic component in saliva such as lactate causing rapid decrease of salivary pH, followed by demineralization of dental hard tissues. Salivary pH significantly decreased during the first 2 months after radiotherapy (median pH = 6.166) compared to baseline (median pH = 6.953), and a subsequent plateau by 6 to 12 months after radiotherapy.[72] Our findings suggested that Trehalose solution spray might increase the saliva volume and pH since the second week after using the Trehalose solution spray, but not CMC solution spray. Moreover, plaque pH after using sucrose mouth-rinse was lower than that after using trehalose mouth-rinse and plaque pH after trehalose mouth-rinse never reached critical pH.[14] Trehalose may therefore partly regulate the salivary pH level by neutralizing the saliva to become less acidic.

The adverse effect of CMC while using as saliva substitute was reported. An interaction of calcium and phosphate resulted in complex formation which decreased demineralizing capacities[73] and interfered with dentin remineralization process.[74, 75] The remineralization effect by CMC solution was reported at pH 6.5 better than pH 5.5.[74] In addition, Trehalose solution is beneficial more than CMC solution in the aspect of patient's satisfaction, better taste and more affordable cost. Subjects using Trehalose solution spray had more satisfaction comparing to that using CMC solution spray. Most of patients preferred Trehalose than CMC solution spray possibly because of the slightly sweet taste and less viscosity of Trehalose.[76] Conversely, CMC salivary substitute had more sticky consistency giving unpleasant feeling to the patients.[77] Collectively, Trehalose solution spray effectively improved oral dryness comparable to CMC solution spray, but the advantage of Trehalose over CMC solution spray is needed for further studies in the larger population in normal situation.

CHAPTER VI CONCLUSION

Trehalose solution spray can effectively improve QoL in HNC patients similar to CMC solution spray. Trehalose solution spray appears to help patients relieve symptoms of dry mouth in post-radiation xerostomia patients with, lower viscosity as compared to CMC solution spray. Thus, Trehalose solution spray can be used as an alternative treatment to relieve oral dryness, apart from conventional treatment with CMC solution spray.

APPENDIX

Sample	Baseline Day0 pH	After Day14 pH	Baseline Day0 Volume	After Day14 Volume
1	6.70	6.62	3.50	3.10
2	5.79	6.19	4.80	5.25
3	6.56	7.03	.75	1.25
4	6.71	6.71	.35	.40
5	5.73	6.42	.50	1.30
6	7.59	7.62	1.40	1.50
7	7.35	7.84	.85	1.30
8	9.00	6.85	.10	.45
9	9.00	7.21	.10	.25
10	9.00	9.00	.05	.05
11	6.70	7.26	.65	.70
12	7.30	7.46	1.75	2.45
13	9.00	9.00	.08	.10
14	6.42	9.00	.35	9.00
15	6.83	9.00	.25	9.00
16	7.53	9.00	.90	9.00
17	7.27	9.00	.25	.10
18	7.96	9.00	.26	9.00
19	6.70	7.85	.25	.35
20	7.15	6.78	.25	.30
21	6.86	6.77	.95	.90
22	6.38	9.00	.24	9.00
23	9.00	9.00	.10	.10
24	6.99	7.61	1.10	1.85
25	9.00	9.00	.05	.05
26	6.75	9.00	.35	9.00
27	9.00	9.00	.20	9.00
28	7.42	9.00	.21	9.00
29	7.61	9.00	.85	9.00
30	7.06	9.00	2.14	9.00
31	6.92	7.47	1.35	1.40
32	6.24	6.60	.65	.55
33	9.00	7.14	.10	.20
34	8.25	7.54	.30	.45
35	7.87	7.91	.25	.30

Sample	Baseline Day0 pH	After Day14 pH	Baseline Day0 Volume	After Day14 Volume
36	7.35	9.00	.75	9.00
37	7.70	7.56	.80	.75
38	6.34	9.00	.25	9.00
39	7.07	9.00	.40	9.00
40	9.00	9.00	.10	.15
41	7.02	9.00	1.00	9.00
42	7.50	7.90	3.50	4.50
43	9.00	6.21	.20	.30
44	6.80	6.50	1.00	1.10
45	7.25	6.53	.40	.80
46	6.66	9.00	1.10	9.00
47	6.45	9.00	1.00	9.00
48	6.73	9.00	.30	.15
49	5.40	6.05	1.10	1.00
50	6.80	6.86	.35	.65
51	5.55	6.74	.40	.45
52	9.00	9.00	.05	.05
53	5.83	5.63	.50	.25
54	7.04	6.35	.35	.45
55	6.87	6.35	1.00	.40
56	6.49	6.34	.75	.75
57	7.02	7.10	2.25	2.15
58	9.00	9.00	9.00	.05
59	6.95	7.90	.40	.45
60	6.49	7.30	1.35	1.75
61	6.74	7.44	1.45	1.50
62	9.00	7.79	.10	.35
63	6.75	7.42	1.35	2.10
64	7.28	7.06	1.75	1.65
65	9.00	9.00	9.00	9.00
66	7.51	9.00	.20	9.00
67	9.00	9.00	.15	9.00
68	5.93	9.00	.90	9.00
69	7.66	9.00	1.00	9.00
70	7.41	8.17	.35	.45

sample	Q1		Q2		Q3		Q4		Q5		Q6		Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14	
1	5	5	6	6	5	4	4	4	5	3	7	3	8	6	8	8	7	4	1	0	6	5	8	7	3	3	4	4
2	0	0	7	7	0	0	8	8	9	7	3	2	8	8	0	0	9	9	9	9	9	9	0	0	0	0	0	0
3	6	4	6	4	0	0	5	2	8	4	3	3	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	3	2	7	5	10	9	10	8	5	5	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	5	3	2	1	2	1	10	9	6	4	2	2	7	7	0	0	0	0	0	0	0	0	5	5	5	5	5	4
6	6	4	7	5	6	6	9	8	6	4	3	3	5	4	0	0	8	7	8	7	6	5	0	0	0	0	0	0
7	2	1	2	2	1	1	3	3	3	2	3	3	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	2	2	10	8	9	8	10	10	10	7	0	0	7	4	6	3	0	0	0	0	0	0	0	0	5	3	0	0
9	0	0	4	3	0	0	3	3	5	2	4	4	10	8	0	0	2	2	2	1	0	0	0	0	0	0	0	0
10	7	6	8	6	0	0	4	4	9	6	4	4	10	10	4	4	3	3	3	3	3	2	0	0	0	0	0	0
11	10	10	2	2	6	6	5	5	8	6	3	3	5	5	1	1	5	5	5	5	5	5	4	4	7	7	10	10
12	7	7	0	0	5	5	10	10	8	5	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	8	5	0	0	10	8	6	3	8	8	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	3	3	0	0	3	3	7	5	5	3	5	3	5	3	5	4	2	1	2	1	0	0	0	0	0	0	0	0
15	0	0	5	3	0	0	3	1	5	5	8	5	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	5	5	5	3	0	0	3	1	5	5	6	6	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	8	8	0	0	6	6	8	4	7	7	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0

sample	Q1		Q2		Q3		Q4		Q5		Q6		Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14	
18	7	7	9	8	0	0	4	4	5	4	6	6	8	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	3	1	6	4	5	5	8	5	5	3	5	5	0	0	3	2	3	2	0	0	0	0	0	0	0	0
20	0	0	9	9	5	4	6	6	5	2	6	3	7	5	6	6	0	0	0	0	0	0	0	0	0	0	0	0
21	5	5	7	5	5	5	6	6	7	5	6	6	7	6	4	3	5	4	4	3	0	0	0	0	0	0	0	0
22	4	3	7	5	4	3	2	2	5	2	8	6	8	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	4	3	7	4	4	3	6	5	6	2	0	0	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	8	6	5	4	4	4	6	4	7	7	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	5	4	6	4	6	5	5	5	0	0	6	5	0	0	0	0	0	0	0	0	0	0
26	0	0	2	2	2	2	0	0	4	2	0	0	8	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	5	5	7	5	0	0	8	6	0	0	2	2	5	3	0	0	0	0	0	0	0	0
28	0	0	4	4	4	4	5	5	5	4	4	4	8	8	0	0	0	0	2	2	0	0	0	0	0	0	0	0
29	0	0	7	5	4	3	5	5	5	3	0	0	8	6	0	0	5	4	5	3	0	0	0	0	0	0	0	0
30	2	2	4	2	4	4	7	5	5	3	3	3	7	7	0	0	0	0	3	3	0	0	0	0	0	0	0	0
31	0	0	8	5	4	3	6	4	8	4	6	5	8	4	6	4	6	4	6	4	3	2	9	7	9	7	9	6
32	5	5	4	3	4	4	7	6	5	4	6	6	6	6	0	0	6	5	5	4	5	5	6	6	6	6	6	4
33	0	0	6	6	5	5	7	6	8	8	0	0	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	5	5	8	7	4	3	8	7	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	2	2	4	4	8	7	3	2	5	3	8	8	2	2	0	0	0	0	0	0	0	0	0	0	0	0

sample	Q1		Q2		Q3		Q4		Q5		Q6		Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14	
36	0	0	3	3	5	5	5	3	7	6	0	0	8	7	2	2	0	0	0	0	0	0	0	0	0	0	0	0
37	5	2	8	5	8	6	8	8	8	6	10	8	10	10	0	0	4	2	4	2	6	4	4	4	4	4	0	0
38	8	6	7	4	4	4	8	4	8	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	7	5	6	3	5	4	7	4	7	7	5	7	7	5	4	7	7	4	7	5	7	6	6	4	0	0	0	0
40	8	6	9	6	5	4	8	8	8	5	5	4	5	4	4	3	6	5	6	5	9	8	6	5	8	8	8	7
41	3	2	7	4	0	0	8	7	7	1	7	5	7	5	0	0	0	0	0	0	0	0	2	1	0	0	0	0
42	0	0	7	7	0	0	10	7	5	2	0	0	8	8	0	0	8	8	8	8	8	8	0	0	10	10	10	10
43	3	3	7	7	4	4	0	0	5	3	5	4	8	8	0	0	6	6	6	6	0	0	5	5	8	8	8	8
44	0	0	5	3	5	5	2	1	6	4	0	0	8	4	0	0	2	0	2	0	0	0	7	7	8	8	8	8
45	6	6	6	6	6	4	7	7	9	6	5	5	8	4	0	0	5	5	5	5	5	5	5	5	5	5	5	5
46	0	0	0	0	0	0	0	0	6	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	5	4	5	5	0	0	0	0	5	3	0	0	8	6	0	0	3	3	3	3	0	0	0	0	0	0	0	0
48	4	3	3	2	0	0	0	0	6	3	0	0	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	7	5	0	0	0	0	8	6	8	4	1	1	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	4	4	4	4	2	2	5	5	8	4	3	3	8	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	5	5	5	2	5	3	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	2	1	5	3	0	0	7	7	0	0	5	5	5	5	5	5	0	0	0	0	0	0

sample	Q1		Q2		Q3		Q4		Q5		Q6		Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14	
53	5	3	0	0	0	0	2	2	8	4	4	4	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	3	3	6	6	7	7	6	5	0	0	8	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	5	5	0	0	4	2	9	7	7	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56	8	6	2	1	2	1	4	3	4	2	0	0	6	3	0	0	4	2	4	2	4	2	0	0	4	2	0	0
57	0	0	4	4	4	4	5	5	5	4	7	7	7	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58	8	8	8	8	0	0	8	6	7	5	0	0	9	9	6	6	0	0	0	0	0	0	0	0	0	0	0	0
59	5	5	5	3	4	2	8	6	4	2	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	4	4	5	3	5	3	7	7	3	0	6	4	6	3	0	0	3	0	3	0	3	2	0	0	7	4	5	2
61	3	3	4	2	2	2	3	3	4	4	0	0	5	8	1	1	3	3	2	2	3	2	2	2	2	2	1	1
62	8	8	8	8	0	0	10	10	8	8	5	5	10	10	7	7	7	7	7	7	7	7	0	0	0	0	0	0
63	3	3	3	3	1	1	5	3	2	1	3	3	3	3	2	2	3	3	2	2	2	2	2	2	2	2	3	3
64	0	0	3	1	5	5	5	3	6	3	0	0	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
65	8	8	8	8	7	7	4	4	7	6	4	4	7	7	6	6	6	6	6	6	5	5	4	4	6	6	2	2
66	0	0	4	2	4	3	5	5	5	4	4	4	8	6	3	2	3	2	3	2	0	0	0	0	0	0	0	0
67	0	0	3	3	3	2	6	4	5	3	0	0	7	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	2	2	4	3	3	3	5	5	4	2	5	5	8	6	0	0	2	2	2	2	0	0	0	0	0	0	0	0
69	7	7	7	6	8	8	8	8	7	5	7	7	7	6	2	2	7	7	7	7	7	7	7	7	7	7	7	7
70	5	5	4	4	6	6	7	7	7	7	0	0	8	8	0	0	4	4	5	4	0	0	0	0	0	0	0	0

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