RESEARCH ARTICLE

**Editorial Process:** Submission:03/26/2023 Acceptance:07/09/2023

# Prophylaxis of Oral Mucositis with Iodine Solution during Concurrent Chemoradiation of Head and Neck Cancer: Preliminary Results of a Double-Blind, Randomized Controlled Trial

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## Abstract

**Objective:** This study aims to evaluate the clinical efficacy of an in-house iodine solution (IS) mouthwash for the prophylaxis of concurrent chemoradiation (CCRT) induced oral mucositis (OM) in head & neck cancer (HNC) patients. **Methods:** This prospective, double-blind, randomized controlled trial was conducted on 20 HNC patients, being treated with definite or postoperative CCRT, at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. The patients were randomly assigned (1:1) to the treatment group or the control group. Patients in the treatment group gargled IS three times daily after meals, while patients in the control group gargled normal saline solutions (NSS). Assessment of OM was performed before starting CCRT, once a week during CCRT, and 4 weeks after CCRT was completed. The primary outcome was Oral Mucositis Assessment Scale (OMAS). **Results:** The mean weekly OMAS, pain score, and impact on swallowing score were not statistically significant in patients who rinsed with IS mouthwash compared to those who received NSS ($p > 0.999$ in every week). There was no difference in the mean onset to OM (all grades) ($p = 0.704$), and the mean duration of OM (all grades) ($p = 0.365$). Severe OM (WHO grade 3-4) occurred in three patients [IS=2, NSS=1] with the median onset of 45.50 and 33.00 days ($p = NA$), and the duration of 8.00 and 57.00 days ($p = NA$) in the IS and NSS groups, respectively. Oral candidiasis occurred in one patient from the NSS group while no secondary infection of oral mucosa was observed in the patients receiving IS mouthwash. **Conclusion:** The study could not reach statistically significance to show that IS mouthwash was effective in of prevention CCRT-induced OM. Further study with a larger number of participants is encouraged.

**Keywords:** Povidone-iodine- oral mucositis- prophylaxis- head and neck cancer- chemoradiotherapy

*Asian Pac J Cancer Prev,* **24 (7)**, 2445-2454

## Introduction

Oral mucositis (OM) is a common complication suffered by almost all head and neck cancer (HNC) patients undergoing radiation treatment. Radiotherapy alone may lead to severe OM for more than 40% of all cases, and adding concurrent chemotherapy can raise the incidence of severe OM to about 70% (Calais et al., 1999; Trotti et al., 2003; Oronsky et al., 2018). The pathophysiology is explained by the direct effect of radiation; it inhibits cell growth, and slow maturation of the primary mucosal barrier in the mouth and throat. Concurrent chemoradiation (CCRT) can directly damage the DNA of basal epithelial cells. It initiates pro-inflammatory cytokines & transcription factors such as IL1, IL6, TNF-α, NF-kB, Wnt, p53, resulting in apoptosis and indirect cell death. This process may further aggravate cytokines, causing more inflammation of oral mucosa (Beumer et al., 1979a; Beumer et al., 1979b; Sonis, 2004; Sonis, 2009; Chaudhry and Ehtesham, 2023). Severe OM may lead to secondary infection, poor nutrition, poor quality of life, and the interruption and delay of radiation therapy. These factors may complicate treatment outcomes (Sonis et al., 2004; Mallick et al., 2016; Chaudhry and Ehtesham, 2023). According to a review by Chaudhry (2023), there is currently no gold standard for the management of oral mucositis since there are no evidence-based recommendations.

The MASCC/ISOO Clinical Practice Guidelines for Oral Mucositis 2014 (Lalla et al., 2014) recommended

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using benzydamine HCl mouthwash, for prevention of OM in HNC patients receiving a moderate dose, of up to 50 Gy of radiation therapy alone. There was no established guideline for the prophylaxis of OM in patients undergoing CCRT at the time this study began. Other prophylactic agents that may have potential to reduce the incidence and severity of OM are nystatin, povidone iodine (PVP-I), sodium bicarbonate solution, normal saline solution (NSS) (Lalla et al., 2014; Chitapanarux et al., 2018). PVP-I mouthwash has the potential to be used as a topical antibiotic, and has an anti-inflammatory effect that may delay the onset, and reduce the severity of, OM. A systematic review (Kanagalingam et al., 2017) has found that there is a moderate scientific evidence for the benefit of PVP-I in OM management thus PVP-I can be recommended for prevention of OM based on the available evidences.

Commercial PVP-I mouthwash is widely available but in Thailand, it is still not reimbursed into Universal Health Coverage (UHC) and Social Security Office (SSO) health program. For long course treatment like CCRT which takes a few months to finish, rinsing with PVP-I daily is considered expensive based on Thai population incomes. Therefore, the Pharmacy Department of Srinagarind Hospital has produced an in-house iodine solution (IS) mouthwash, which contains the same active ingredients as the commercial PVP-I mouthwash. It is cheaper and can be reimbursed into UHC and SSO health program. This study was done to find out the clinical efficacy of this mouthwash for prophylaxis of CCRT induced OM.

## Materials and Methods

*Study design*

This study was a single institute, prospective, double-blind, randomized controlled trial, conducted at Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand from January to December 2019. The study protocol and patient informed consent document were approved by the Khon Kaen University Ethics Committee for Human Research (Ref. No. HE611584). The trial was registered in the UMIN Clinical Trials Registry (Ref. No. UMIN000042920).

*Patients*

Head and neck cancer patients scheduled to undergo concurrent chemoradiation at Division of Radiation Oncology, Khon Kaen University, were enrolled in this study.

*The inclusion criteria were as follows*

1) Patients should be diagnosed with head and neck cancer without distant metastasis.

2) Patients should be between 18 -70 years old of age.

3) Patient should be receiving concurrent chemotherapy with a platinum-based agent.

4) Oral mucosa should be included in the radiation field.

5) The planned radiation dose to the primary tumor should exceed 50 Gy.

*The exclusion criteria were as follows*

1) Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Score more than 2.

2) Patients with an allergy to iodine and/or seafood.

3) Patients who were unable to take part in the follow up schedule.

4) Patients who were pregnant or lactating.

5) Patients who had undergone prior radiation therapy.

6) Patients who were diagnosed with more than one primary cancer.

7) Patients who were diagnosed with hematologic malignancies.

8) Patients who were to undergo radiation therapy with altered fractionation.

9) Patients who were previously treated with hyperbaric oxygen therapy.

*Randomization and masking*

After obtaining informed consent, the patients were randomly assigned to the treatment or control group, by stratified simple random sampling. The patients were first stratified with primary cancer site (Oral cavity vs Oropharynx vs Nasopharynx vs Nasal cavity), and stage groups (I vs II vs III vs IV). Opaque envelopes containing a card marked with the letter A or B were then picked by the patients, assigning themselves to either the treatment or control group.

*Concurrent chemoradiation*

All patients were treated with either definitive or postoperative concurrent chemoradiation of head and neck cancers. The total dose of external beam irradiation to the primary tumor was 66-70 Gy. A daily dose of 1.8-2 Gy was given five times a week, with either 3D-CRT, or IMRT/VMAT technique. Radiotherapy machines were 6-MV linear accelerators (iX or TrueBeam, Varian Medical systems, Palo Alto, CA). Oral cavities were contoured based on consensus guidelines (Brouwer et al., 2015) for CT-based delineation of organs at risk in the head and neck region. Chemotherapy was either cisplatin weekly (40 $mg/m^2$), cisplatin tri-weekly (100 $mg/m^2$) or carboplatin weekly (AUC2).

*Mucositis prophylaxis*

IS and NSS mouthwashes were prepared by the Manufacturing Unit, Pharmacy Department, Srinagarind Hospital, Khon Kaen University. Coloring agents were used to color NSS light brown to mimic the color of IS. Both solutions were packaged in a 450-milliliter tea-colored plastic bottle to preserve IS from sunlight and blind both patients & investigators. The mouthwashes were coded to either A or B by the manufacturer. The code was then revealed at the end of the study. All patients were given a 30-milliliter glass for mouthwash measurement at the time of recruitment. They were instructed to gargle with 30 milliliters of mouthwash for 30 seconds, three times a day after meal, from the first day of CCRT to the day of completion. They were also assigned to standard oral hygiene care from the MASCC/ISOO guidelines (Lalla et al., 2014; Elad et al., 2020).

*Oral examination*

An oral examination was done before the start of CCRT, at weekly intervals during CCRT, at the end of CCRT, and 4 weeks after completion of CCRT, using the Oral Mucositis Assessment Scale (OMAS) (Sonis et al., 1999) and World Health Organization (WHO) criteria for grading of oral mucositis (Spijkervet et al., 1989; Wilkes, 1998).

*Study outcomes*

The primary outcome of this study was OMAS. Secondary outcomes were; pain score, impact on swallowing score, incidence, severity, onset, and duration of OM, analgesic drug use, total treatment break, and secondary infection of oral mucosa.

*Statistical analysis*

Data were collected and managed using REDCap electronic data capture tools hosted at https://md.redcap.kku.ac.th/ (Harris et al., 2009; Harris et al., 2019). The demographic characteristics of the participants were described using frequency and percentage for categorical data. For continuous data, the mean and standard deviation or the median and interquartile range were used. Patient data were compared between the two groups using the Fisher's Exact test or the Pearson Chi-Square test, for categorical data. The Independent-Samples T-test was used for continuous data with a normal distribution, and the Mann-Whitney U-test was used for continuous data with a nonparametric distribution. The OMAS score, pain score, and impact on swallowing score, were analyzed using the Generalized Estimating Equations (GEE) model and then compared weekly between the two groups by Bonferroni test. The incidence and severity of OM were analyzed using the Mann-Whitney U test. The onset and duration of OM, time to analgesic drug, and total treatment break, were compared between the two groups using the Independent-Samples T-test or the Mann-Whitney U test. The data were analyzed with IBM SPSS Statistics Version 19 (IBM Inc., New York, NY) and STATA Version 10.1 (StataCorp LP., College Station, TX). All test statistics were two-sided, and a p-value of less than 0.05 was considered statistically significant.

## Results

From January to December 2019, a total of 65 patients were referred to the Division of Radiation Oncology, for multimodal treatments of head and neck cancer. Of those sixty-five patients who were potentially eligible, forty-five patients did not meet the inclusion criteria, therefore twenty patients were included and randomly assigned to two groups (each 10 patients) (Figure 1). Five patients withdrew from the study (three discontinued CCRT, and two could not tolerate the side effects of the mouthwash). Of the two patients who decided to stop using the mouthwash, one came from each group. The reported mouthwashes' adverse effects were nausea and unfavorable taste/odor. One patient did not complete the follow up examination after finishing CCRT. A total of 14 patients completed the study (six from the IS group, and eight from the NSS group). All 20 patients' data were analyzed per 'intention-to-treat' analysis.

*Demographic Characteristics*

Distribution of the patients (Table 1) is based on; sex, age, ECOG Performance Status, primary cancer site, cancer staging, aim of treatment, concurrent chemotherapy regimen, radiation technique, radiation dose, oral cavity dose, radiation volume, and the duration of treatment.

Participants in this study consisted of twelve men and eight women, with mean ages of 53.90 and 56.30 years in the treatment and control groups respectively. Primary cancer sites were; oral cavity (30%), oropharynx (30%), nasopharynx (30%) and nasal cavity (10%). Most of the patients had locally advanced disease; Stage III (35%) and Stage IV (50%). These were assigned to definitive treatment (80%), while the rest were post-operative (20%). Radiation techniques were 3D-CRT (50%) and IMRT/VMAT (50%). The most common concurrent chemotherapy regimen was weekly cisplatin (55%). The median radiation dose was 70 Gy in both groups. The mean oral cavity doses were 59.30 and 49.72 Gy, the mean radiation volumes were 1269.99 and 1404.59 $cm^3$ and the mean durations of treatment were 64.40 and 57.80 days, in the treatment & control groups respectively. Note that the mean oral cavity dose was about 10 Gy higher in the IS group. There is no statistically significant difference in characteristic data between the two groups.

*Oral Mucositis Assessment Scale (OMAS)*

Mean overall OMAS scores were 7.44 (±6.45) and 7.28 (±6.25) in the treatment & control groups respectively. Weekly OMAS scores are summarized in [Table 2]. Overall mean difference was -0.40 (95% CI [-3.95, 3.15], p-value = 0.825). There is no statistically significant difference in weekly OMAS score (Figure 2) between the two groups (p-value > 0.999 in every week). The maximum OMAS score of the IS group was 24 in week five of CCRT, while the NSS group was 24 in week seven. Most common location of OM (Table 3) was soft palate (72.2%) and the second was oral tongue (64.7%).

*Pain score and impact on swallowing*

The weekly mean pain score [Fig. 3] showed no statistically significant difference between the two groups, with p-value > 0.999 in every week. Overall mean pain scores were 3.93 in the IS group, and 3.14 in the NSS group, with a maximum pain score of 9 in both groups at week two and week three, respectively. The impact on swallowing score (Figure 4) also showed no statistically significant difference (p-value > 0.999).

*Incidence, severity, onset, and duration of oral mucositis*

All patients developed OM (Table 4). Severe OM (WHO grade 3-4) was reported in three patients (15%). Of the three patients who developed severe OM, two were from the IS group, while the other was from the NSS group. The severity of OM by WHO grading is summarized in (Table 5). The mean WHO scores were 2.0 and 1.9 in the IS group and NSS groups respectively. There is no statistically significant difference of mucositis

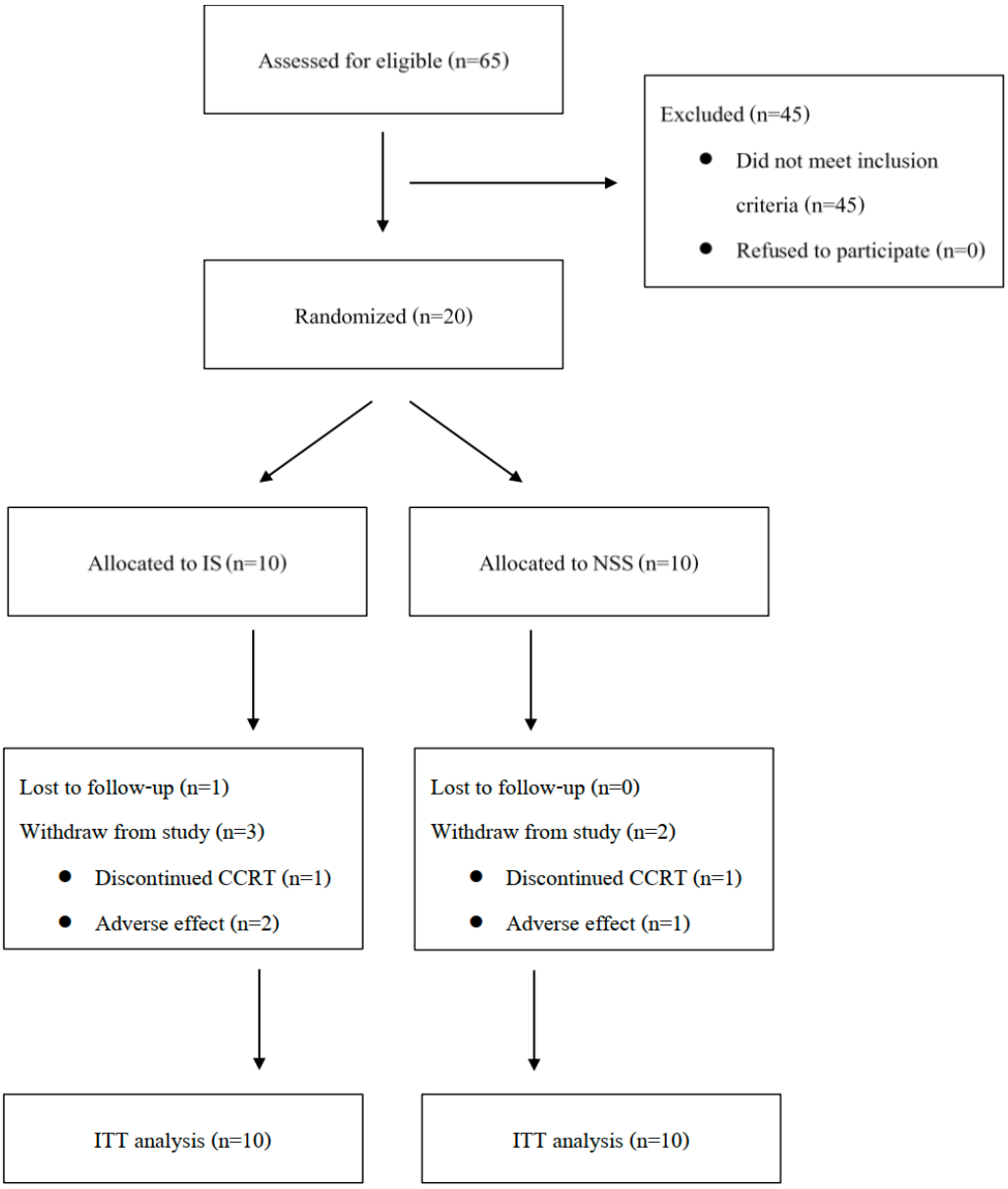


Figure 1. CONSORT Flow Chart of Participants in This Study

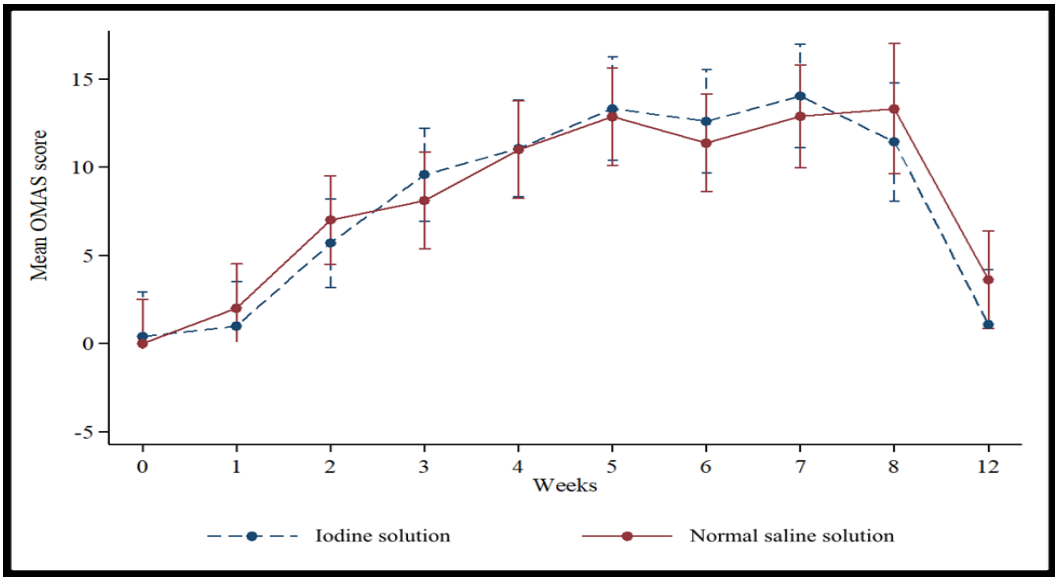


Figure 2. Mean Weekly OMAS Score

Table 1. Demographic Characteristics Presented as Frequency and Percentage Unless Otherwise Specified

| Variables | Iodine solution (n=10) | NSS (n=10) | p-value |
|---|---|---|---|
| Sex | | | >0.999[a] |
| Male | 6 (60.0%) | 6 (60.0%) | |
| Female | 4 (40.0%) | 4 (40.0%) | |
| Mean age in years (± SD) | 53.90 (7.48) | 56.30 (12.54) | 0.610[b] |
| ECOG | | | >0.999[a] |
| 0 | 7 (70.0%) | 6 (60.0%) | |
| 1 | 3 (30.0%) | 4 (40.0%) | |
| Primary cancer site | | | 0.721[a] |
| Oral cavity | 3 (30.0%) | 3 (30.0%) | |
| Oropharynx | 4 (40.0%) | 2 (20.0%) | |
| Nasopharynx | 2 (20.0%) | 4 (40.0%) | |
| Nasal cavity | 1 (10.0%) | 1 (10.0%) | |
| Stage | | | 0.443[a] |
| I | 1 (10.0%) | 1 (10.0%) | |
| II | 0 (0.0%) | 1 (10.0%) | |
| III | 5 (50.0%) | 2 (20.0%) | |
| IV | 4 (40.0%) | 6 (60.0%) | |
| Radiotherapy aim | | | 0.582[a] |
| Definitive | 9 (90.0%) | 7 (70.0%) | |
| Post-operation | 1 (10.0%) | 3 (30.0%) | |
| Chemotherapy regimens | | | 0.236[a] |
| Weekly cisplatin | 5 (50.0%) | 6 (60.0%) | |
| Tri-weekly cisplatin | 4 (40.0%) | 1 (10.0%) | |
| Weekly carboplatin | 1 (10.0%) | 3 (30.0%) | |
| Techniques | | | >0.999[a] |
| 3D-CRT | 5 (50.0%) | 5 (50.0%) | |
| IMRT/VMAT | 5 (50.0%) | 5 (50.0%) | |
| Median radiation dose in Gy (IQR) | 70.00 (66.45 to 70.00) | 70.00 (67.50 to 70.00) | 0.926[c] |
| Mean oral cavity dose in Gy (± SD) | 59.30 (10.47) | 49.72 (14.10) | 0.102[b] |
| Mean volume of RT in $cm^3$ (± SD) | 1269.99 (338.38) | 1404.59 (611.08) | 0.550[b] |
| Mean RT duration in days (± SD) | 64.40 (23.41) | 57.80 (18.80) | 0.496[b] |

[a], p-value from Fisher's Exact test or Pearson Chi-Square test; [b], p-value from Independent-Samples T test; [c], p-value from Mann-Whitney U test

Table 2. Summary of Overall and Weekly Mean OMAS

| Mean OMAS | Iodine solution | NSS | Mean difference (95%CI) | p-value |
|---|---|---|---|---|
| Overall | 7.44 (± 6.45) | 7.28 (± 6.25) | -0.40 (-3.95 to 3.15)[a] | 0.825[b] |
| Baseline | 0.40 (± 1.26) | 0.00 (± 0.00) | -0.40 (-5.48 to 4.68) | >0.999[c] |
| Week 1 | 1.00 (± 1.70) | 2.00 (± 2.94) | 1.00 (-4.08 to 6.08) | >0.999[c] |
| Week 2 | 5.70 (± 3.62) | 7.00 (± 5.44) | 1.30 (-3.78 to 6.38) | >0.999[c] |
| Week 3 | 9.44 (± 3.94) | 7.88 (± 5.41) | -1.46 (-6.91 to 3.99) | >0.999[c] |
| Week 4 | 10.88 (± 4.29) | 10.75 (± 5.92) | -0.07 (-5.66 to 5.51) | >0.999[c] |
| Week 5 | 13.43 (± 7.30) | 12.63 (± 4.17) | -0.45 (-6.20 to 5.29) | >0.999[c] |
| Week 6 | 12.71 (± 3.77) | 11.13 (± 5.19) | -1.24 (-6.98 to 4.51) | >0.999[c] |
| Week 7 | 14.14 (± 3.67) | 12.57 (± 6.00) | -1.15 (-7.04 to 4.75) | >0.999[c] |
| Week 8 | 11.00 (± 7.00) | 11.50 (±5.45) | 1.89 (-5.25 to 9.02) | >0.999[c] |
| Follow-up | 1.33 (± 2.42) | 3.38 (± 3.25) | 2.53 (-3.42 to 8.48) | >0.999[c] |

[a], Correlation coefficient with 95% confidence interval from generalized estimating equations (GEE) model; [b], p-value from GEE model; [c], Comparing mean OMAS between IS and NSS group using Bonferroni test

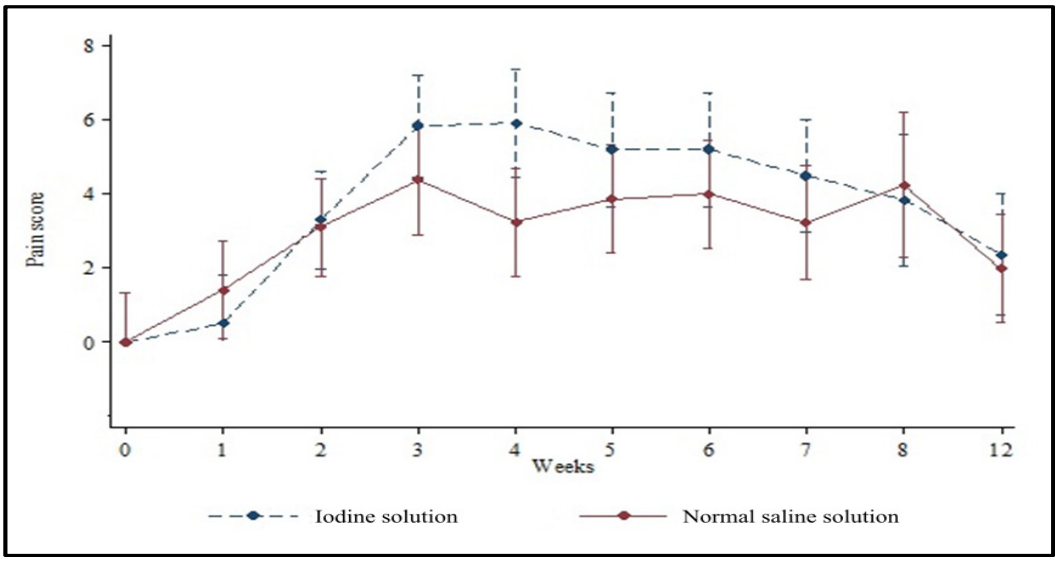


Figure 3. Mean Weekly Pain Score

severity between IS and NSS (p-value > 0.999).

The mean onsets of OM (Table 6) were 12.70 and 11.80 days (p-value = 0.704), while the median onsets of severe OM were 45.50 and 33.00 days (p-value = NA), in the IS and NSS groups respectively. Onset is slightly longer in the IS group for all grades of OM, but no statistically significant difference was demonstrated.

The median durations of OM were 72.00 and 88.00 days (p-value = 0.365), while the durations of severe OM

Table 3. Summary of OM Location

| Location of OM | Percentage |
|---|---|
| Lips | 20.00% |
| Cheeks | 46.70% |
| Tongue | 64.70% |
| Floor of mouth | 26.70% |
| Soft palate | 72.20% |
| Hard palate | 53.30% |

Table 4. Incidence of Oral Mucositis by Severity

| Incidence of OM | Iodine solution (n=10) | NSS (n=10) | p-value |
|---|---|---|---|
| Mild to moderate oral mucositis (WHO 1-2) | 8 | 9 | >0.999[a] |
| Severe oral mucositis (WHO 3-4) | 2 | 1 | NA |

[a], p-value from Mann-Whitney U test

Table 5. Severity of Oral Mucositis by Maximum WHO Grade at Any Point of Time during CCRT

| WHO grade | Iodine solution (n=10) | NSS (n=10) | p-value |
|---|---|---|---|
| 0 | 0 | 0 | NA |
| 1 | 2 | 2 | >0.999[a] |
| 2 | 6 | 7 | >0.999[a] |
| 3 | 2 | 1 | NA |
| 4 | 0 | 0 | NA |
| Mean | 2 | 1.9 | >0.999[a] |

a, p-value from Pearson Chi-Square test

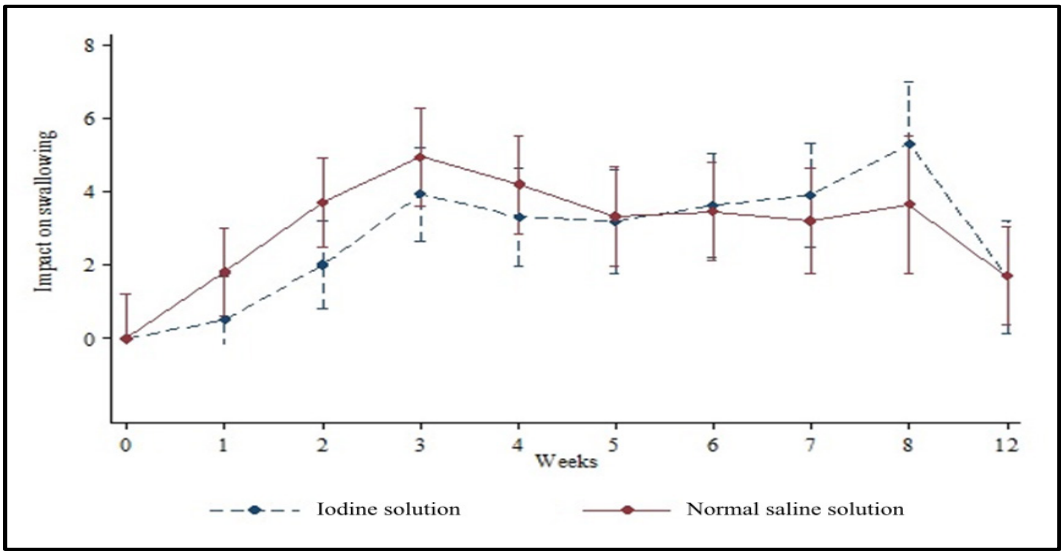


Figure 4. Mean Weekly Impact on Swallowing Score

Table 6. Summary of Secondary Outcomes in Days Presented as mean ± SD Unless Otherwise Specified

| Secondary outcomes | IS (n=10) | NSS (n=10) | p-value |
|---|---|---|---|
| Onset to OM (all grades) | 12.70 (± 5.72) | 11.80 (± 4.66) | 0.704[a] |
| Onset to severe OM (WHO 3-4) [median, IQR] | 45.50 (37.00 to 54.00) | 33.00 (NA) | NA |
| Duration of OM (all grades) [median, IQR] | 72.00 (67.00 to 75.00) | 88.00 (71.50 to 92.00) | 0.365[b] |
| Duration of severe OM (WHO 3-4) | 8.00 (NA) | 57.00 (NA) | NA |
| Time to analgesic drug | 21.29 (± 10.16) | 19.67 (± 13.56) | 0.810[a] |
| Total treatment break | 15.25 (± 5.91) | 7.00 (± 6.10) | 0.131[a] |
| Tube feeding [frequency, percentage] | 3 (30%) | 4 (40%) | 0.639[c] |

[a], p-value from Independent-Samples T test; [b], p-value from Mann-Whitney U test; [c], p-value from Pearson Chi-Square test

were 8.00 and 57.00 days (p-value = NA), in the IS and NSS groups respectively. There was a shorter duration for all grades of OM in the IS group, but the difference was not statistically significant. Note that severe OM duration was potentially significantly shorter in IS group.

*Analgesic drug use, treatment break and secondary infection*

Analgesic drug use was observed in 13 patients (65%) of whom seven were from the IS group, and six were from the NSS group. All 13 patients were prescribed 0.5% Xylocaine Mouthwash and instructed to gargle 30 milliliters three times a day, 30 minutes before a meal. The mean times to analgesic drug were 21.29 and 19.67 days (p-value = 0.810), in the IS and NSS groups respectively. No statistically significant difference was observed.

A total of seven patients (35%) had a treatment break during CCRT. Four patients were from the IS group, and the rest from the NSS group. The reasons for the treatment interruption were; neutropenia (n=3), moist desquamation of neck (n=3), and pulmonary TB (n=1). None of the participants had a treatment break because of intolerable OM. Median durations of treatment break were 15.20 and 7.00 days in the IS and NSS groups respectively (p-value = 0.131), showing no statistically significant difference. There was also no difference in tube feeding rate (p-value = 0.639).

Secondary infection of oral mucosa was noted in one patient from the NSS group, who developed oral candidiasis that required a topical antifungal drug. All patients in the IS group did not show a secondary bacterial or fungal infection of oral mucosa during CCRT.

## Discussion

The objective of this study was to prove the efficacy of an in-house IS mouthwash, for prophylaxis of OM in HNC patients during CCRT. OM happens in almost all patients whose oral mucosa was included in the radiation fields. Chemotherapy alone also causes adverse effects including OM. Combining chemotherapy and radiation increases the incidence and severity of mucositis. There was no established guideline suggesting an effective treatment agent or intervention, for prevention of OM during CCRT at the time this study began.

Povidone-iodine is one of the local antimicrobial agents which have been proved to be safe and effective in antiseptic and wound healing for a long time (Kanagalingam et al., 2017). Povidone-iodine complexes slowly release free iodine into a medium until equilibrium. The main active ingredient is free iodine, which has broad-spectrum anti-microbial effects, inhibiting critical cellular mechanisms via the oxidation of nucleotides, amino acids, and fatty acids, in cell membranes (Kanagalingam et al., 2015). A review (Paulson, 2003) has stated that it is effective against both gram-negative and gram-positive bacteria, yeasts, protozoa and viruses. It also has anti-inflammatory effects by inhibiting pro-inflammatory cytokines arising from the host response. These effects have been proved to be clinically relevant, in several conditions (Konig et al., 1997; Beukelman et al., 2008). A systematic review (Kanagalingam et al., 2017) has found that there is a moderate scientific evidence for the benefit of PVP-I in OM management and also encouraged additional studies.

This study has not demonstrated statistically significant difference of the weekly OMAS, pain score, and impact on swallowing score, between the two groups. The mean onset and duration of OM (all grades) were not different. The onset and duration of severe OM (WHO grade 3-4) were potentially better in the IS group, but no statistically significant differences were found. Comparing the results to the previous data from a PVP-I study (Rahn et al., 1997) reported that mean onset of mucositis was 2.25 weeks in the 1.25% PVP-I group, and 1.5 weeks in the control group. The mean total duration of mucositis was 2.75 weeks in the PVP-I group and 9.25 weeks in the control group. Our results were similar with a mean onset of 12.70 days (1.81 weeks) and 11.80 days (1.69 weeks) in the IS and NSS groups respectively. With a mean total duration of 77 days (11 weeks) and 84 days (12 weeks) in the IS and NSS groups respectively, our study was inferior. One of the reasons might be that in the Rahn (1997), all patients received prophylaxis with nystatin, dexpanthenol, rutoside and immunoglobulin along with the intervention and control mouthwashes. A four-arm double-blind study (Madan et al., 2008) conducted to evaluate the effectiveness of three alcohol-free mouthwashes in patients undergoing head and neck cancer radiotherapy. They found that the 1% PVP-I group had a significantly lower mucositis score (mean WHO score = 0.30). Compared to our results with the mean WHO score 2.0 in IS group, our study was inferior. The main reason was that the patients in our study underwent CCRT causing higher grade of OM, while the population in Madan study receiving RT alone.

There are a few reasons to explain insignificant data of our study. First, the population in this study was too small to detect any significant differences between the two groups, leading to underpower of the study. Secondly, there may be a concentration issue of iodine-based mouthwash. The solution used in this study contained free iodine with a concentration of 0.25 mg/mL (0.025%). A concentration of PVP-I ranging between 0.1-1%, showed a more rapid bactericidal effect than a full-strength 10% PVP-I solution (Selvaggi et al., 2003). Stock 10% PVP-I contains approximately 1% of free iodine (Ferguson et al., 2003). Hence a 0.1-1% PVP-I solution contains free iodine of 0.01-0.1%. This is theoretically comparable to our solution with free iodine of 0.025%. However, a recent systematic review (Kanagalingam et al., 2017) has found that only randomized studies using PVP-I with concentrations ranging between 0.5 and 1%, showed positive results in alleviation of OM related symptoms. A trial (Rao et al., 2014) comparing a 0.1% PVP-I and a turmeric gargle in HNC patients undergoing CCRT or RT alone, has confirmed the above statement from Kanagalingam (2017) by showing that 0.1% PVP-I did not have significant benefit in prevention of radiation-induced OM. It may be assumed that the anti-inflammatory effect needs a higher concentration than the anti-microbial effect, and the IS mouthwash in our study, although was effective as a local antiseptic agent from our result that no secondary infection was observed in IS group, may not contain enough free iodine to be effective against inflammatory mucositis.

Thirdly, there was a radiation technique issue to be noted. Radiation techniques were not clearly described in prior studies about PVP-I for OM prevention. Madan (2008) stated that their participants received external irradiation from a cobalt-60 radioactive source which used a conventional 2D technique, while Rahn (1997) and Rao (2014) reported using a LINAC 6 MV without describing the radiation technique. Radiation techniques also play an important role in reducing radiation-induced complications such as OM. A study Bahl et al., (2017) reported that modern techniques such as IMRT and VMAT for head and neck cancer can significantly reduce acute toxicity of mucositis and xerostomia, compared to conventional 2D radiotherapy. Many studies Gupta et al., (2012); Kouloulias et al., (2013) and Gupta et al., 2018) reported that there was no significant difference in the incidence and severity of OM between 3D-CRT & IMRT/VMAT. All participants in our study received external radiation using either 3D-CRT (50%) or IMRT/VMAT techniques (50%). This may explain the lower incidence of severe OM (WHO 3-4) in our study (15%), when compared to the historical data (Calais et al., 1999; Trotti et al., 2003; Oronsky et al., 2018) that reported the incidence of CCRT-induced severe OM about 70%, reflecting in the similar results between the treatment & control groups. Less incidence of OM requires more sample size to detect any significant benefit from using IS mouthwash as a prophylactic agent.

Lastly, there was an issue of radiation dose to oral cavity. Mean oral cavity dose, although was not statistically significantly different, was about 10 Gy higher in the IS group from the different in the majority of primary cancer site between the two groups. The majority in the IS group was oropharyngeal cancer, while it was nasopharyngeal cancer in the NSS group. The radiation dose to the primary cancer overlapped more volumes of oral cavity in the IS group, resulting in higher mean oral cavity dose. A 10-Gy difference could lead to higher OMAS in the IS group. Thus, when compared to NSS, using IS mouthwash resulted in the similar outcomes in terms of CCRT-induced OM prevention.

Apart from iodine-based mouthwashes, there are some randomized controlled trials (RCT) studying other interventions to prevent OM during CCRT such as low-level laser therapy, benzydamine HCl mouthwash, Rebamipide gargle, and probiotics. Three RCTs (Antunes et al., 2013; Gautam et al., 2013; Oton-Leite et al., 2015) showed that low-level laser therapy was effective in reducing severity of CCRT-induced OM. About 80% of participants in Antunes (2013) and all participants in Gautam (2013) and Oton-Leite (2015) received conventional 2D radiotherapy technique. Chitapanarux (2018) found that benzydamine HCl mouthwash was superior to basic oral care in reducing the severity of OM. Note that in this study, almost half of the patients (about 40%) were treated with conventional 2D radiotherapy technique. A study Chaitanya et al., (2017) found that Rebamipide gargle was effective for prolonging the onset and reducing the severity of OM in HNC patients undergoing CCRT, with 3D-CRT or IMRT techniques. Two RCTs (Chattopadhyay et al., 2014; Tsujimoto et al., 2015) showed the effectiveness of oral glutamine in reducing severity, delaying onset and duration of CCRT-induced OM. Radiation technique was not clearly described in both studies. A randomized study (Jiang et al., 2019) was conducted using only IMRT technique, to evaluate the effect of a probiotic combination on the severity of OM, in locally advanced nasopharyngeal carcinoma undergoing CCRT. They showed that the probiotic combination modifies gut microbiota, enhances the immune response of patients, and significantly reduces the severity of OM. At the time our study was being conducted, the latest update of the MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy (Ariyawardana et al., 2019; Hong et al., 2019; Yarom et al., 2019; Zadik et al., 2019; Elad et al., 2020; Yarom et al., 2020) was published. Recommendations with level of evidence (LoE) for prevention of OM in HNC patients treated with CCRT were low-level laser therapy (LoE I), oral glutamine (LoE II), and benzydamine HCl mouthwash (LoE II). Iodine-based mouthwashes, Rebamipide gargle, and probiotics need additional evidences to be included in the guideline.

The strength of this study was its prospective double-blind randomized design. To our knowledge we are the first to do this among studies on iodine-based mouthwash for prevention of CCRT-induced OM in HNC. The limitations of this preliminary study were its low volumes of participants (n=20). This resulted in underpower to detect statistical differences between the IS and NSS groups. Also, we did not strictly check for mouth-washing compliance in out-patient department. The formula of IS

mouthwash could be further developed by increasing free iodine concentration to at least 0.05% and adding some sweeteners and flavoring agents to avoid unfavorable metallic taste and odor of the mouthwash. Though the unfavorable taste may be the results from placebo effect and radiation effect to the taste buds.

In conclusion, this study could not reach statistically significance to show that IS mouthwash was effective in prevention of CCRT-induced OM. Further study with a larger number of participants is encouraged.

## Author Contribution Statement

Study concept and design: YN, OC, and KT. Data collection: YN. Analysis and interpretation of data: YN and KT. Drafting of the manuscript: YN, NS, SK, and KT. Review and editing: YN, OC, SS, NS, CS, SK, MP, and KT. All authors contributed to the article and approved the submitted version..

## Acknowledgements

The authors would like to express our sincere gratitude to Chedsada Noppawinyoowong, a survivor of cancer and the pharmacist who created the recipe for the iodine solution used in this study. We acknowledge the Manufacturing Unit, Pharmacy Department, Srinagarind Hospital for supplying gargle solutions used in this study. We acknowledge Brian C. Dobson for editing the manuscript. We also would like to thank all the patients who inspired us to look for a way to provide better treatment, with less toxicity.

*Funding*

This study is supported by an invitation research grant from Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (Ref No. IN62147). The funder had no role in the design of the study, nor in the collection, analysis, interpretation of the data, and writing the manuscript.

*Approval*

This article was part of a thesis in physician residency training for Diploma Thai Board of Radiation Oncology approved by Radiation Oncology Residency Training Committee, Thai Association of Radiation Oncology (THASTRO).

*Ethical consideration*

The study protocol and patient informed consent document were approved by the Khon Kaen University Ethics Committee for Human Research (Ref. No. HE611584). The trial was registered in the UMIN Clinical Trials Registry (Ref. No. UMIN000042920).

*Availability of data*

The study datasets are not publicly available due to privacy of the patients and ethical concerns.

*Conflict of interest*

The authors declare no conflict of interest in this study.

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