

## Original article

# Comparative efficacy of duo-gargling with sodium bicarbonate solution and Benzydamine hydrochloride (Diffiam®) to single gargling with Benzydamine hydrochloride (Diffiam®) in head and neck cancer participants who are receiving concurrent chemoradiotherapy for mucositis prevention and quality of life assessment: a preliminary analysis

Siraphob Sriprasert<sup>1</sup>, Anussara Prayongrat<sup>2</sup>, Chanida Vinayanuwattikun<sup>1,\*</sup>

<sup>1</sup>*Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*

<sup>2</sup>*Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*

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## Abstract

**Background:** Radiation-induced oral mucositis (RIOM) is a common complication of concurrent chemoradiotherapy (CCRT) in head and neck cancer (HNC). Benzydamine HCl is an established anti-inflammatory rinse for preventing RIOM, but it is not known whether adding sodium bicarbonate, which buffers oral pH and reduces microbial load, provides any added benefit.

**Objective:** To compare duo-gargling (Benzydamine HCl followed by sodium bicarbonate) with Benzydamine HCl alone for RIOM prevention in HNC patients receiving cisplatin-based CCRT.

**Methods:** In this preliminary analysis of a single-center, randomized, single-blinded trial, HNC patients receiving curative-intent CCRT were randomized 1:1 to duo-gargling or single gargling four times daily. The primary endpoint was the blinded-assessed Oral Mucositis Assessment Scale (OMAS) score at week 7. Secondary endpoints included CTCAE v5.0 grading and supportive-care needs. Mixed-effects models were used for longitudinal analysis.

**Results:** Twenty-one patients were analyzed (duo-gargling n = 10; single gargling n = 11) with balanced baseline characteristics. Mean week-7 OMAS score did not differ between groups ( $17.20 \pm 4.89$  vs.  $18.55 \pm 7.84$ ; mean difference 1.35, 95% CI -4.19 to 6.88;  $P = 0.647$ ), and there was no significant difference at any week. Grade  $\geq 3$  mucositis at week 7 was lower with duo-gargling (10.0% vs. 36.4%) but not significant. Opioid prescription at week 3 was significantly lower with duo-gargling (0.0% vs. 45.5%;  $P = 0.035$ ).

**Conclusion:** In this preliminary analysis, adding sodium bicarbonate to Benzydamine HCl did not significantly reduce OMAS scores compared with Benzydamine HCl alone. Duo-gargling did show fewer severe mucositis events and lower early opioid use, but these findings need to be confirmed in the full study.

**Keywords:** benzydamine , chemoradiotherapy, head and neck cancer, oral mucositis, sodium bicarbonate

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**\*Correspondence to:** Chanida Vinayanuwattikun, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and The King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand  
E-mail: Chanida.Vi@chula.ac.th

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Oral mucositis, a frequent complication in head and neck cancer patients undergoing concurrent chemoradiotherapy (CCRT), is characterized by painful inflammation and ulceration. This condition often leads to treatment interruptions, nutritional deficits, and reduced quality of life.<sup>(1)</sup> The pathogenesis involves direct cytotoxic damage to rapidly dividing mucosal cells and amplified inflammatory responses mediated by cytokines such as TNF- $\alpha$  and IL-1 $\beta$ .<sup>(2)</sup>

Several clinical trials have illustrated the anti-inflammatory, analgesic, and antiseptic properties of Benzydamine HCl for preventing RIOM in HNC patients receiving radiation and concurrent chemoradiotherapy, when compared to sodium bicarbonate.<sup>(1)</sup> Similarly, Rastogi, *et al.*<sup>(2)</sup> reported that Benzydamine HCl reduced inflammation and delayed mucositis onset in radiotherapy patients.

In contrast, sodium bicarbonate rinses, commonly used for their pH-neutralizing and antimicrobial properties, show limited prophylactic benefits when used alone.<sup>(3)</sup> Other interventions including Aloe vera<sup>(4)</sup> and iodine solutions<sup>(5)</sup>, probiotics<sup>(6)</sup>, and honey<sup>(7)</sup> have shown mixed efficacy, often limited by tolerability or compliance. Manuka honey, for example, reduced mucosal injury but was poorly accepted by patients because of its taste.<sup>(7)</sup> Others such as allopurinol mouthwash also showed limited success and safety concerns.<sup>(8)</sup>

However, no study has investigated the potential synergy between sodium bicarbonate and Benzydamine HCl. By neutralizing oral pH and reducing microbial load, sodium bicarbonate may enhance the anti-inflammatory and analgesic effects of Benzydamine HCl. Adjunctive oral care protocols have shown mixed results in similar settings<sup>(9)</sup>; however, antimicrobial rinses such as povidone-iodine have not consistently outperformed normal saline, under-scoring the need to explore other combination strategies.

We therefore conducted a randomized controlled trial to evaluate whether adding sodium bicarbonate to Benzydamine HCl provides better mucositis prevention than Benzydamine HCl alone. Combining the pH-buffering effect of sodium bicarbonate with

the anti-inflammatory and analgesic action of Benzydamine HCl may reduce mucositis severity and limit treatment interruptions in HNC patients undergoing CCRT.

## Methods

### Study design and population

We conducted a prospective, single-center, randomized controlled, single-blinded trial of HNC patients who were curatively treated with CCRT at the King Chulalongkorn Memorial Hospital during January to April 2026. Inclusion criteria were histologically confirmed squamous cell carcinoma with primary tumor locations including the oral cavity, oropharynx, nasopharynx, or hypopharynx/supraglottis. All patients were scheduled for curative-intent CCRT with concurrent cisplatin and had adequate organ function, defined as a creatinine clearance  $\geq 60$  mL/min, total bilirubin  $\leq 1.5 \times$  the upper limit of normal (ULN), AST/ALT  $\leq 2.5 \times$  ULN, absolute neutrophil count  $\geq 1,500/\text{mm}^3$ , and platelet count  $\geq 100,000/\text{mm}^3$ . Concurrent cisplatin was given either as a weekly (40 mg/m<sup>2</sup>) or three-weekly (100 mg/m<sup>2</sup>) regimen at the treating physician's decision, and both definitive and post-operative adjuvant treatment were eligible. An ECOG performance status of 0–2 was permitted. Exclusion criteria were severe comorbidities (e.g., uncontrolled cardiovascular disease or diabetes), active infection, prior chemotherapy or radiotherapy for HNC within the previous 3 months, and a history of allergy to Benzydamine HCl or sodium bicarbonate. Supportive treatments, including analgesic usage, nasogastric tube insertion, and hospitalization, were allowed by the judgment of the patient's physician as part of standard medical care. 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 the Faculty of Medicine, Chulalongkorn University (IRB No. 0809/68; COA No. 0071/2026). The trial was registered at [clinicaltrials.in.th](https://clinicaltrials.in.th) (ID: TCTR20260126005), and all patients were provided with written informed consent before participation.

### **Treatment**

Radiotherapy was planned using the Eclipse system (version 11.0; Varian, Palo Alto, CA, USA). Patients received a total dose of 66–70 Gy in 33–35 fractions using 3D-CRT, IMRT, VMAT, or proton beam therapy (PBT). Standard dose constraints for organs at risk were applied: maximum doses to 0.3 cc of the brainstem and spinal cord were limited to <54 Gy and <45 Gy, respectively. Mean doses were limited to <26 Gy for the parotid glands and <40 Gy for the oral cavity in non-oral cavity cancers.

Photon treatments were delivered via a Varian linear accelerator equipped with dynamic multi-leaf collimators, while PBT utilized a dedicated proton system. Setup accuracy was verified with daily electronic portal imaging and weekly cone-beam CT. Concurrent chemotherapy consisted of cisplatin administered either weekly (40 mg/m<sup>2</sup>) or every three weeks (100 mg/m<sup>2</sup>), selected at the treating physician's discretion. The cumulative cisplatin dose received during chemoradiotherapy was recorded for each participant, and interruptions of either radiotherapy or chemotherapy were documented. Radiotherapy interruption was defined as any unplanned break in radiotherapy due to treatment-related toxicity, and chemotherapy interruption was defined as omission or postponement of a scheduled cisplatin cycle.

### **Randomization, masking, and intervention**

Patients were randomly assigned in a 1:1 ratio to receive either Benzydamine HCl with sodium bicarbonate or Benzydamine HCl alone using computer-generated block randomization with a block size of four. The oral rinse prescription involved gargling 4 times a day for 30 seconds each, starting on the first day of CCRT. Patients in the experimental group rinsed with 15 mL of 0.15% Benzydamine HCl for 30 seconds, immediately followed by 15 mL of sodium bicarbonate solution for 30 seconds (one sachet of sodium bicarbonate 5 mEq dissolved in 1 liter of normal saline for irrigation; final concentration approximately 5 mEq/L or 0.042% w/v). The other group rinsed with 15 mL of 0.15% Benzydamine HCl alone for 30 seconds. Randomization was stratified by two factors considered likely to influence mucositis severity: 1) concurrent cisplatin schedule (weekly vs. three-weekly) and 2) mean oral-cavity radiation dose ( $\geq 40$  Gy vs. <40 Gy), yielding four strata. To support and monitor adherence, the assigned mouth-rinse solutions were dispensed weekly by the project nurse

(two bottles per week), and compliance was reviewed with each participant at every weekly follow-up visit; all participants reported using the assigned regimen throughout treatment, although adherence was not quantified numerically.

### **Study visit, assessment procedure and outcome**

Radiation-induced oral mucositis (RIOM) was evaluated by an investigator blinded to the assigned mouthwash regimen. Instruction on the gargling technique was provided to all participants by the project nurse, using a standardized written and verbal protocol; the same nurse dispensed the assigned solutions and reviewed compliance at each weekly follow-up visit. The project nurse was separate from the outcome assessor, who remained blinded to treatment allocation and performed all OMAS and CTCAE evaluations throughout the study. Blinding of the assessor was maintained by keeping the randomization list entirely with the project nurse and by instructing participants not to disclose their assigned regimen to the assessor. Because the duo-gargling group performed an additional gargling step, participants were aware of their own regimen (single-blinded design); however, the outcome assessor had no access to the allocation record at any point and remained unaware of group assignment throughout the study. Two assessment tools were used: The Oral Mucositis Assessment Scale (OMAS) and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The OMAS score served as the primary outcome of this study. The oral cavity was examined at nine anatomical sites: 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. Each site was assessed for ulceration or pseudomembrane and erythema. Ulceration or pseudomembrane was scored on a scale of 0 to 3: 0 = no lesion, 1 = lesion < 1 cm<sup>2</sup>, 2 = lesion 1–3 cm<sup>2</sup>, and 3 = lesion > 3 cm<sup>2</sup>. Erythema was scored on a scale of 0 to 2: 0 = none, 1 = mild to moderate, and 2 = severe. The OMAS score was the sum across all nine sites (range 0–45).

Secondary outcomes included the severity of oral mucositis per NCI-CTCAE v5.0, patient-reported oral pain on a numerical rating scale, use of analgesic medications (including opioids), need for topical anesthetics, nasogastric tube insertion, hospitalization, body weight change, and adverse events related to

the study mouthwashes. Supportive treatments, including antifungal or antibiotic use, were also recorded when clinically indicated. Nasogastric tube placement was classified as prophylactic when placed before significant mucositis, or therapeutic when placed for mucositis-related inability to maintain oral intake. There was no fixed protocol-defined threshold for prophylactic or therapeutic placement; the decision was made at the discretion of the treating physician, based mainly on weight loss exceeding 10% of baseline together with other clinical factors such as tumor site, and swallowing status.

Weekly assessments during CCRT were conducted by the blinded assessor. Demographic data, disease characteristics, treatment details, radiation dose, chemotherapy regimen, treatment compliance, and supportive treatment data were collected from case record forms and the hospital database. OMAS and NCI-CTCAE assessments were performed at seven time points, once weekly from week 1 through week 7 of CCRT. Patient-reported quality of life (EORTC QLQ-H&N35) was assessed at four time points, at weeks 1, 3, 5, and 7.

### **Statistical analysis**

The sample size was calculated to test the hypothesis that duo gargling (sodium bicarbonate plus Benzydamine HCl) would reduce the week-7 OMAS score compared with Benzydamine HCl alone. Using G\*Power version 3.1 for a two-tailed independent-samples t-test with an effect size (Cohen's *d*) of 0.7, corresponding to a clinically meaningful 2-point difference on the OMAS scale, a two-sided alpha of 0.05, and 80% power at a 1:1 allocation ratio, 34 participants per group (68 total) were required. After allowing for an anticipated 10% dropout rate, the target enrollment was increased to 38 participants per group, for a total of 76 participants. Because enrollment is still ongoing and has been slower than expected, we performed this preliminary analysis on the first 21 participants (27.6% of the target) to examine early trends in mucositis outcomes. This early analysis was not part of the original study plan and did not use formal interim-analysis methods, so the results are intended to explore patterns.

Continuous variables are reported as mean  $\pm$  standard deviation or median (IQR), depending on the distribution of the data, while categorical variables are expressed as frequency and percentage. Between-group differences in baseline characteristics were

assessed using the independent t-test or Mann–Whitney U test for continuous variables, and Fisher's exact test for categorical variables.

To evaluate outcomes over time including OMAS scores, CTCAE severity grading, and supportive care requirements mixed-effects models were applied to appropriately account for the repeated-measures nature of the data. These models included all randomized participants and used all available data without imputation, so that participants with a missing assessment at a given week were still included based on their other visits. Findings are presented as mean differences or proportions accompanied by 95% confidence intervals and corresponding p-values.

Statistical significance was defined as a two-sided p-value of less than 0.05. All analyses were carried out using Stata version 19.5 (StataCorp LLC, College Station, TX, USA).

### **Results**

The trial schema is shown in **Figure 1**. Of 26 patients screened for eligibility, 5 did not proceed to randomization: 4 were excluded for not meeting eligibility criteria, comprising prior head and neck irradiation (re-irradiation,  $n = 2$ ), receipt of induction chemotherapy ( $n = 1$ ), and a switch from cisplatin to carboplatin due to inadequate renal function ( $n = 1$ ), and 1 withdrew consent before randomization. The remaining 21 eligible patients were randomized (10 to duo gargling, 11 to single gargling), and all received their allocated intervention and completed the full course of chemoradiotherapy with cisplatin. All 21 randomized participants were included in the analysis, with the intention-to-treat and per-protocol populations being identical (**Table 1**).

A total of 21 patients were randomized to the duo gargling group ( $n = 10$ ) and the single gargling group ( $n = 11$ ). The mean age was  $61.18 \pm 10.31$  years in the duo gargling group and  $59.99 \pm 12.39$  years in the single gargling group. Male participants predominated in both groups (80.0% vs. 54.5%). Approximately half of all patients had a history of smoking. The most common primary tumor sites were the oral cavity and the hypopharynx/supraglottis, and the majority presented with locally advanced disease (stage III–IV). Most patients had an ECOG performance status of 0–1 and received weekly cisplatin (90.0% vs. 90.9%). The median oral radiation dose was 40.8 Gy in the duo gargling group and 42.0 Gy in the single gargling group, with no significant difference between

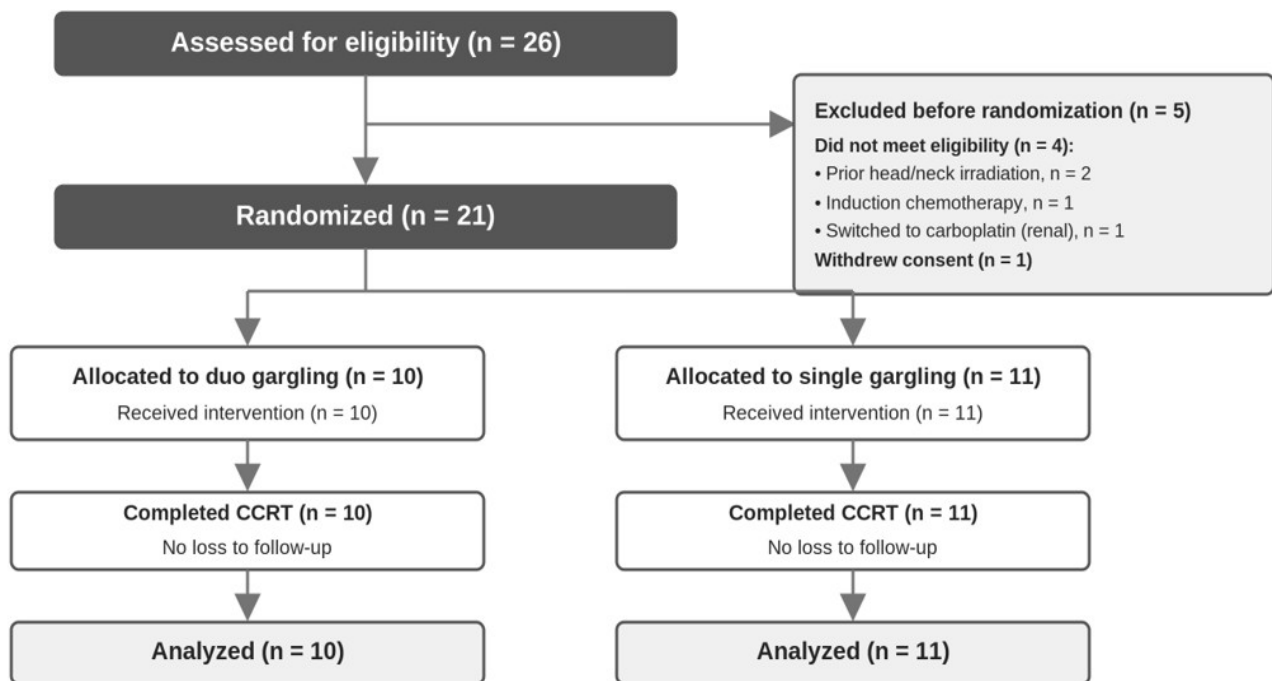


**Figure 1.** CONSORT flow diagram

groups. VMAT was the predominant radiation technique used in both groups. Baseline characteristics were well balanced between groups. Four patients had oropharyngeal cancer (one in the duo gargling group and three in the single gargling group); p16 immunohistochemistry was positive in two of the four patients (one in each group) and negative in the remaining two (both in the single gargling group). p16 testing was not applicable to the non-oropharyngeal tumors.

### **Efficacy**

The primary endpoint was the Oral Mucositis Assessment Scale (OMAS) score at week 7. The mean OMAS score at week 7 was  $17.20 \pm 4.89$  in the duo gargling group and  $18.55 \pm 7.84$  in the single gargling group. There was no statistically significant difference between the two groups (mean difference 1.35, 95% CI -4.19 to 6.88;  $P = 0.647$ ).

Longitudinal analysis using a mixed-effects model demonstrated that OMAS scores increased progressively in both groups throughout the treatment course, peaking around weeks 5–6 before plateauing at week 7. No significant between-group difference in OMAS score was observed at any time point from week 1 to week 7 (**Table 2, Figure 2**).

### **CTCAE grading and cumulative incidence of grade $\geq 3$ mucositis**

No grade  $\geq 3$  mucositis was observed in either group during weeks 1–3. Grade  $\geq 3$  events first appeared at week 4. By week 7, the proportion with grade  $\geq 3$  mucositis was 10.0% in the duo gargling group and 36.4% in the single gargling group. The overall cumulative incidence of grade  $\geq 3$  mucositis across both groups at week 7 was 33.3% (7/21; 95% CI 17.2–54.6), as shown in **Figure 3**. No statistically significant between-group differences in CTCAE grading were observed at any time point.

### **Supportive care**

As radiation dose accumulated, the proportion of patients requiring supportive care (analgesics, topical anesthetics, and feeding-tube support) rose progressively in both groups (**Table 3**).

Xylocaine viscous was the most frequently prescribed agent, used by up to 70.0% – 73.0% of patients in both groups by week 4. The only statistically significant between-group difference was opioid prescription at week 3, which was notably higher in the single gargling group (45.5% vs. 0.0%;  $P = 0.035$ ). Rates of nasogastric tube retention, hospital admission, and antibiotic or antifungal use were low and comparable throughout the study.

**Table 1.** Baseline characteristics by treatment group

|                                                | Duo gargling (n = 10) | Single gargling (n = 11) | P-value |
|------------------------------------------------|-----------------------|--------------------------|---------|
| <b>Age (years), mean <math>\pm</math> SD</b>   | 61.18 $\pm$ 10.31     | 59.99 $\pm$ 12.39        | 0.816   |
| <b>Weight (kg), mean <math>\pm</math> SD</b>   | 67.50 $\pm$ 14.48     | 60.24 $\pm$ 9.36         | 0.184   |
| <b>Oral radiation dose (Gy), median (IQR)</b>  | 40.8 (32, 58)         | 42.0 (32, 60)            | 0.778   |
| <b>Sex, n (%)</b>                              |                       |                          |         |
| Male                                           | 8 (80.0%)             | 6 (54.5%)                | 0.361   |
| Female                                         | 2 (20.0%)             | 5 (45.5%)                |         |
| <b>Smoking history, n (%)</b>                  |                       |                          |         |
| Never smoker                                   | 5 (50.0%)             | 4 (36.4%)                | 0.670   |
| Former/current smoker                          | 5 (50.0%)             | 7 (63.6%)                |         |
| <b>Primary tumor site, n (%)</b>               |                       |                          |         |
| Nasopharynx                                    | 2 (20.0%)             | 1 (9.1%)                 | 0.732   |
| Oral cavity                                    | 3 (30.0%)             | 3 (27.3%)                |         |
| Oropharynx                                     | 1 (10.0%)             | 3 (27.3%)                |         |
| Hypopharynx/supraglottis                       | 4 (40.0%)             | 4 (36.4%)                |         |
| <b>p16 status in oropharynx (n = 4), n (%)</b> |                       |                          |         |
| p16-positive                                   | 1                     | 1                        |         |
| p16-negative                                   | 0                     | 2                        |         |
| <b>Prognostic stage (AJCC 8th), n (%)</b>      |                       |                          |         |
| Early-stage (I–II)                             | 2 (20.0%)             | 2 (18.2%)                | 1.000   |
| Locally advanced (III–IVB)                     | 8 (80.0%)             | 9 (81.8%)                |         |
| <b>ECOG performance status, n (%)</b>          |                       |                          |         |
| 0                                              | 5 (50.0%)             | 4 (36.4%)                | 0.670   |
| 1                                              | 5 (50.0%)             | 7 (63.6%)                |         |
| <b>Treatment intent, n (%)</b>                 |                       |                          |         |
| Definitive CCRT                                | 5 (50.0%)             | 8 (72.7%)                | 0.387   |
| Post-operative CCRT                            | 5 (50.0%)             | 3 (27.3%)                |         |
| <b>Concurrent chemotherapy regimen, n (%)</b>  |                       |                          |         |
| Weekly cisplatin                               | 9 (90.0%)             | 10 (90.9%)               | 1.000   |
| Triweekly cisplatin                            | 1 (10.0%)             | 1 (9.1%)                 |         |
| <b>Radiation technique, n (%)</b>              |                       |                          |         |
| VMAT                                           | 10 (100.0%)           | 8 (72.7%)                | 0.204   |
| IMRT                                           | 0 (0.0%)              | 2 (18.2%)                |         |
| Other                                          | 0 (0.0%)              | 1 (9.1%)                 |         |

P-values: independent t-test or Mann–Whitney U test for continuous; Fisher's exact test for categorical. Significance  $P < 0.05$ .

**Table 2.** Longitudinal OMAS score from week 1 to week 7

| Time point | Duo gargling<br>mean $\pm$ SD | Single gargling<br>mean $\pm$ SD | Mean difference<br>(95% CI) | P-value |
|------------|-------------------------------|----------------------------------|-----------------------------|---------|
| Week 1     | 0.50 $\pm$ 1.08               | 0.55 $\pm$ 1.04                  | 0.05 (-0.86, 0.95)          | 0.92    |
| Week 2     | 3.50 $\pm$ 3.84               | 5.27 $\pm$ 3.52                  | 1.77 (-1.39, 4.93)          | 0.28    |
| Week 3     | 7.90 $\pm$ 5.72               | 10.45 $\pm$ 4.18                 | 2.55 (-1.77, 6.88)          | 0.25    |
| Week 4     | 12.60 $\pm$ 8.50              | 14.91 $\pm$ 5.84                 | 2.31 (-3.99, 8.61)          | 0.47    |
| Week 5     | 17.60 $\pm$ 7.96              | 17.91 $\pm$ 6.83                 | 0.31 (-6.07, 6.69)          | 0.93    |
| Week 6     | 16.80 $\pm$ 6.14              | 18.80 $\pm$ 6.23                 | 2.00 (-3.42, 7.42)          | 0.48    |
| Week 7     | 17.20 $\pm$ 4.89              | 18.55 $\pm$ 7.84                 | 1.35 (-4.19, 6.88)          | 0.65    |

P-values were calculated using the mixed-effects model. Statistical significance was defined as  $P < 0.05$ .

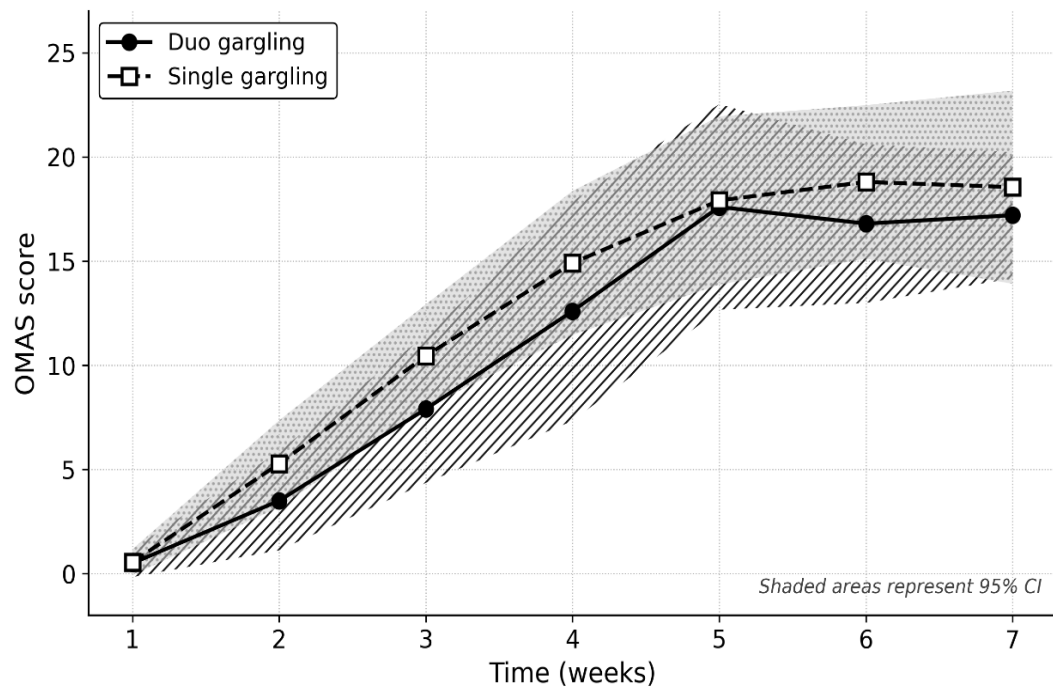


**Figure 2.** Mean OMAS scores over time by treatment arm (weeks 1–7).  
Shaded areas represent 95% CI

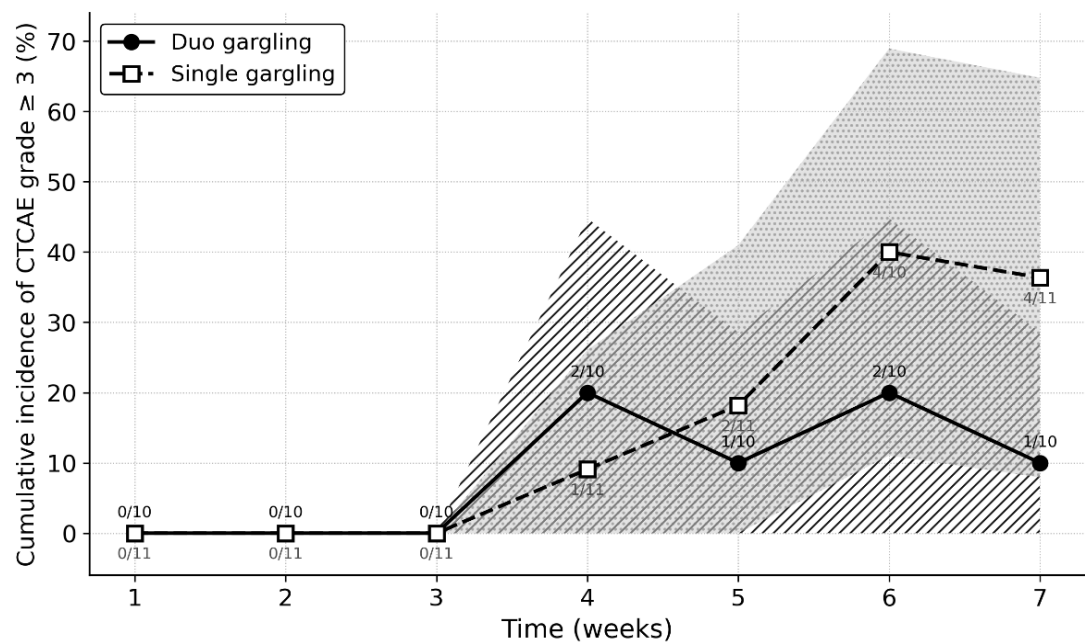


**Figure 3.** Cumulative incidence of CTCAE grade  $\geq 3$  oral mucositis across both treatment groups combined (weeks 1–7).  
Shaded area represents 95% CI

**Table 3.** Supportive care outcomes by treatment group (weeks 1–7).

| Outcome                                         | Wk 1        | Wk 2         | Wk 3          | Wk 4         | Wk 5         | Wk 6         | Wk 7         |
|-------------------------------------------------|-------------|--------------|---------------|--------------|--------------|--------------|--------------|
| <b>CTCAE grade <math>\geq 3</math>, n/N (%)</b> |             |              |               |              |              |              |              |
| Duo gargling                                    | 0/10 (0%)   | 0/10 (0%)    | 0/10 (0%)     | 2/10 (20%)   | 1/10 (10%)   | 2/10 (20%)   | 1/10 (10%)   |
| Single gargling                                 | 0/11 (0%)   | 0/11 (0%)    | 0/11 (0%)     | 1/11 (9.1%)  | 2/11 (18.2%) | 4/10 (40%)   | 4/11 (36.4%) |
| <i>P</i> -value                                 | 1.000       | 1.000        | 1.000         | 0.586        | 1.000        | 0.628        | 0.311        |
| <b>Prescribed xylocaine viscous, n/N (%)</b>    |             |              |               |              |              |              |              |
| Duo gargling                                    | 1/10 (10%)  | 3/10 (30%)   | 3/10 (30%)    | 7/10 (70%)   | 6/10 (60%)   | 6/10 (60%)   | 6/10 (60%)   |
| Single gargling                                 | 1/11 (9.1%) | 3/11 (27.3%) | 6/11 (54.5%)  | 8/11 (72.7%) | 8/11 (72.7%) | 8/11 (72.7%) | 5/11 (45.5%) |
| <i>P</i> -value                                 | 1.000       | 1.000        | 0.387         | 1.000        | 0.659        | 0.659        | 0.670        |
| <b>Prescribed opioid, n/N (%)</b>               |             |              |               |              |              |              |              |
| Duo gargling                                    | 0/10 (0%)   | 0/10 (0%)    | 0/10 (0%)     | 2/10 (20%)   | 2/10 (20%)   | 3/10 (30%)   | 1/10 (10%)   |
| Single gargling                                 | 1/11 (9.1%) | 3/11 (27.3%) | 5/11 (45.5%)  | 5/11 (45.5%) | 4/11 (36.4%) | 3/11 (27.3%) | 4/11 (36.4%) |
| <i>P</i> -value                                 | 1.000       | 0.214        | <b>0.035*</b> | 0.361        | 0.635        | 1.000        | 0.311        |
| <b>Retained NG tube, n/N (%)</b>                |             |              |               |              |              |              |              |
| Duo gargling                                    | 0/10 (0%)   | 0/10 (0%)    | 1/10 (10%)    | 2/10 (20%)   | 2/10 (20%)   | 2/10 (20%)   | 3/10 (30%)   |
| Single gargling                                 | 1/11 (9.1%) | 2/11 (18.2%) | 2/11 (18.2%)  | 3/11 (27.3%) | 4/11 (36.4%) | 5/11 (45.5%) | 5/11 (45.5%) |
| <i>P</i> -value                                 | 1.000       | 0.476        | 1.000         | 1.000        | 0.635        | 0.361        | 0.659        |
| <b>Required hospital admission, n/N (%)</b>     |             |              |               |              |              |              |              |
| Duo gargling                                    | 0/10 (0%)   | 0/10 (0%)    | 0/10 (0%)     | 0/10 (0%)    | 1/10 (10%)   | 0/10 (0%)    | 2/10 (20%)   |
| Single gargling                                 | 0/11 (0%)   | 0/11 (0%)    | 0/11 (0%)     | 0/11 (0%)    | 1/11 (9.1%)  | 1/11 (9.1%)  | 0/11 (0%)    |
| <i>P</i> -value                                 | 1.000       | 1.000        | 1.000         | 1.000        | 1.000        | 1.000        | 0.214        |

\* $P < 0.05$ . *P*-values calculated using Fisher's exact test. NG, nasogastric tube. One participant in the single gargling group had a missing assessment at week 6; the denominator for that week is therefore 10.

**Table 4.** Treatment delivery and toxicity-related outcomes

| Outcome                                                      | Duo gargling<br>(n = 10) | Single gargling<br>(n = 11) | <i>P</i> -value |
|--------------------------------------------------------------|--------------------------|-----------------------------|-----------------|
| Cisplatin cumulative dose (mg/m <sup>2</sup> ), median (IQR) | 232.5 (206, 240)         | 225.0 (200, 240)            | 0.797           |
| Weight loss during CRT (kg), mean $\pm$ SD                   | 5.18 $\pm$ 3.22          | 4.21 $\pm$ 4.19             | 0.562           |
| Weight loss during CRT (%), mean $\pm$ SD                    | 8.19 $\pm$ 4.70          | 7.25 $\pm$ 6.35             | 0.707           |
| RT interruption, n (%)                                       | 3 (30.0%)                | 3 (27.3%)                   | 1.000           |
| Chemotherapy interruption, n (%)                             | 4 (40.0%)                | 5 (45.5%)                   | 1.000           |
| Prophylactic NG tube, n (%)                                  | 0 (0.0%)                 | 4 (36.4%)                   | 0.090           |
| Therapeutic NG tube, n (%)                                   | 3 (30.0%)                | 3 (27.3%)                   | 1.000           |

NG = nasogastric tube; *P*-values were calculated using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Statistical significance was defined as  $P < 0.05$ .

### Treatment delivery and toxicity-related outcomes

Treatment delivery and toxicity-related outcomes are summarized in **Table 4**. The cumulative cisplatin dose was comparable between the duo and single gargling groups (median 232.5 vs. 225.0 mg/m<sup>2</sup>;  $P = 0.797$ ), as were weight loss during chemoradiotherapy, radiotherapy interruptions, and chemotherapy interruptions. No patient in the duo gargling group required a prophylactic nasogastric tube, compared with four (36.4%) in the single gargling group, although this difference did not reach statistical significance ( $P = 0.090$ ). Therapeutic nasogastric-tube placement was similar between groups. Although the difference in prophylactic nasogastric-tube placement did not reach statistical significance ( $P = 0.090$ ), the effect size was clinically meaningful, with an absolute risk difference of 36.4% (95% CI 7.9% to 64.8%) between the single and duo gargling groups.

### Discussion

This preliminary analysis of an ongoing randomized controlled trial found no statistically significant difference in OMAS scores between patients receiving Benzydamine HCl combined with sodium bicarbonate (duo gargling) and those receiving Benzydamine HCl alone (single gargling) at week 7 (mean difference 1.35, 95% CI -4.19 to 6.88;  $P = 0.647$ ), with no significant difference detected at any time point across the seven-week treatment course. This result may reflect the different ways the two agents work. Benzydamine HCl acts directly on the inflammatory process that drives mucositis, suppressing the pro-inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$ , while also providing local analgesic and antimicrobial effects.<sup>(10,11)</sup>

These cytokines are key downstream effectors of the NF- $\kappa$ B pathway central to mucositis<sup>(12)</sup>, Benzydamine may attenuate this inflammatory cascade indirectly. Sodium bicarbonate works mainly by raising oral pH, reducing microbial load, and clearing mucus.<sup>(13)</sup> These actions support only oral hygiene and comfort but do not have the molecular injury that causes mucositis. Since Benzydamine HCl already targets the main inflammatory pathway, sodium bicarbonate may add little extra protection.

Our results fit the existing evidence. Chitapanarux *et al.* showed that Benzydamine HCl produced lower OMAS scores than sodium bicarbonate alone during chemoradiotherapy<sup>(1)</sup>, confirming Benzydamine as the stronger single agent, which is why it formed the backbone of both arms in our study. Benzydamine's efficacy was first established<sup>(14)</sup> and later supported by subsequent reports<sup>(15, 16)</sup>, although its benefit appears smaller at the higher radiation doses used with concurrent chemotherapy.<sup>(2)</sup> Evidence for sodium bicarbonate, by contrast, remains weak. A recent systematic review found only low-quality support for its use<sup>(13)</sup>, and current MASCC/ISOO guidelines include it only as basic oral care.<sup>(17)</sup> The lack of added benefit from sodium bicarbonate is unsurprising. Interest in this question nonetheless continues, as shown by an ongoing RCT of sodium bicarbonate vs saline gargling in nasopharyngeal carcinoma.<sup>(18)</sup> Beyond sodium bicarbonate, other topical agents tested for radiation-induced oral mucositis have shown mixed results, which helps place our findings in context. Chlorhexidine, once widely used, was shown in a randomized trial to provide no benefit and even worsen mucositis-related symptoms, and it is now recommended against<sup>(19)</sup> due to its own taste alteration, staining and discomfort. In a recent Thai randomized study, povidone-iodine gargling was associated with significantly less severe radiation-induced oral mucositis than Benzydamine HCl in head and neck cancer patients receiving chemoradiotherapy.<sup>(20)</sup> Combination magic mouthwash formulations such as doxepin or a diphenhydramine-lidocaine-antacid rinse have reduced mucositis-related pain, but with effects below the minimal clinically important difference.<sup>(21)</sup> Overall, no topical agent has proven clearly better than the rest. Our finding of a small, non-significant difference between the two groups is consistent with this body of evidence.

Some secondary outcomes also differed between groups, though these should be viewed with caution. At week 3, fewer patients in the duo gargling group needed opioid painkillers (0.0% vs. 45.5%;  $P = 0.035$ ).

Grade  $\geq 3$  mucositis at week 7 was also lower with duo gargling (10.0% vs. 36.4%), and no duo gargling patient needed a prophylactic feeding tube (vs. 36.4%), but neither of these reached statistical significance ( $P = 0.311$  and  $P = 0.090$ ). These signals matter clinically, because mucositis-related pain and poor oral intake are major drivers of opioid use, tube feeding, weight loss, and treatment delays.<sup>(22, 23)</sup> It should also be noted that opioid use does not depend on mouth pain alone; head-and-neck cancer patients may take painkillers for pain in the neck or other irradiated areas, which is not always caused by oral mucositis. The analyses involved many comparisons in a small sample, the primary OMAS endpoint showed no difference, and prophylactic feeding-tube placement reflects a physician's pre-emptive decision rather than mucositis severity itself.<sup>(24)</sup> These observations are therefore hypothesis-generating only.

## Limitations

This study has several limitations. First, it is a preliminary analysis of 21 of the 76 planned participants, performed while the trial is still enrolling. This early analysis was not pre-planned and did not use formal interim-analysis methods, so it is underpowered and all comparisons should be considered exploratory. Second, the single-center design and small sample limit generalizability. Randomization was stratified by concurrent cisplatin schedule and mean oral-cavity radiation dose; because tumor site and treatment intent (definitive vs. postoperative) influence mucositis largely through the radiation dose delivered to the oral cavity<sup>(25)</sup>, stratifying by oral-cavity dose was expected to capture much of their effect while avoiding over-stratification in this small sample, although some residual confounding cannot be excluded. This analysis focused on the acute mucositis phase during chemoradiotherapy, with assessment concluding at week 7. Finally, adherence to the gargling regimen was followed qualitatively through weekly dispensing and patient report but was not measured numerically. A further consideration concerns the primary endpoint itself. Although the OMAS is a validated and widely used instrument for grading mucositis severity<sup>(26)</sup>, its erythema component involves a degree of subjective judgment, and the available mucositis scales (WHO, NCI-CTCAE, and OMAS) capture overlapping but not identical aspects of mucosal injury.<sup>(27)</sup> This measurement variability may reduce sensitivity to detect small between-group differences, particularly in a small sample.

## Conclusion

In this preliminary analysis, adding sodium bicarbonate to Benzydamine HCl did not significantly reduce OMAS scores compared with Benzydamine HCl alone in head and neck cancer patients receiving concurrent chemoradiotherapy. A few secondary signals, most notably lower early opioid use, favored the combination, but these were exploratory and need confirmation. The completed, fully powered trial will determine whether duo gargling offers any real clinical advantage. The final analysis will also incorporate patient-reported quality-of-life outcomes, which were not assessed in this preliminary report, to provide a more comprehensive evaluation of combination gargling.

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## Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Data sharing statement

The data sets generated or analyzed during the present study are available for non-commercial purposes from the corresponding author upon reasonable request.

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