Journal of the Formosan Medical Association 122 (2023) 723–730

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

Original Article

Efficacy of polyacrylate silver salt/polyvinylpyrrolidone-based liquid oral gel in management of concurrence chemoradiotherapy-induced oral mucositis

Hsiao-Lei Chin [a], Kuo-Piao Chung [a], Hsin-Cheng Liu [b,c], Rung-Shu Chen [b], Hao-Hueng Chang [d,e,**,1], Min-Huey Chen [b,d,*,1]

[a] College of Public Health, National Taiwan University, Taiwan
[b] Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taiwan
[c] College of Management, National Yang Ming Chiao Tung University, Taiwan
[d] Department of Dentistry, National Taiwan University Hospital, Taiwan
[e] School of Dentistry, National Taiwan University, Taiwan

Received 26 April 2022; received in revised form 14 November 2022; accepted 8 December 2022

KEYWORDS
Chemoradiotherapy;
Neck and head cancer;
Polyacrylate silver salt;
Oral gel;
Oral mucositis

Background/Purpose: Acute oral mucositis (OM) is a painful complication of concurrent chemoradiotherapy (CCRT). This severe adverse symptom may impact on patient's quality of life, lead to malnutrition. Thus, finding more effective methods in OM management is very important. The purpose of this study is to evaluate the efficacy of polyacrylate silver salt/Polyvinylpyrrolidone-based liquid oral gel (named as polyacrylate silver salt oral gel) in improving the symptomatic relief of CCRT-induced oral mucositis and oral dysfunction in neck and head cancer patients.

Methods: In this study, 24 oral cancer patients underwent CCRT and having OM grade 2 or higher were randomly assigned into the test group and the control group. Both groups followed Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines for the management of mucositis, but adding rinsing with 15 g oral gel right after oral hygiene treaded the test group. Clinical OM and oral function were assessed weekly for 4 consecutive weeks till 5–10 days after the completion of radiotherapy. For evaluation, Common Terminology Criteria for Adverse Events (CTCAE) v3.0 was used for collecting the data of OM grade.

* Corresponding author. Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Department of Dentistry, National Taiwan University Hospital, No.7, Chung-Shan South Road, Taipei, 100, Taiwan.
** Corresponding author. Department of Dentistry, National Taiwan University Hospital, School of Dentistry, National Taiwan University, No.7, Chung-Shan South Road, Taipei, 100, Taiwan. Fax: +886 2 23224552.
E-mail addresses: changhh@ntu.edu.tw (H.-H. Chang), minhueychen@ntu.edu.tw (M.-H. Chen).
[1] Equal contribution.

https://doi.org/10.1016/j.jfma.2022.12.007

Results: The results showed that polyacrylate silver salt oral gel had better effect for relieving the oral mucositis. There were statistically significant differences in OM grades (1.59 vs. 2.8, $p < 0.0001$) between the test group and the control group.
Conclusion: Our clinical studies demonstrated that polyacrylate silver salt oral gel is an effective interventional option in terms of rapid mucositis healing.

Introduction

Oral mucositis (OM) is an extremely painful, and unavoidable complication of chemoradiotherapy. Not only does it reduce the patient's quality of life, it also increases healthcare cost.[1] Prevalence varies by cancer and cancer treatment. Patients with head and neck cancer who received 60Gy RT had a tendency to develop OM.[2] OM usually occurs at cumulative dose of about 15 Gy (Gy) and reaches a severity at 30 Gy. As studied, it was up to 96.7% of head and neck cancer patients who have OM while undergoing concurrent chemoradiotherapy (CCRT) treatment, of which 61% had OM grade 3—5.[1—3] Ulcers usually begin to heal at 2—4 weeks after radiotherapy completion.[4]

Recent management of OM has primarily involved supportive care to reduce the risk and severity, including oral hygiene,[5] cryotherapy, use of helium-neon lasers, the construction of radiation fields to protect the oral tissues during irradiation, use of mouthwashes, administered pharmacological agents and oral mucosal protectants.[6,7]

Mouthwashes with anti-inflammatory, anesthetic, analgesic, antipyretic and antimicrobial properties are commonly used in the treatment of OM. In particular, antimicrobial mouthwashes are recommended. However, the use of mouthwashes containing ingredients such as chlorhexidine, hydrogen peroxide, calcium phosphate, or allopurinol had been reported no scientific evidence for their effectiveness in managing OM.[8,9]

Oral mucosal protectants come in water-insoluble gel form and water-soluble liquid gel form. Oralog and Nincort are water-insoluble gel forms and Caphosol, Episil, GelClair, and MuGard are water-soluble liquid gel forms. Most of water-insoluble oral gel contains anti-inflammatory drugs and need to be applied by hand to the top of each ulcerated mucosa area. Water-soluble oral liquid gels, on another hand, are much easier to use. Oral liquid gel is a water-soluble gel similar to mouthwash. The oral liquid gel contains water-soluble polymer thickeners such as polyvinylpyrrolidone, sodium salt of poly acrylic acid, hydroxyethyl cellulose, sodium carboxymethyl cellulose … etc. During gargling, the liquid gel forms a temporary protective layer on damaged mucosa. Oral liquid gels have been proven to aim at alleviating pain and discomfort caused by OM. However, the data on the efficacy of oral liquid gels in managing mucositis-related symptoms are scarce.[10—15]

Silver has been playing a very important role in wound dressing for the treatment of chronic wound such as burn wound and ulcer wound of diabetes.[16,17] Silver in the form of ions or nanoparticles is a very effective antimicrobial agent which capable of reducing the bioburden of the wound. Silver nitrate sticks are known for treatment of oral ulcer. However, silver is not used in mouthwash or oral gel to treat OM.

The structure of the polyacrylate silver salt has both the very effective antimicrobial property of silver ions and the safety property of high molecular polymer. A liquid oral gel using this ingredient was also developed. A clinic trial was conducted at National Taiwan University Hospital to evaluate the efficacy of polyacrylate silver salt oral gel in management of CCRT-induced OM.

Methods

Study design

This was a prospective, randomized, single-blind, parallel-arm, and single-center study involving patients with head and neck cancer treated with CCRT in the Department of Oncology, National Taiwan University Hospital. All subjects provided written informed consent. The IRB permission was obtained from Clinical Trial Research Committee of National Taiwan University Hospital (No. 202001014DSC).

Participants

Eligibility criteria for participants included: 1) male and female, age 25—70 years; 2) head and neck cancer; 3) under concurrent chemoradiotherapy, CCRT, treatment (received 60—70 Gy of radiotherapy in 33 fractions, 5 fractions/week plus Intravenous infusions of chemotherapy once a week); and 4) verified clinical diagnosis of OM grade 2 or higher (according to the dentist's clinical diagnosis).

Allocation

The enrolled patients were stratified by oral cancer and the rest of types of head and neck cancers first, then were randomized with an allocation ratio 1:1 to the test group intervened with polyacrylate silver salt oral gel (which would be used the abbreviation of "PSS" oral gel as instead in the later part of this paper) or to the control group (without intervention).

Oral examinations which including assessment of OM grade and oral function were conducted at enrolling. These data were baseline and marked as T_0. Standard oral hygiene education was introduced to all eligible recruiters at T_0. Standard oral hygiene procedures including oral hygiene 4

times a day, at least, following gargling with salt water were demanded.

Intervention

PSS oral gel interventions started from T_0 and lasted for 4–5 weeks until around 5–10 days of RT completion. PSS group was instructed to gargle with 15 g of PSS oral gel for 1 min after meals and before going to bed. Both groups of patients would be able to treat with Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for the management of mucositis[18] if required under the doctor's appropriate consideration.

The patient basically returned to the hospital once a week (about every 5 fractions of RT) for four consecutive weeks for oral examination and recorded the condition of the oral mucosa. The first time check was for baseline data collection and recorded as T_0. One week after T_0 was the second time for checking and recorded as T_1, the second week after T_0 for checking was recorded as T_2, the third week after T_0 for checking was T_3, and the fourth week after T_0 for checking was T_4. However, in some patients, the interval was slightly more than 7 days or less than 7 days due to earlier or later OM onset.

Outcomes

The main outcomes of the study included the severity of OM grade (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI- CTC/ CTCAE V3).

Polyacrylate silver salt oral gel

Nasil Oral Gel (Non-sterile) (TFDA medical device No. 007636, produced by SilvRight Biotech Ltd. Co.) is a kind of polyacrylate silver salt oral gel and also a type of liquid oral dressing. The main ingredients are Poly(sodium acrylate-co-silver acrylate) (be named as polyacrylate silver salt, PSS), polyvinylpyrrolidone and hydroxyl propyl methylcellulose. The function of Polyvinylpyrrolidone and hydroxyl propyl methylcellulose was treated as thickeners. The concentration of PSS is 300 ppm. The molecular weight of PSS was over 5 million and too huge to penetrate skin and mucosa.

The LD50 of the concentrated PSS aqueous solution was estimated to be greater than 10000 mg/kg in the rats. According to Globally Harmonized System of Classification and Labeling of Chemicals (GHS) Classification Criteria for Acute Toxicity,[19] its performance was fell into the most demanding range of Category 5, 2000 mg/kg ~ 5000 mg/kg (https://en.silvright.com).

The antimicrobial effectiveness of PSS had been verified by performing the antimicrobial effectiveness test which followed the procedures described in United States Pharmacopeia 35 National Formulary 30 Microbiological Test (51) Antimicrobial Effectiveness Testing (USP 35 NF 30 Microbiological Test <51>).[20] By testing the antimicrobial effectiveness for *Escherichia coli*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Klebsiella pneumonia and Pseudomonas Aeruginos, the results showed the antimicrobial rate is larger than 99.999% after 1 min contacting time (https://en.silvright.com).

Assessment tool

OM grade was measured by Common Terminology Criteria for Adverse Events (CTCAE) v.3.

Common Terminology Criteria for Adverse Events (CTCAE)

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) had published a standardized definition of adverse events (AEs), known as the Common Terminology Criteria for Adverse Events (CTCAE, also called "common toxicity criteria" [CTC]), to describe the severity of organ toxicity in patients receiving cancer treatment. It was widely used for grading oral mucositis.[21] The scale ranges from 0 to 5, with higher scores corresponding to worse mucositis.

Statistical analysis

Data analysis was performed using SAS 9.4. The mean and standard deviation of the dependent outcomes for each group were described distinctly.

Our trial was a repeated measurement design. The purpose of the analysis was to examine and compare response trends over time. Repeated measures data can provide better information and more precise estimates when calculating correlations between measures within a subject, which is especially useful to a small sample size.[22] We used mixed model analysis to analyze the repeated

Table 1 Baseline demographic data and clinical features of the participants.

Baseline Characteristics	PSS group (n = 12)	Control group (n = 12)	*p*
Gender			
Male	8 (67%)	10 (83%)	
Female	4 (33%)	2 (17%)	
Age (yrs)[a]	57.20 (9.68)	55.25 (10.25)	$p = 0.6424$
RT fractions at baseline T_0[b]	15.5 (5.18)	15.25 (3.49)	$p = 0.8910$
OM grades at baseline T_0[b]	2.88 (0.43)	2.83 (0.39)	$p = 0.8204$
Site of tumor			
Floor of Mouth	3	2	$X^2 = 3.342$
Gingiva	1	3	$p = 0.6473$
Tongue	3	3	
Buccal mucosa	4	3	
Retromolar Trigone	0	1	
Hard Palate	1		

*significant level at $p < 0.05$.
[a] The data are expressed as population of the sample and %.
[b] The data are expressed as arithmetic mean and standard deviation.

Table 2 Comparisons of OM grade (graded by NCI-CTCAE guideline) BETWEEN/WITHINgroup.

A. The comparison of OM grade 'BETWEEN' the groups by term

Term	PSS group, (n = 12)		Control group, (n = 12)		Difference of OM grade (PSS−Control)	*p*
	The mean of RT fraction[a]	OM grade[b]	The mean of RT fraction[a]	OM grade[b]		
T_0	15.5 fx	2.88 (0.43)	15.3 fx	2.83 (0.39)	0.042	0.8204
T_1	20.8 fx	2.54 (0.50)	19.7 fx	2.75 (0.45)	−0.208	0.2884
T_2	25.2 fx	2.25 (0.87)	24.7 fx	2.88 (0.43)	−0.625	0.0235[d]
T_3	29.3 fx	1.83 (0.58)	29.0 fx	2.91 (0.47)	−1.083	<0.0001[e]
T_4	6.1 days[b] (post of RT)	1.59 (0.51)	6.8 days[b] (post of RT)	2.80 (0.43)	−1.208	<0.0001[e]

B. The comparison of OM grade between term 'WITHIN' group

PSS group			Control group		
The Difference of OM grade between term (- better/+worse)		*p*	The Difference of OM grade between term (- better/+worse)		*p*
T_0 to T_1	−0.34	0.0162[d]	T_0 to T_1	−0.08	0.5416
T_1 to T_2	−0.29	0.0967	T_1 to T_2	+0.13	0.4737
T_2 to T_3	−0.42	0.0207[d]	T_2 to T_3	+0.03	0.8142
T_3 to T_4	−0.24	0.0943	T_3 to T_4	−0.08	0.4000
T_0 to T_4	−1.29	<0.0001[e]	T_0 to T_4	−0.03	0.7640

C. *Candida albicans* infection

	PSS group	Control group
Candida albicans infection[c]	1	5

[a] The data are indicated as the average of times of RT fractions (fx) that patients had taken at T^0-T^3 and the average days after RT completion at T^4.
[b] The data are expressed as arithmetic mean and standard deviation.
[c] Determination of eligible cases must be based on the diagnosis by a senior dentist and a radiologist oncology with a prescription Mycotin (nystatin).
[d] Two-sample t test with significant level at $p < 0.05$.
[e] Two-sample t test with significant level at $p < 0.0001$.

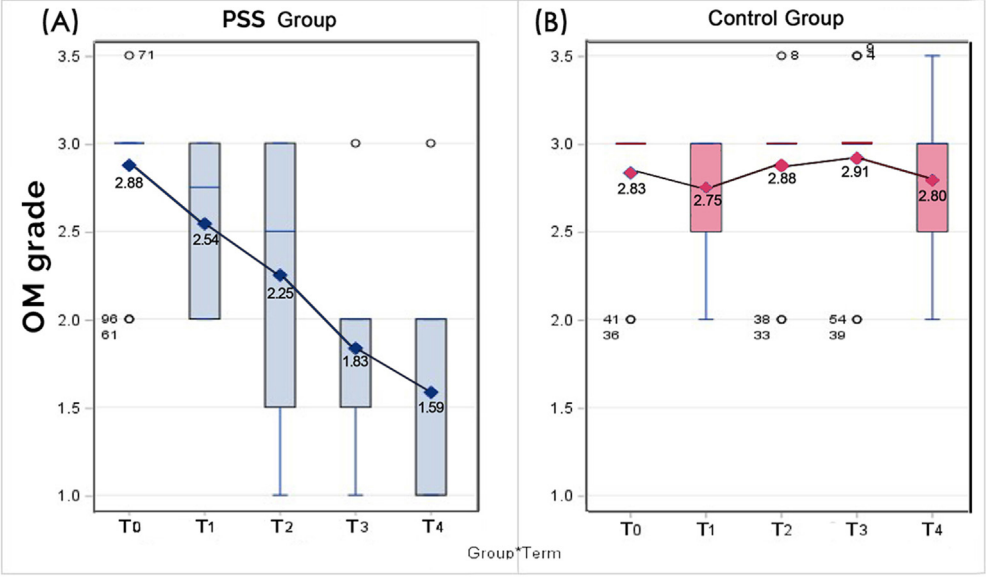

Figure.1 OM grade for PSS group (A) and the control group (B) by term (T_0, T_1, T_2, T_3 & T_4).

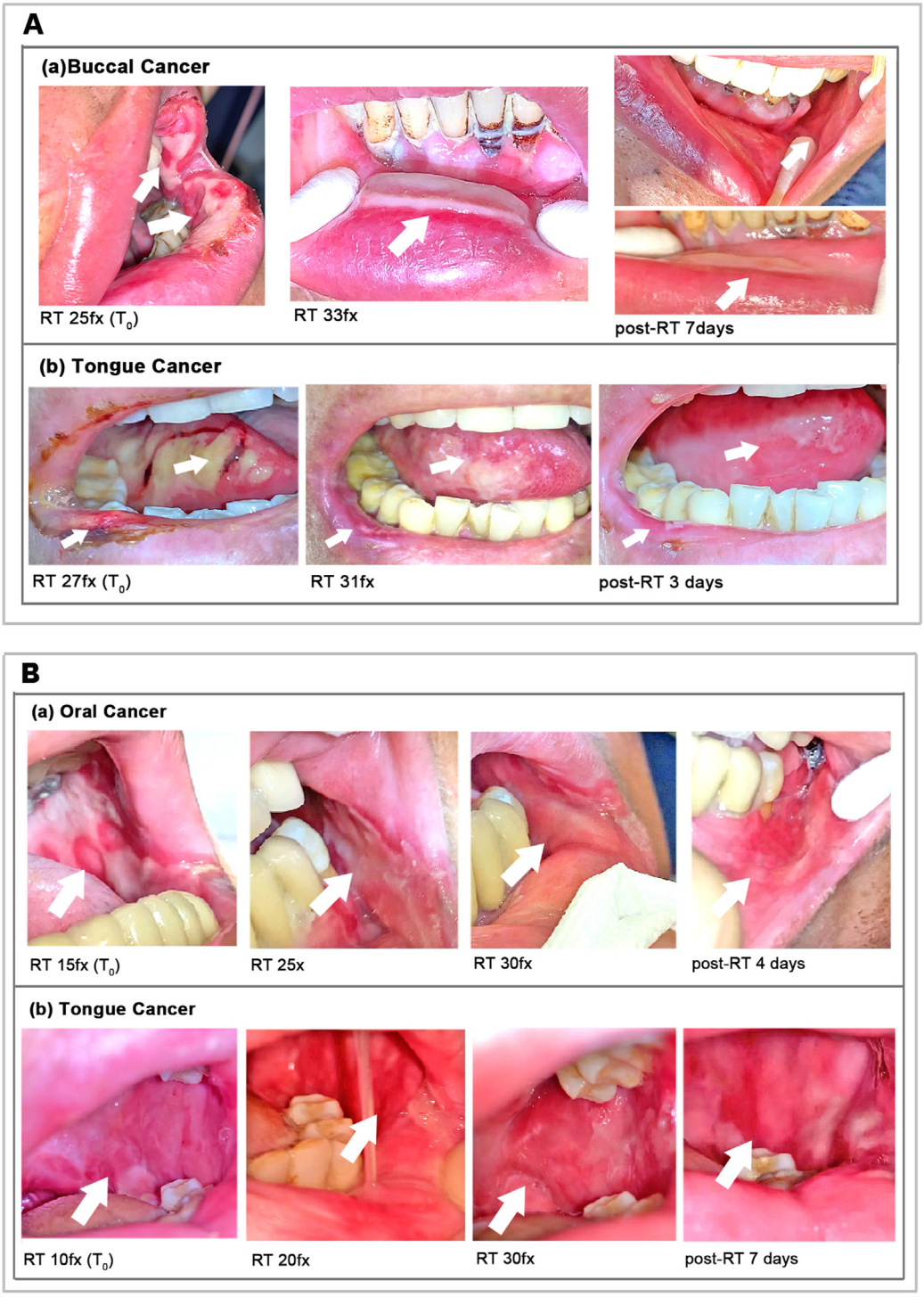

Figure.2 (A) Patients with PSS oral gel intervention at mid-late RT phase (a) Buccal cancer, T_0 at 25fx; (b) Tongue caner, T_0 at 27fx; (B) Patients with PSS oral gel intervention at early-mid RT phase (a) Oral cancer, T_0 at 10fx; (b) Tongue cancer, T_0 at 15fx; RT:radiotheropy. fx: RT fraction.

measurement dataset. SAS PROC MIXED's mixed model analysis was applied. When data were not available, we used the last-observation-carried-forward strategy for intention-to-treat analysis (LOCF-ITT). Significance was defined as a p-value less than 0.05.

Ethics approval

The institutional review board (IRB) approval was obtained from National Taiwan University Hospital (IRB number 202001014DSC).

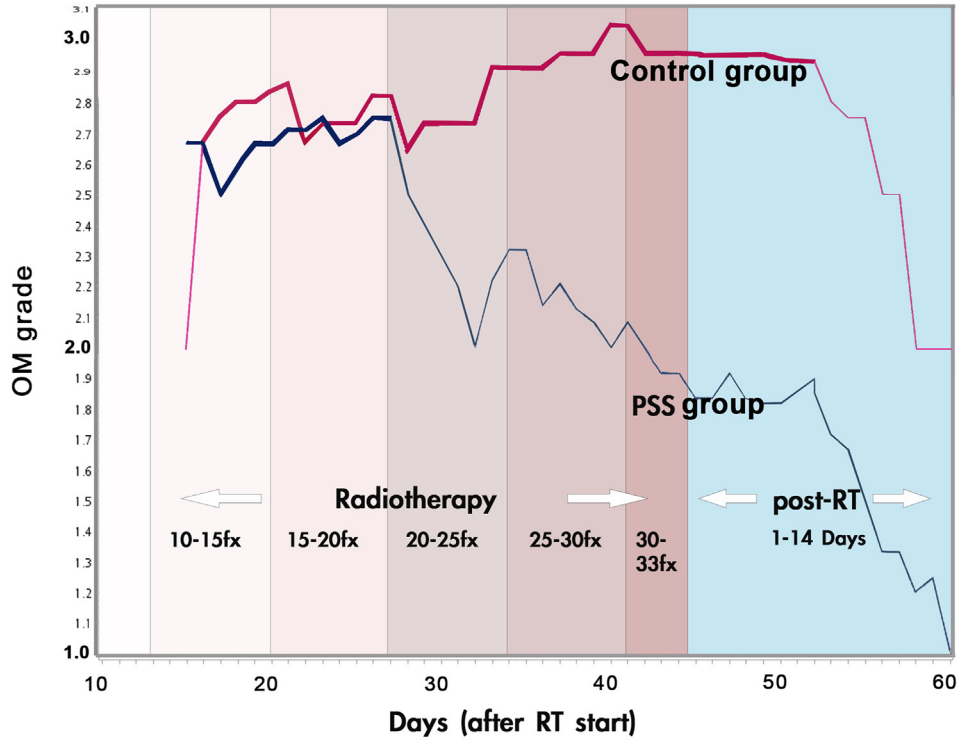

Figure 3 Change of OM grade by days for PSS group and the control group. RT:radiotheropy. fx: RT fraction.

Results

24 eligible oral cancer patients were included. The PSS group consisted of 12 patients including 8 males (67%) and 4 females (33%). The control group consisted of 12 patients including 10 males (83%) and 2 females (17%).

The CCRT treatment plan for malignancy consisted of a radiation dosage of 66—70 Gy in 33 divided fractions over a period of 6—7 weeks and chemotherapy using injection cisplatin weekly.

Baseline findings in PSS group and control group

A summary statistics of the 24 oral cancer patients was listed in Table 1. The data of demographic variables (gender and age), RT status (RT fractions) and disease characteristics (OM grade and site of tumor) at baseline T_0 all showed no significant differences between PSS group and the control group (Table 1).

Clinical response

Change of CTCAE OM grades

Comparing with the control group, patients who gargled with PSS oral gel 4 times a day had a significant improvement in OM status. The mean difference in OM grade at T_4 was 1.21 (1.59 vs. 2.8, $p < 0.0001$). Term-by-Term comparison between groups showed statistically significant difference in all terms except T_1 (T_2: 2.25 vs. 2.88, $p = 0.0235$; T_3: 1.83 vs. 2.91, $p < 0.0001$ and T_4: 1.59 vs. 2.80, $p < 0.0001$) (Table 2A). The OM grade decreased at T_1 in both groups, but the decrease was lager in PSS group. After that, the improvement trend in PSS group carried out to the end of the study T_4 (Fig. 1A). As to the control group, although the OM grade decreased slightly during the first week of follow-up, the severity of OM began to worsen as the cumulative CCRT toxicity increased and no sign to turn better until 6.8 days after the completion of RT (Table 2A & Fig. 1B).

Repeated measures designs were useful to understand how the scores of these measures differ from term-to-term after the same group of subjects has been measured multiple times. The key point was to compare the differences within a group at different points of time.

For PSS group, the longitudinal data of the OM grades showed a continuing decrease at each term, and the decrease of OM grade from T_2 to T_3 was largest and significant (Table 2B, Fig. 1A). This period was around from 2nd to 3rd week after the intervention, and the average number of RT fractions was between around 25 and 29.

Discussions

Studies had shown that saline rinse and oral hygiene education program had positive impact on mucositits management of cancer patients who undergoing RT/CCRT.[23] Our data of the control group matched this result at T_1. There was an OM grade improvement from 2.83 at T_0 to 2.75 at T_1 (Fig. 1A). However, standard oral hygiene regimens and education were not sufficient to consistently maintain this improvement while RT was kept going. Oppositely, gargling with PSS oral gel in PSS group could keep a sustained improvement on the severity of OM in PSS group (Fig. 1A) and the clinical observations supported these data (Fig. 2).

While analyzing by days, the clinical symptoms of oral mucositis began to become apparent around the third week of radiotherapy (it's around approximately RT 15 fractions, cum. 21 Gy), thereafter, for the control group, as the cumulative toxicity of CCRT increased, the severity of OM continued to worsen and the severity plateau phase of OM grade 3 had persisted for more than 35 days (Fig. 3), and these data were similar to Sali Al-Ansari's findings.[4] In contrast, for the PSS group, the severity plateau phase of OM grade 3 persisted approximately 15 days which was almost 20 days shortened than that of the control group (Fig. 3). These results showed that the recovery of mucositis occurred in PSS group, and the patients of PSS group had relatively better oral health-related quality of life.

The oral mucosal environment is rich in microorganisms such as bacteria, fungi and viruses. Lack of careful oral care can lead to further complications of oral mucositis. Oral candidiasis is one of these adverse symptoms. The data in Table 2 showed that compared to 1 case of *Candida albicans* infection in PSS group, 5 cases in the control group were comparative higher. This outcome implicated that the antimicrobial properties of PSS could be effective to *C. albicans*, however, further studies to clarify this effect might be needed.

We also suggested that the antimicrobial effect of PSS oral gel protects the mucosa from microbial flora that can further ulcerate and inflame following epithelial rupture. Therefore, this might explain why it was observed that OM could be maintained in a patchy pseudomembrane state or improved better if subjects had intervened with PSS oral gel in early-mid stage of RT (around 10—15 fractions) and avoided OM to progress to a confluent pseudomembranous or deeper ulceration (Fig. 2B).

In conclusion, oral care by using silver acrylate copolymer oral gel for head and neck malignancies undergoing CCRT is an effective interventional option to improve the severity of oral mucositis.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgment

The authors like to thank the core facilities of the Medical Research Center, National Taiwan University Hospital and the Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University. This study was funded by the National Taiwan University Hospital and the National Science and Technology Council, Taiwan, R.O.C.

References

1. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and- neck malignancies. *Int J Radiat Oncol Biol Phys* 2007;**68**(4):1110—20.
2. Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer* 2006;**106**:329—36.
3. Noronha Vanita, et al. Post hoc analysis of a randomized controlled trial comparing concurrent chemoradiation with cisplatin versus nimotuzumab-cisplatin, focusing on acute oral mucositis. *J Egypt Nat Cancer* 2021;**33**:12—9.
4. Sali Al-Ansari, Zecha Judith AE M, Barasch Andrei, Jan de Lang Fred R Rozema, Raber-Durlacher Judith E. Oral mucositis induced by anticancer therapies. *Curr Oral Health Rep* 2015;**2**: 202—11.
5. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: Part 1, pathogenesis and prophylaxis of mucositis. *Head Neck* 2003;**25**:1057—70.
6. da Cruz Campos Maria Ines, Campos Celso Neiva, Aarestrup Fernando Monteiro, Vieira Aarestrup Beatriz Julião. Oral mucositis in cancer treatment: natural history, prevention and treatment (Review). *Mol Clin Oncol* 2014;**2**:337—40.
7. Lalla Rajesh V, Sonis Stephen T, Peterson Douglas E. Management of oral mucositis in patients with cancer. *Dent Clin* 2008; **52**(1):61—78.
8. Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, et al. Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;**90**:39—47.
9. Porta C, Moroni M, Nastasi G. Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. *Am J Clin Oncol* 1994;**17**:246—7.
10. Moneim Ahmed Esmat Abdel, Ana Guerra-Librero, Florido Javier, Shen Ying-Qiang, Beatriz Fernández-Gil, Darío Acuña-Castroviejo, Escames Germaine. Oral mucositis: melatonin gel an effective new treatment. *Int J Mol Sci* 2017;**18**:1003—23.
11. Villa A, Mucositis Sonis ST. Pathobiology and management. *Curr Opin Oncol* 2015;**27**:159—64.
12. Allison RR, Ambrad AA, Arshoun Y, Carmel RJ, Ciuba DF, Feldman E, et al. Multi-institutional, randomized, double-blind, placebo-controlled trial to assess the efficacy of a mucoadhesive hydrogel (MuGard) in mitigating oral mucositis symptoms in patients being treated with chemoradiation therapy for cancers of the head and neck. *Cancer* 2014;**120**:1433—40.
13. Quinn B. Efficacy of a supersaturated calcium phosphate oral rinse for the prevention and treatment of oral mucositis in patients receiving high-dose cancer therapy: a review of current data. *Eur J Cancer Care* 2013;**22**:564—79.
14. Buchsel PC. Polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair®): a bioadherent oral gel for the treatment of oral mucositis and other painful oral lesions. *Expet Opin Drug Metabol Toxicol* 2008;**4**:1449—54.
15. Raphael MF, den Boer AM, Kollen WJ, Mekelenkamp H, Abbink FC, Kaspers GJ, et al. Caphosol, a therapeutic option in case of cancer therapy-induced oral mucositis in children? Results from a prospective multicenter double blind randomized controlled trial. *Support Care Cancer* 2014;**22**:3—6.
16. Yang Y, Hu H. A review on antimicrobial silver absorbent wound dressings applied to exuding wounds. *J Microb Biochem Technol* 2005;**7**:228—33.
17. Leaper DJ. Silver dressings: their role in wound management. *Int Wound J* 2006;**3**:282—94.
18. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014;**120**:1453—61.
19. United Nations. *Globally harmonized system of classification and labelling of chemicals*. 2019. 8th revised ed. Available from: https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev08/ST-SG-AC10-30-Rev8e.pdf.
20. General Chapter: USP. Antimicrobial Effectiveness testing <51>. In: USP—NF. Rockville, MD: USP; Mar 30, 2020. https://doi.org/10.31003/USPNF_M98790_03_01.

21. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;**47**:13—47.
22. Yeh Chyon-Hwa. *Analyses of repeated measure data*, vol. 13. Taipei Medical University Biostatistics Research Center Biostatistics eNews; 2016.
23. Huang Md B-S, Wu S-C, Lin C-Y, Fan K-H, Chang JT-C, Chen S-C, et al. The effectiveness of a saline mouth rinse regimen and education programme on radiation- induced oral mucositis and quality of life in oral cavity cancer patients: a randomised controlled trial. *Eur J Cancer Care* 2018;**27**: e12819.