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Research article

A prospective randomized study comparing the efficacy between povidone-iodine gargling and benzydamine hydrochloride for mucositis prevention in head and neck cancer patients receiving concurrent chemoradiotherapy

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ABSTRACT

Background: Concurrent chemoradiation (CCRT) has been the standard treatment for organ preservation or locally advanced head and neck cancer (LAHNC). Radiation-induced oral mucositis (RIOM) is an important treatment-limiting toxicity. Benzydamine hydrochloride was recommended to prevent oral mucositis. Povidone-iodine had also been adopted to use as an oral rinse to prevent mucositis.

Objective: This study compared the efficacy between benzydamine hydrochloride and 0.1% povidone-iodine to prevent RIOM in HNC patients who received concurrent chemoradiotherapy.

Methods: We conducted a randomized control study in HNC patients receiving CCRT with curative intent. The stratification factors were primary site of disease, treatment modality, chemotherapy regimen, and schedule. The primary outcome was RIOM assessed by Oral Mucositis Assessment Scale (OMAS). Secondary outcomes included RIOM assessed by NCI-CTCAE, use of analgesic, antibiotics and anti-fungal drugs, hospitalization, and participant satisfaction.

Results: There were 83 participants recruited for this study with 71 completing the trial. Demographic characteristics were well-balanced between both arms. The univariate regression analysis revealed that povidone-iodine correlated with less RIOM compared to benzydamine hydrochloride (coefficient −2.25, 95% CI -4.37 to −0.012, *p*-value 0.03). The incidence of grade III-IV CTCAE RIOM during the study period was 51.4% with benzydamine hydrochloride compared to 26.5% with 0.1% povidone iodine (*p*-value 0.032). The peak incidence of grade III-IV CTCAE RIOM occurred in the 7th week of treatment (40.5% vs. 11.8%, *p*-value 0.01). This indicated the efficacy of povidone-iodine to prevent severe RIOM which usually most severity in the last week of CCRT treatment. The multivariate analysis revealed that the CCRT setting (definitive vs. adjuvant) and gargling agents (povidone-iodine vs. benzydamine hydrochloride were the factors associated with RIOM.

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Conclusion: This study demonstrated higher efficacy of 0.1% povidone-iodine gargle than benzydamine hydrochloride in mucositis prevention.

1. Introduction

Head and neck cancer (HNC) is the 10th most prevalent form of cancer in Thailand [1]. A multidisciplinary approach incorporation surgery, radiation and systemic therapy is the current standard treatment [2]. Concurrent chemoradiotherapy (CCRT) is also the standard of care for post-operative high-risk patients and the definitive treatment for unresectable patients [3–13]. Radiation-induced oral mucositis (RIOM) is one of the most frequent complications with an incidence of 40–80% among irradiated patients. CCRT increases the likelihood of RIOM 1.2–1.5 times greater than radiation alone [14–16]. Radiation and chemotherapy affect the mucosal membrane by repetitive production of reactive oxygen species from proinflammatory cytokines, healing process impairments, and also secondary bacterial infection, resulting in ulcer and pseudomembrane development [17]. RIOM also can have negative effects on treatment outcomes and increase the cost of overall treatment [15].

Several clinical trials have illustrated the anti-inflammatory, analgesic, and antiseptic properties of benzydamine hydrochloride (Difflam®) to prevent RIOM in HNC who received radiation and concurrent chemoradiation. Compared to normal saline, sodium bicarbonate, or chlorhexidine [18–21], benzydamine hydrochloride was shown to reduce inflammatory cytokine-like tumor necrosis factor alpha or interleukin and promote an anti-inflammatory and antimicrobial effect towards some bacteria [21–23]. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) recommends benzydamine hydrocholride as the standard of care for patients who received both radiation and concurrent chemoradiation [24–27]. Various gargling agent or mouth care such as Lactobacillus brevis CD2, honey, curcumin and povidone-iodine had been studied to prevent cancer treatment related mucositis [28–30]. Povidone-iodine mouth wash has an antiseptic effect by decreasing bacterial and viral infection via by oxidation of bacterial cell membranes. It also has anti-inflammatory properties that can reduce proinflammatory cytokines and promote healing signals [31–33] which has shown efficacy to prevent RIOM compared to the use of conventional gargling agents such as sodium bicarbonate and chlorhexidine [34–36]. Concurrent chemoradiotherapy usually correlates with a higher incidence of RIOM than single radiation modality. Therefore, we investigated the efficacy of our in-house 0.1% povidone-iodine solution to prevent RIOM compared to benzydamine hydrochloride (Difflam®) in RIOM prevention for HNC patients receiving CCRT.

2. Methods

2.1. Study design and population

We conducted a randomized trial of HNC patients who were curatively treated with CCRT at the King Chulalongkorn Memorial Hospital during February 2020 to October 2021. Inclusion criteria were age $\geq$18-year-old, ECOG performance status of 0–2, and primary HNC tumor locations including oral cavity, oropharynx, nasopharynx, hypopharynx, and supraglottic larynx. We excluded patients who had the primary disease located at the salivary gland, paranasal sinus, nasal, or ear canal. Patients with a history of allergic reactions to povidone-iodine or benzydamine hydrochloride were excluded from this study. Supportive treatments including analgesic, antibiotics, or anti-fungal usage, nasogastric tube insertion, and hospitalization were allowed by judgement of the patient's physician. The trial was conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki and approved by the Institutional Review Board of Chulalongkorn University (IRB No. 587/62). All patients provided written informed consent. This trial was registered at clinicaltrials.in.th # TCTR 20200722005.

2.2. Treatment

Radiotherapy was performed using the Eclipse treatment planning system (Eclipse version 11.0, Varian, Palo Alto, CA, USA). Radiation techniques included three-dimensional conformal radiation therapy (3D-CRT), volumetric modulated arc therapy (VMAT), or intensity-modulated radiation therapy (IMRT) with a total dose of 66–70 Gy in 33–35 fractions. Dose constraints for organs at risk were a dose to 0.3 cc of brain stem and spinal cord $<$54Gy and $<$45Gy, respectively, a mean dose to the parotid gland $<$26 Gy, and a mean dose to the oral cavity $<$40 Gy for non-oral cavity cancer. Radiotherapy was delivered using a linear accelerator (Varian Medical Systems Inc., Palo Alto, CA, USA) with dynamic 80–120 leaf multi-leaf collimators. Treatment verification included daily electronic portal images and weekly cone-beam CT as standard practice in our institute. Patients were assigned to receive concurrent chemotherapy with either cisplatin or carboplatin at the discretion of the treating physician.

2.3. Randomization, masking, and intervention

To compared the efficacy between benzydamine hydrochloride and 0.1% povidone-iodine to prevent RIOM, participants were assigned by a computer-generated allocation using a block size of four with a 1:1 ratio of receiving either our institution's in-house 0.1% povidone-iodine (menthol flavor) treatment or benzydamine hydrochloride (Difflam®). The gargling, prohibit swallowing, prescription was described 4 times a day for 30 s each, starting on the first day of CCRT. The protocol didn't prohibit the period before

or after gargling without eat or drink. The 0.1% povidone-iodine gargle was an in-house formula which was adjusted for more favorable taste and smell. We stratified the study participants according to 4 factors: 1) primary disease site (oral cavity/oropharynx vs. non-oral cavity/oropharynx), 2) treatment modality (post-operative or definite CCRT), 3) treatment schedule (weekly vs. 3-week), and 4) chemotherapy regimen (cisplatin vs. carboplatin).

2.4. Study visit, assessment procedure and outcome

The evaluation of RIOM was performed by one of investigators who was blinded to the assigned gargling agent using 2 assessment systems: 1) oral mucositis assessment scale (OMAS), and 2) National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The OMAS, which was the primary end point of the study, defined by an ulcer or pseudomembrane score and erythema score. The definition of ulcer or pseudomembrane score was range 0–3 in each area; 0 = no ulcer or pseudomembrane, 1 = less than 1 cm^2, 2 = 1–3 cm^2, and 3 = more than 3 cm^2. The erythema score ranged from 0 to 2 in each area; 0 = no redness, 1 = not severe, and 2 = severe. Final composite OMAS score (range 0–45) included both erythema and ulcer scores in 9 areas in the oral cavity including upper lip, lower lip, right buccal mucosa, left buccal mucosa, right lateral and ventral tongue, left lateral and ventral tongue, floor of mouth, soft palate, and hard palate [37]. The secondary end points included the CTCAE version 5.0, defining mucositis by grade I–V: Grade I = asymptomatic or mild symptoms, grade II = moderate pain or ulcer without interfere oral intake, grade III = severe pain and interfere oral intake, grade IV = life threatening required urgent intervention, and grade V = dead. Additional secondary endpoints were the rate of analgesic use, hospitalization, NG insertion, antibiotics use and anti-fungal use. Participants answered a satisfaction questionnaire (range 1–5; 1 = most dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = strongly satisfied) at the 1st and 5th week of the treatment product in terms of gargle taste, color, smell, package and comfort, efficacy by pain relief, burn relief, decrease tingling, less dryness after use, ease of eating and swallowing, better appetite after use, less sticky saliva, and overall satisfaction (range from 0 to 100) comparing patient satisfaction of both gargles. Schedule visits with the assessor were conducted once a week for 7 weeks during CCRT and 4-weeks after complete treatment. Demographic characteristics of participants and supportive treatments were extracted from the hospital database. Dose-volume histogram data were analyzed for the oral mean dose and volume of oral cavity receiving 30 and 40 Gy (V30 and V40).

2.5. Statistical analysis

The sample size of the study was calculated based on the hypothesis that in-house 0.1% povidone-iodine gargle might provide better efficacy than benzydamine hydrochloride (Difflam®) by greater than at least a 1 point difference in the median OMAS score at any time point [20]. To obtain 80% power, a 5% effect size, and assuming a 15% drop out rate, we calculated that the study needed to enroll 80 study participants. Categorical data were analyzed using Chi-square or Fisher's exact test. Independent T-tests and Mann-Whitney U tests were used to analyze continuous data as appropriate. Linear regression analysis was performed to identify significant covariates among clinical parameters. An ANOVA test was conducted to compare satisfaction scores between the two treatments. All analyses were conducted using R package version 3.6.3.

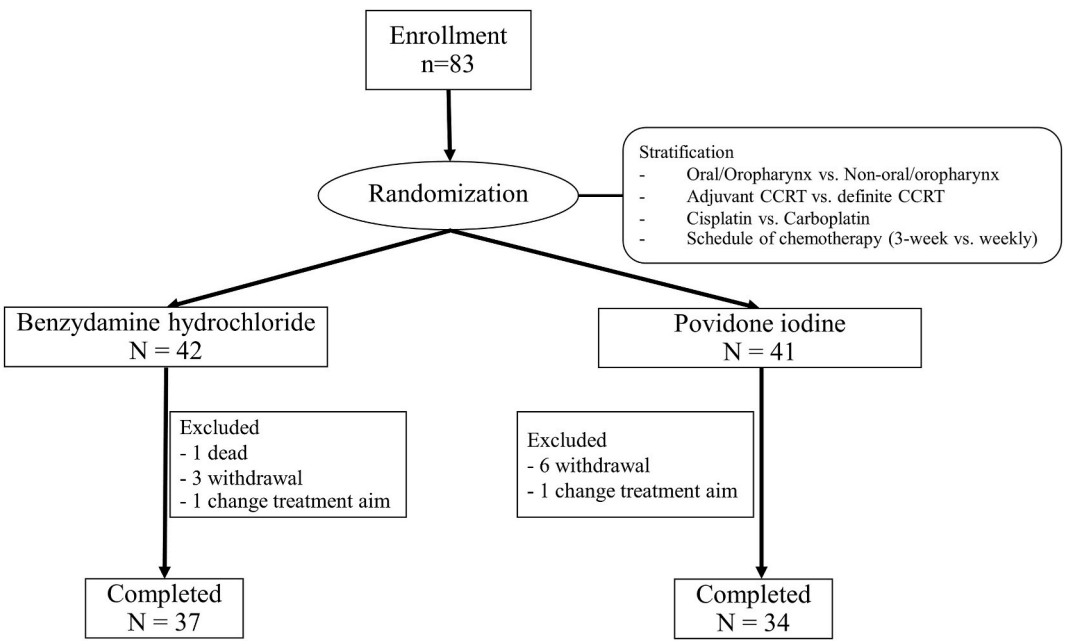

Fig. 1. Schema of the study protocol.

3. Results

The schema of the study protocol is shown in Fig. 1. Eighty-three participants were enrolled. Twelve participants withdrew their study consent. Reasons included nine participants (6 in 0.1% povidone iodine and 3 in benzydamine hydrochloride) refusing to use assigned gargling agent due to non-favor with taste or smell, two participants changing the schedule of radiation to palliative attempt, and one dying due to disease progression. The remaining 71 participants received complete CCRT treatment with 37 subjects in the benzydamine hydrochloride (Difflam®) group, and 34 patients in the 0.1% povidone-iodine group.

The median age of participants was 57 [range 34–86]. Male participants (73.5%) were predominant. The majority of subjects were former/current smoker (63.9%). The primary site of disease was located in the oral cavity and oropharynx (66.3%) followed by the nasopharynx, hypopharynx and supraglottic area (33.7%). Most of the participants had locally advanced stage III-IV by AJCC 8th classification (77.1%) and received definitive CCRT (61.4%). VMAT and IMRT were common radiation techniques in our study (91.6%). Mean oral dose in this cohort was 48.9 Gy. There was no significant difference in the mean oral dose between groups (55.2 Gy in benzydamine hydrochloride group vs. 48.5 Gy in 0.1% povidone-iodine group). Oral/oropharynx volume percentage for patients receiving radiation doses of 30 and 40 Gy (V30 and V40) were calculated. Median V30 and V40 was 84.3% and 72.7% and. 86.9% and 65% in Benzydamine hydrochloride and 0.1% Povidone-iodine, respectively. The majority of the participants received concurrent cisplatin either weekly (67.5%) or three-weekly (18.1%). Baseline characteristics were well-balanced between arms (Table 1).

3.1. Efficacy

All RIOM cases occurred after the 2nd week of CCRT. During treatment, the median weekly OMAS score ranged from 0 to 9 in benzydamine hydrochloride and 0–6 in 0.1% povidone-iodine was shown in Fig. 2. The univariate regression analysis revealed that povidone-iodine correlated with less RIOM compared to benzydamine hydrochloride (coefficient −2.25, 95% CI -4.37 to −0.012, *p*-value 0.03). The incidence of grade III-IV CTCAE RIOM during the entire period was 51.4% with benzydamide hydrochloride compared to 26.5% with 0.1% povidone iodine (*p*-value = 0.032). The peak incidence of grade III-IV CTCAE RIOM was documented at the 7th week of treatment, with the benzydamine hydrochloride significantly higher than 0.1% povidone iodine (40.5% vs. 11.8%, *p*-value 0.01) (Fig. 3). This indicated the efficacy of povidone-iodine to prevent severe RIOM which usually most severity in the last week of CCRT treatment.

Supportive treatments including topical analgesic, opioids and nasogastric tube insertion were not statistically significant between both arms (Table 2). Topical analgesic (xylocaine viscous) and opioids were prescribed higher in benzydamine hydrochloride than 0.1% povidone-iodine; 97.3% and 94.6% vs. 88.2% and 82.3%, respectively. In this study, NG tube was placed before enrolled into the study in 10 (23.8%) vs. 9 (22%) in benzydamine hydrochloride vs. 0.1% povidone-iodine respectively. It had to include in CTCAE grading per definition. Retain NG tube feeding due to severe RIOM was found in 9 (21.4%) in benzydamine hydrochloride vs. 7 (17%) in 0.1% povidone-iodine which was not significant difference. No differences were found in the rate of antibiotic, anti-fungal treatment and hospitalization in both arms (*p*-value 0.78, 0.70 and 0.87, respectively). We assessed the compliance of gargling treatment in all patients and found no significant difference between arms with a compliance rate of 93.8% with benzydamine hydrochloride and 89.8% with 0.1% povidone iodine, respectively (*p*-value 0.503).

Table 1
Demographic characteristics of the study participants.

Baseline characteristics		All N = 83	Benzydamine hydrochloride N = 42	Povidone-iodine N = 41	*p*-value
Age	Median age [Range]	57 [34–86]	59 [39–86]	55 [34–76]	0.109
Sex	Male	61 (73.5%)	33 (78.6%)	28 (68.3%)	0.295
Smoking	Never	30 (36.1%)	13 (31.0%)	17 (41.5%)	0.325
	Current/Former	53 (63.9%)	29 (69.0%)	24 (58.5%)	
Primary site	Oral site	55 (66.3%)	28 (66.7%)	27 (65.9%)	0.939
	Non oral	28 (33.7%)	14 (33.3%)	14 (34.1%)	
Stage	I-II	19 (22.9%)	8 (19.0%)	11 (26.8%)	0.405
	III-IV	64 (77.1%)	34 (81.0%)	30 (73.2%)	
ECOG	0	39 (47.0%)	18 (42.9%)	21 (51.2%)	0.451
	1–2	44 (53.0%)	24 (57.1%)	20 (48.8%)	
Radiation type	Adjuvant CRT	32 (38.6%)	15 (35.7%)	17 (41.5%)	0.596
	Definite CRT	51 (61.4%)	27 (64.3%)	24 (58.5%)	
Radiation technique	3D-CRT	7 (8.4%)	3 (7.1%)	4 (9.8%)	0.673
	VMAT/IMRT	76 (91.6%)	39 (92.9%)	37 (90.2%)	
Oral cavity volume radiation dose	Mean oral dose (Gy) [IQR]	48.9 [35.5–62.5]	55.2 [33.4–61.6]	48.5 [35.6–63.4]	0.964
	V30 (%)[IQR]	86.5 [57.3–100.0]	84.3 [56.4–100.0]	86.9 [56.5–99.5]	0.982
	V40 (%) [IQR]	66.6 [36.3–96.8]	72.7 [33.4–97.5]	65.0 [36.5–97.3]	0.819
Chemotherapy regimen	Cisplatin weekly	56 (67.5%)	28 (66.7%)	28 (68.3%)	0.709
	Cisplatin triweekly	15 (18.1%)	7 (16.7%)	8 (19.5%)	
	Carboplatin weekly	12 (14.5%)	7 (16.7%)	5 (12.2%)	

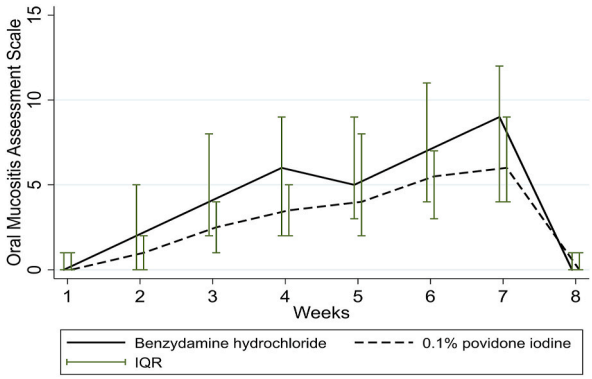

Fig. 2. Shown median OMAS and interquatile range according to each follow-up time point assessment (1st-8th week) in 2 treatment arms; benzydamine hydrochloride vs. 0.1% povidone-iodine.

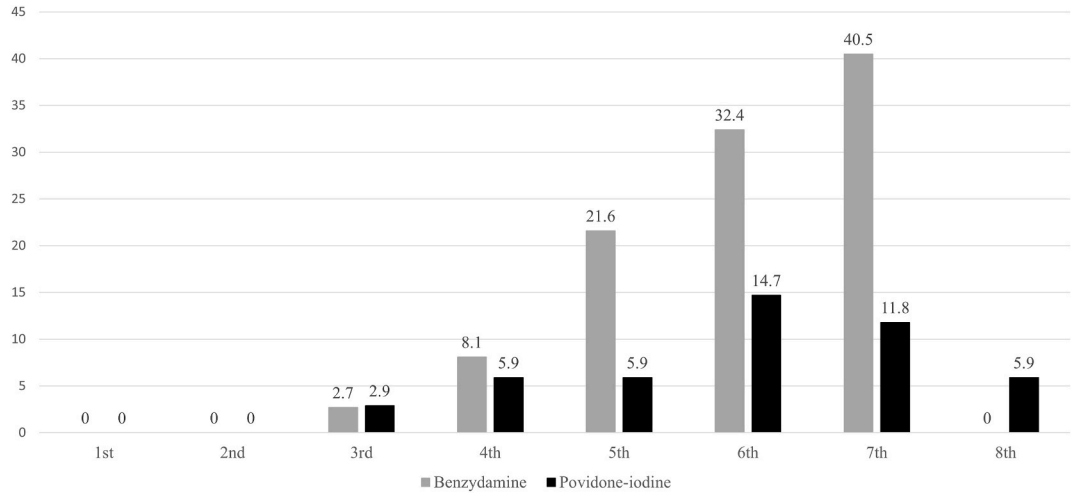

Fig. 3. Shown of NCI-CTCAEAE grade III-IV according to each follow-up time point assessment (1st-8th week) in 2 treatment arms; benzydamine hydrochloride vs. 0.1% povidone-iodine.

Table 2
Results of secondary end points of the study including CTCAE version 5.0, rate of analgesic use, hospitalization, NG insertion, antibiotics use and antifungal use for.

End points	Benzydamine hydrochloride (N = 37)	Povidone-iodine (N = 34)	*p*-value
NCI-CTCAE Grade I/II	18 (48.6%)	25 (73.5%)	0.032
NCI-CTCAE Grade III/IV	19 (51.4%)	9 (26.5%)	
Xylocaine use	36 (97.3%)	30 (88.2%)	0.136
Opioid use	35 (94.6%)	28 (82.3%)	0.103
NG tube	19 (51.4%)	16 (47.1%)	0.718
Hospitalization	6 (16.2%)	6 (17.6%)	0.872
Antibiotics prescription	12 (32.4%)	10 (29.4%)	0.783
Antifungal prescription	19 (51.4%)	19 (55.9%)	0.702

3.2. Participant satisfaction

We analyzed the satisfaction of gargling usage at the 1st and 5th weeks of treatment. Participants using benzydamine hydrochloride had more overall satisfaction than those using the in-house 0.1% povidone-iodine. The mean overall satisfaction score at the 1st and 5th week was higher in benzydamine hydrochloride than 0.1% povidone-iodine (45.3 $\pm$ 5.0 vs. 40.1 $\pm$ 6.1, *p*-value <0.001). Benzydamine hydrochloride gargling was superior than 0.1% povidone-iodine in terms of color, smell, package, comfort, and pain relief

(p-value <0.01) (Table S1).

3.3. Univariate and multivariate analysis factors correlated with OMAS score

We conducted an analysis to identify clinical factors associated with the OMAS score. In the univariate analysis, we found a significantly higher RIOM risk with the adjuvant CCRT setting (coefficient 4.06, 95% CI 2.06 to 6.07, p-value <0.001), oral/oropharynx as the primary site (coefficient 3.58, 95% CI 1.47 to 5.68, p-value 0.001), and oral cavity radiation dose (coefficient 0.13, 95% CI 0.06 to 0.19, p-value <0.001). Povidone-iodine gargling was associated with reduced RIOM risk (coefficient −2.25, 95% CI -4.37 to – 0.012, p-value 0.03). The multivariate analysis revealed that the adjuvant CCRT setting was the strongest factor associated with RIOM (coefficient 3.34, 95% CI 0.95 to 5.73, p-value 0.006) (Table 3).

4. Discussion

We conducted a randomized clinical trial to compare the efficacy of RIOM prevention between benzydamine hydrochloride (Difflam®) and in-house 0.1% povidone-iodine gargle for HNC patients who received CCRT. Benzydamine hydrochloride has previously shown superiority in prevention compared to sodium bicarbonate, normal saline and chlorhexidine and has been adopted as the current standard treatment in CCRT and radiotherapy [18–20,36,36]. Despite evidence of preventing RIOM, benzydamine hydrochloride has not been on the Thailand national drug list and is quite expensive. Evidence has accumulated showing that povidone-iodine gargling can be effective in preventing RIOM in a single radiotherapy modality, however, there remains a lack of evidence for efficacy among patients receiving concurrent chemoradiotherapy which has a higher incidence of RIOM. We choose the OMAS score as the primary end point due to its high inter-observer reproducibility and validated system [37]. The OMAS score represents the degree of mucositis which reflects inflammation by degree of erythema and ulcer or pseudomembrane. CTCAE which is the secondary outcome of this study is a composite endpoint between the degree of mucositis and functional outcomes such as pain management and nutritional support. Our study showed better RIOM prophylaxis using 0.1% povidone-iodine in both outcome assessments: OMAS score (coefficient - 2.25, 95% CI -4.37 to −0.012, p-value 0.03) and grade ¾ NCI-CTCAE toxicity assessment (26.5%) compared to benzydamine hydrochloride (51.4%). Povidone-iodine gargling which has an antiseptic effect and anti-inflammatory properties that can reduce proinflammatory cytokines and promote healing signals shown higher efficacy than benzydamine hydrochloride [31–33]. Our data support 0.1% povidone-iodine as a potentially new and better option for head and neck cancer patients who receive concurrent chemoradiotherapy.

In addition to our findings on the gargling agent, we identified some significant clinical factors that were correlated with RIOM in chemoradiotherapy treatment. The multivariate regression yielded results showing that the adjuvant CCRT after surgery was a strong factor correlated with RIOM (coefficient 3.34, 95% CI 0.95 to 5.73, p-value 0.006). Higher oral cavity radiation dose was also an important and significant factor correlated with RIOM (coefficient 0.09, 95% CI 0.02 to 0.15, p-value 0.009). Those 2 clinical factors associated with severity of RIOM can help physicians plan the best prophylaxis schema for chemoradiotherapy patients to decrease treatment toxicity.

While 0.1% povidone-iodine showed superior efficacy, participants reported lower satisfaction in terms of taste, color, smell, package, comfort, pain relief and overall scoring compared to benzydamine hydrochloride. Our in-house 0.1% povidone-iodine gargling was composed of 0.1% povidone iodine mixed with taste and smell enhancers (0.2% W/W; menthol, methyl salicylate, propylene glycol, and glycerin in various concentration). This information will allow us to further improve these aspects of our product.

The author would like to state some limitations of our study. First, our study was conducted in a single tertiary-referral hospital in Bangkok, Thailand. Second, twelve participants received concurrent carboplatin due to contraindication to cisplatin which is an adoptive concurrent treatment for the radiation in our center. Third, in our center, prophylaxis gastrostomy or NG placement before CCRT in locally advanced head and neck cancer is not a standard protocol. However, these factors allowed us to evaluate the true efficacy of 0.1% povidine-iodine in preventing RIOM in locally advanced head and neck cancer in patients who received concurrent chemoradiotherapy. Povidone-iodine gargle shown promising efficacy to prevent mucositis in head and neck cancer who received concurrent chemoradiotherapy.

Author contribution statement

Danita Kannarunimit, Attapol Chotirut: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Anussara Prayongrat, Piyada Sitthideatphaiboon, Chawalit Lertbusayanukul, Sarin Kitpanich, Chakkapong Chakkabat: Performed the experiments; Wrote the paper.

Chanida Vinayanuwattikun: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data; Wrote the paper.

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Table 3
Linear regression analysis of OMAS with clinical parameters.

Clinical factors	Univariate Coefficient (95%CI)	*p*-value	Multivariate Coefficient (95%CI)	*p*-value
Treatment arm	Ref	0.03	Ref	0.02
- Benzydamine hydrochloride				
- 0.1% povidone-iodine	−2.25 (−4.37 to −0.012)		- 2.15 (−3.99 to – 0.32)	
Age	Ref	0.67		
- ≤ 60 year	- 0.48 (−2.75 to 1.78)			
- > 60 year				
Sex	Ref	0.50		
-Male				
-Female	0.84 (−1.66 to 3.35)			
Smoking status	Ref	0.07		
- Former/current				
- Never	1.98 (−0.22 to 4.19)			
Primary site	Ref	0.001	Ref	0.96
- Non-Oral/Oropharynx				
- Oral/oropharynx	3.58 (1.47–5.68)		0.05 (−2.55 to 2.65)	
Staging	Ref 1.32 (−1.18 to 3.81)	0.29		
- Stage I-II				
- Stage III-IV				
Treatment modality	Ref	<0.001	Ref	0.006
- Definitive CRT				
- Adjuvant CRT	4.06 (2.06–6.07)		3.34 (0.95–5.73)	
Radiation technique	Ref	0.32		
- 3D-CRT				
- VMAT/IMRT	−1.93 (−5.84 to 1.98)			
Concurrent chemotherapy	Ref	0.62		
- Cisplatin				
- Carboplatin	−0.89 (−4.56 to 2.77)			
Oral cavity radiation dose-volume	0.13 (0.06–0.19)	<0.001	0.09 (0.02–0.15)	0.009
- Mean oral dose	0.07 (0.03–0.10)	<0.001		
- V30	0.07 (0.03–0.10)	<0.001		
- V40				

Additional information

Supplementary content related to this article has been published online at [URL].

Data sharing statement

The data associated with this study will be made available in anonymised format from the corresponding author upon reasonable request.

Declaration of interest's statement

The authors declare no competing interests.

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Appendix. ASupplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e15437.

Abbreviations

HNC = Head and neck cancer, RIOM = radiation-induced oral mucositis, MASCCI/ISOO = The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology, CCRT = concurrent chemoradiation, OMAS = Oral Mucositis Assessment Scale, NCI-CTCAE v.5 = The National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, NG= Nasogastric tube.

References

[1] W. Imsamran, P. Supaatagorn, I. Chiawiriyabunya, K. Namthaisong, M. Wongsena, *Cancer in Thailand 2018*. 2018, Cancer Registry Unit, National Cancer Institute Thailand, Bangkok, 2018.
[2] NCCN, <head-and-neck.pdf> 1, NCCN, 2021.
[3] J.S. Cooper, et al., Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck, Int. J. Radiat. Oncol. Biol. Phys. 84 (5) (2012) 1198–1205.
[4] D.J. Adelstein, et al., An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer, J. Clin. Oncol. 21 (1) (2003) 92–98.
[5] J.S. Cooper, et al., Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 350 (19) (2004) 1937–1944.
[6] J. Bernier, et al., Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer, N. Engl. J. Med. 350 (19) (2004) 1945–1952.
[7] J. Bernier, et al., Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501), Head Neck 27 (10) (2005) 843–850.
[8] V. Noronha, et al., Once-a-Week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial, J. Clin. Oncol. 36 (11) (2018) 1064–1072.
[9] M. Ghi, et al., Concomitant chemoradiation in locally advanced head and neck squamous cell carcinoma: a literature-based meta-analysis on the platinum concomitant chemotherapy, J. Clin. Oncol. 29 (2011).
[10] P. Szturz, et al., Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data, Oncol. 22 (9) (2017) 1056–1066.
[11] M. Al-Sarraf, et al., Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099, J. Clin. Oncol. 16 (4) (1998) 1310–1317.
[12] J. Guan, et al., A meta-analysis of weekly cisplatin versus three weekly cisplatin chemotherapy plus concurrent radiotherapy (CRT) for advanced head and neck cancer (HNC), Oncotarget 7 (43) (2016) 70185–70193.
[13] I. Chitapanarux, et al., Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial, Eur. J. Cancer 43 (9) (2007) 1399–1406.
[14] O. Hansen, et al., Importance of overall treatment time for the outcome of radiotherapy of advanced head and neck carcinoma: dependency on tumor differentiation, Radiother. Oncol. 43 (1) (1997) 47–51.
[15] L.S. Elting, et al., Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies, Int. J. Radiat. Oncol. Biol. Phys. 68 (4) (2007) 1110–1120.
[16] M. Vera-Llonch, et al., Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma, Cancer 106 (2) (2006) 329–336.
[17] S.T. Sonis, Mucositis: the impact, biology and therapeutic opportunities of oral mucositis, Oral Oncol. 45 (12) (2009) 1015–1020.
[18] K. Kin-fong Cheng, J. Ka Tsui Yuen, A pilot study of chlorhexidine and benzydamine oral rinses for the prevention and treatment of irradiation mucositis in patients with head and neck cancer, Cancer Nurs. 29 (5) (2006) 423–430.
[19] M. Rastogi, et al., Role of benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients treated with radiotherapy (>50 Gy) with or without chemotherapy, Support. Care Cancer 25 (5) (2017) 1439–1443.
[20] T.T. Chitapanarux, J. Petsuksiri, D. Kannarunimit, K. Katanyoo, C. Chakkabat, et al., Randomized control trial of benzydamine HCl versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis, Support. Care Cancer 26 (3) (2018) 879–886.
[21] P.A. Quane, G.G. Graham, J.B. Ziegler, Pharmacology of benzydamine, Inflammopharmacology 6 (2) (1998) 95–107.
[22] A. Guglielmotti, et al., Benzydamine protection in a mouse model of endotoxemia, Inflamm. Res. 46 (9) (1997) 332–335.
[23] M. Sironi, et al., Benzydamine inhibits the release of tumor necrosis factor-α and monocyte chemotactic protein-1 byCandida albicans-stimulated human peripheral blood cells, Int. J. Clin. Lab. Res. 27 (2) (1997) 118–122.
[24] R.V. Lalla, et al., MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy, Cancer 120 (10) (2014) 1453–1461.
[25] S. Elad, et al., MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy, Cancer 126 (19) (2020) 4423–4431.
[26] R.V. Lalla, F.D. Ashbury, The MASCC/ISOO Mucositis Guidelines: dissemination and clinical impact, Support. Care Cancer 21 (11) (2013) 3161–3163.
[27] A. Ariyawardana, et al., Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines, Support. Care Cancer 27 (10) (2019) 3985–3995.
[28] V, D.E.S, Lactobacillus brevis CD2 for prevention of oral mucositis in patients with head and neck tumors: a multicentric randomized study, Anticancer Res. 39 (4) (2019) 1935–1942.
[29] Y.T. Yu, et al., Effects of 9 oral care solutions on the prevention of oral mucositis: a network meta-analysis of randomized controlled trials, Medicine (Baltim.) 99 (16) (2020), e19661.
[30] J. Kanagalingam, et al., Povidone-iodine for the management of oral mucositis during cancer therapy, Onco Rev. 11 (2) (2017) 341.
[31] O. Traore, S.F. Fayard, H. Laveran, An in-vitro evaluation of the activity of povidone-iodine against nosocomial bacterial strains, J. Hosp. Infect. 34 (3) (1996) 217–222.
[32] A.R. McLure, J. Gordon, In-vitro evaluation of povidone-iodine and chlorhexidine against methicillin-resistant Staphylococcus aureus, J. Hosp. Infect. 21 (4) (1992) 291–299.
[33] P.L. Bigliardi, et al., Povidone iodine in wound healing: a review of current concepts and practices, Int. J. Surg. 44 (2017) 260–268.
[34] M.K.M. Valeh, A. Mansouri, H. Kamranzadeh, K. Gholami, K. Heidari, et al., Factors affecting the incidence and severity of oral mucositis following hematopoietic stem cell transplantation, Int. J. Hematol. Oncol. Stem Cell Res. 12 (2018) 142–152.
[35] R. Rahn, et al., Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy, Dermatology 195 (Suppl 2) (1997) 57–61.
[36] P. Madan Kumar, et al., The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial, J. Cancer Res. Therapeut. 4 (1) (2008) 3–8.
[37] S.T. Sonis, et al., Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group, Cancer 85 (10) (1999) 2103–2113.