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REVIEW ARTICLE

The effectiveness of mouthwashes in alleviating radiation-induced oral mucositis in head and neck cancer patients: a systematic review

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Abstract

Objective The aim of the study was to perform a systematic literature search and meta-analysis to reveal the most effective mouthwash for head and neck cancer patients who are experiencing radiation therapy-induced mucositis.

Methods Using two electronic databases, a literature search and data interpretation were systematically performed as follows: (i) problem specification, (ii) devising of a literature search plan, (iii) literature search and retrieval of publications, and (iv) meta-analysis and data interpretation. The main problem was specified as follows: what mouthwash is effective in alleviating oral mucositis for head and neck cancer patients who are undergoing radiotherapy?

Results The literature search yielded 354 titles and abstracts. After reviewing the extracted literature, 25 publications met the inclusion criteria for this study and 17 of 25 were eventually evaluated in the meta-analysis.

Conclusion The results of the meta-analysis indicated that the use of a mouthwash that includes anti-inflammatory properties contributes the most to alleviating oral mucositis in patients who are undergoing radiotherapy to treat head and neck cancer.

Keywords Head and neck neoplasms · Radiotherapy · Oral mucositis · Mouthwash

Introduction

Head and neck cancers comprise a group of cancers that originate in the mouth, throat, nose, or neck (typically in the pharynx). The prevalence of this type of cancer (i.e., in the lip and oral cavity, pharynx, and larynx) is relatively high with as many as 5.5 million people being affected worldwide (in 2015) [1] and around 9527 new cases occurring in Japan (in the same year) according to a report of the Japan Society for Head and Neck Cancer [2]. The treatment for head and neck cancer includes surgery, radiotherapy, and chemotherapy, given either alone or in combination. It is essential to preserve speech and swallowing function for patients following the treatment. Although radiotherapy is advantageous in terms of functional preservation, acute mucositis is one of the inevitable adverse side effects. Severe oral mucositis has been observed in 56% of patients undergoing radiotherapy for head and neck cancer [3]. This condition causes insufferable pain leading to a reduction in appetite and potential malnutrition [4]. Careful management of acute mucositis is essential to decrease patient discomfort and to avoid unwanted interruption of the radiotherapy treatment, which is shown to compromise local control of primary lesions [5]. Several papers reported that an interruption of the radiotherapy treatment of more than 1 or 2 weeks elicited a significantly higher risk of loco-regional recurrence and/or residual tumors [6, 7]. Therefore, reducing the incidence of radiation-induced oral mucositis is critical, and maintaining good oral hygiene has been shown to be beneficial [8]. It is recommended that early dental intervention is undertaken before the start of radiotherapy, and oral care is the preferred method to prevent oral mucositis and to minimize the risk of secondary infections. Specifically, the available guidelines recommend the use of non-medicated oral rinses in addition to standard mechanical tooth cleaning options such as toothbrushing and flossing [3]. However, there is insufficient evidence to make practical clinical recommendations for the

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best options to manage radiation-induced mucositis. Additionally, no guidelines are available for certain agents that are occasionally recommended, such as saline and sodium bicarbonate mouthwashes [9].

Therefore, the aim of this study was to perform a systematic literature search to determine the most effective mouthwash to reduce severe oral mucositis resulting from radiotherapy.

Methods

To guarantee an efficient approach, we conducted the current literature review in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [10] as well as the centre for reviews and dissemination (CRD) guidelines to perform high-quality reviews in health care [11]. The following steps were followed: (1) problem specification; (2) formulation of a plan to conduct a literature search; (3) literature search and retrieval of publications, and (4) data extraction, data interpretation, quality assessment, and data synthesis. These steps are discussed below.

1. The problem was specified as follows:

What (type of) mouthwash is effective in reducing oral mucositis in head and neck cancer patients who are undergoing radiotherapy?

2. Plan for the literature search.

Two electronic databases were consulted: (a) PubMed and (b) the Japan Medical Abstracts Society (JMAS) database. Next, a thorough search was performed within the full reference lists provided by these databases. The inclusion criteria (formulated in accordance with the 2009 CRD guidelines for undertaking reviews in health care, see [11]), were as follows:

- Population: head and neck cancer patients treated with radiotherapy
- Study design: primary study
- Outcome: oral mucositis (and/or reduction thereof)
- Outcome measures: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) [12] or Common Terminology Criteria for Adverse Events (CTCAE) [3] or World Health Organization (WHO) oral mucositis grading scale or National Cancer Institute Common Toxicology Criteria (NCI-CTC) oral mucositis grading scale for radiation therapy [3]
- Language: English or Japanese.

3. Literature search and publication retrieval

The authors identified full-text publications that met the criteria, and then proceeded to extract and tabulate the studies' characteristics and results. Any arising inclusion ambiguity regarding the studies was solved through discussion among the authors.

4. Data extraction, interpretation, quality assessment, and data synthesis.

Only papers reporting separated descriptions concerning mucositis grade were included (i.e., studies reporting averaged data over grade groups were not included). Cochrane's criteria concerning the risk of assessment bias was used for the included studies [13]. The risk ratio (RR) was used as a summary statistic for the meta-analysis. The Chi square index was used to assess the statistical heterogeneity, with the level of significance set at $p < 0.05$. We used a random-effects meta-analysis to address heterogeneity. Meta-analyses were undertaken in Review Manager [14] and results are shown as forest plots of RRs and their 95% confidence intervals (CI).

Additional analyses per mouthwash type

We planned the data synthesis for three clinically relevant subgroups. That is, we used additional meta-analyses to evaluate the effectiveness according to the type of mouthwash used (i.e., antibacterial agents, anti-inflammatory agents, and mucosal protective solutions).

Results

Study selection

Search strategies from two databases are shown in Tables 1 and 2. Figure 1 shows the flowchart of the study selection. The literature search yielded 354 titles and abstracts. After reviewing this literature, 25 publications that met the inclusion criteria of this study were selected and were subjected to further analysis [15–39]. Table 3 summarizes the characteristics of the included studies. Of these 25 publications, 17 were ultimately included in the meta-analysis.

We found that 14 publications [15, 19, 21, 24, 26, 28–31, 33–36, 38] reported that the intervention group was more effective than the control group in reducing the effects of oral mucositis, although another 10 studies [16, 18, 20, 22, 23, 25, 27, 32, 37, 39] showed no significant differences between the 2 groups. One publication reported that the results were different depending on treatment type (i.e., radiation alone or chemoradiation therapy) [17]. Next, of

Table 1 Search strategies and number of publications retrieved from the search in PubMed

	Indexing terms	Publications (*n*)
#1	Head and Neck Neoplasms [MeSH] OR Head and Neck Cancer [MeSH]	141,199
#2	Radiotherapy [MeSH] OR Radiation Therapy [MeSH]	182,833
#3	Oral Mucositis [MeSH] OR Stomatitis [MeSH]	10,392
#4	Dental care [MeSH] OR Oral care [non-MeSH]	67,559
#5	Mouthwash [MeSH] OR Mouth Rinse [non-MeSH]	6534
#6	#4 OR #5	73,259
#7	#1 AND #2 AND #3 AND #6	235

Entry date: 1 January 2000 to 31 December 2017

Database search date: 15 October 2018

Limits: (1) Human, (2) English, Japanese

Table 2 Search strategies and number of publications retrieved from the search in Japan Medical Abstracts Society (JMAS)

	Indexing terms	Publications (*n*)
#1	頭頸部癌 (head and neck cancer)	66,655
#2	放射線治療 (radiation therapy)	49,170
#3	口腔粘膜炎 (oral mucositis)	5802
#4	口腔ケア (oral care)	10,606
#5	マウスウォッシュ (mouthwash)	4651
#6	#4 or #5	14,875
#7	#1 AND #2 AND #3 AND #6	119

Publication date: free

Only original articles

Database search date: 27 October 2018

The search in JMAS was performed in Japanese (English translation of Japanese search terms in parentheses)

the 25 included studies, 4 used a potentially effective mouthwash (i.e., povidone-iodine, licorice, and benzydamine) as a control group [20, 23, 26, 37]. Three of these four studies reported no significant differences between the intervention and control groups, which could be attributed to the use of a potentially effective agent as a control.

Risk of bias assessment

The risk of bias across the individual studies and their overall summary is shown in Fig. 2. Measures to ensure blinding of the participants and personnel, and blinding of outcome assessment were 6/19 (31.6%) and 4/19 (21.1%), respectively.

Synthesis of results

Based on 1798 patients in the intervention and control groups from the 17 studies in the summary, the intervention to ease mucositis was around 0.84 (95% CI 0.78, 0.91), with substantial heterogeneity (45%) (Fig. 2). There were significant differences between the intervention and control groups when studying a wide range of agents to reduce mucositis in patients treated with radiotherapy.

Based on these findings, we included 17 publications in the meta-analysis [15–19, 21–25, 27, 31–33, 37–39] and will now discuss the intervention further. Although the intervention group was more effective, the included studies varied in terms of: (1) a wide variety of mouthwash, (2) indices used to measure outcomes, and (3) their targeted subject groups. The types of mouthwash can be further classified into: (a) antibacterial activity (five studies) [22, 25, 32, 37, 39], (b) anti-inflammatory agents (three studies) [15, 17, 31], (c) mucosal protective effective solutions (four studies) [16, 24, 33, 38] or (d) others (five studies) [18, 19, 21, 23, 27]. We performed a meta-analysis to evaluate the effectiveness according to the aforementioned types (a–c). Other types (d) were not included in the meta-analysis as the agents of the intervention group (i.e., calcium phosphate, platelet gel, rhG-CSF, and aloe vera) did not show comparable effects. The result of the meta-analysis for type a (antibacterial activity mouthwash) studies is shown in Fig. 3. In this group, based on 740 patients in the intervention and control groups from the summary of these five publications, the intervention for easing mucositis was about 1.00 (95% CI 0.90, 1.11). There was no significant difference between the intervention and control groups in reducing oral mucositis for patients having less than a grade 3 profile when treated using radiotherapy. In the type b (anti-inflammatory mouthwash) studies, based on 345 patients in the intervention and control groups from the summary of three publications, the intervention for easing mucositis was 0.60 (95% CI 0.50, 0.73) (Fig. 4). There was a significant difference between the intervention and control groups in reducing oral mucositis for patients having less than a grade 3 profile when treated using radiotherapy. In the type c (mucosal protective effect mouthwash) studies, based on 279 patients in the intervention and control groups from the four publications in the

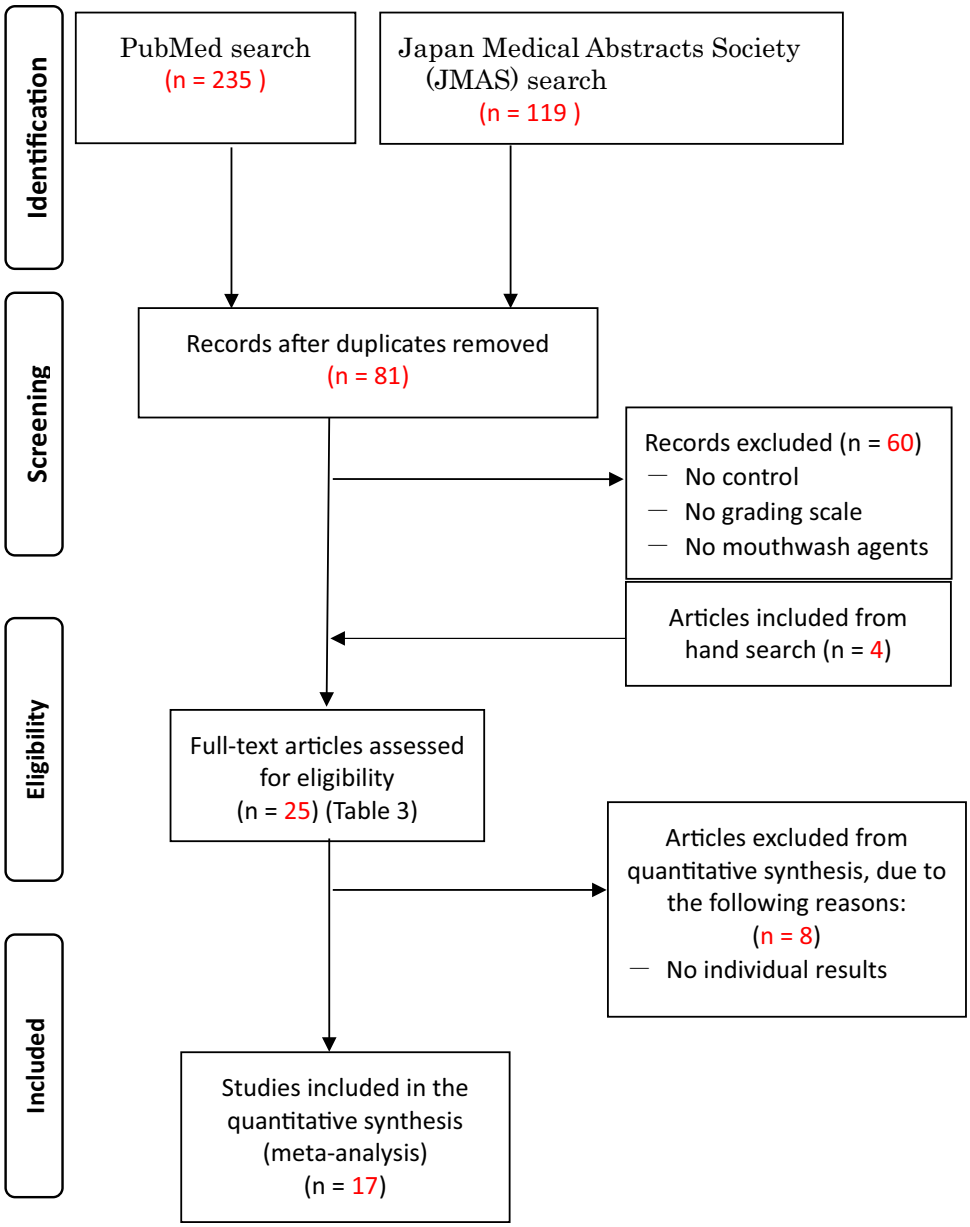

Fig. 1 PRISMA flow diagram of the selection of studies for the systematic review

analysis, the intervention for easing mucositis was 0.73 (95% CI 0.53, 1.02) (Fig. 5). There was no significant difference between the intervention and control groups in reducing the oral mucositis level for patients having less than a grade 3 profile when treated using radiotherapy.

Discussion

Although oral mucositis is an inevitable adverse effect regularly occurring during radiotherapy, it is critical to reduce it as much as possible to diminish patient discomfort. Common interventions include supplementary oral care by a dentist or dental hygienist. However, there is currently no consensus among dental practitioners concerning whether mouthwash treatments have beneficial effects on oral mucositis during radiotherapy. With this systematic review, we aim to report on the effectiveness of the various mouthwashes used in oral health care in controlling oral mucositis in head and neck cancer for patients who are receiving radiotherapy. This meta-analysis suggests that the use of mouthwash containing an anti-inflammatory agent can be regarded as the most effective method to reduce oral mucositis during radiotherapy treatment. The characteristics of individual studies are described below.

Table 3 Characteristics of the included publications (25 publications)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Najafi (2017) [15]	Glycyrrhiza glabra ($n=19$)	Placebo ($n=18$)	WHO	Unclear	At least 50	Significant differences were found in the maximum grade of mucositis between the intervention and control groups	○
Yokota (2017) [16]	2% rebamipide liquid ($n=31$) 4% rebamipide liquid ($n=32$)	Placebo ($n=31$)	CTCAE ver. 3.0	3D-CRT or IMRT	At least 60	The incidence of grade ≥ 3 oral mucositis 2% rebamipide 29%, 4% rebamipide 25%, placebo 39% The rebamipide 2% and 4% groups showed a trend of delaying the time to onset of grade ≥ 3 oral mucositis compared with placebo, although the difference between the groups was not statistically significant	○
Rastogi (2017) [17]	Benzydamine rinse Radiotherapy alone ($n=33$, B) Chemoradiotherapy ($n=30$, D)	Saline rinse Radiotherapy alone ($n=29$, A) Chemoradiotherapy ($n=28$, C)	WHO, CTCAE ver. 4.0	3D-CRT	60–70	Radiotherapy alone arm (A and B) Patients in group B had lesser grade 3 as compared to group A, 62.1 versus 36.4% ($p = 0.038$) Chemoradiotherapy arm (C and D) Grade 3 in groups C and D were less but not statistically different, 64.3 versus 43.3% ($p = 0.091$)	○
Wong (2017) [18]	Caphosol plus standard care ($n=103$)	Standard care ($n=107$)	CTACE ver. 4.0	3D-CRT or IMRT	60–65	No significant differences in the incidence of more than G3 mucositis between intervention and control groups	○

Table 3 (continued)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Bonfili (2017) [19]	Platelet gel supernatant (PGS) + standard oral care ($n = 16$)	Standard oral care ($n = 64$)	WHO	3D-CRT	66–70	A Cox proportional hazard model indicated that patients treated with standard supportive medical treatments experienced a 2.7-fold increase (hazard ratio = 2.7; 95% confidence interval, 1.3–5.7; $p = 0.0074$) in the occurrence of WHO grade 3/4 mucositis over the group treated by PGS in association with standard supportive medical treatment. In addition, patients treated by standard supportive medical treatment alone experienced WHO grade 3/4 toxicity earlier than PGS users ($p = 0.0074$)	○
Ghalayani (2017) [20]	Triamcinolone ($n = 30$)	Licorice ($n = 30$)	WHO	2-D cobalt-based technique	56–60	No significant differences, although there was no neutral control group, so both may have in fact been effective	×
Liang (2017) [21]	rhG-CSF mouthwash ($n = 34$)	Saline containing vitamin B12, gentamicin, and dexamethasone ($n = 30$)	RTOG	IMRT	Median dose: 73.92	Intervention group had a significantly lower incidence of oral mucositis of grade 3 or above (38.2% vs 66.7%, $p = 0.02$)	○

Table 3 (continued)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Diaz-Sanchez (2015) [22]	0.2% Bioadhesive chlorhexidine gel ($n=4$)	Placebo gel ($n=3$)	WHO	Unclear	70	The integrity of the mucosa to the WHO scale for mucositis was slightly higher in the study group than in the control group, but without obtaining statistically significant differences ($p > 0.05$)	○
Sahebjamee (2015) [23]	Aloe vera mouthwash ($n=13$)	0.15% Benzydamine mouthwash ($n=13$)	WHO	Unclear	50–70	No significant differences between the two groups ($p = 0.35$) No significant differences in the start time and duration of mucositis from the beginning of radiotherapy, or in the maximum mucositis grade	○
Allison (2014) [24]	Mucoadhesive hydrogel (MuGard) ($n=37$)	Sham-control (SC SC consisted of flavored saline bicarbonate rinse) ($n=41$)	WHO	Unclear	50–72	WHO scores on the last day of radiation therapy ($p = 0.038$) MuGard in ulcerative mucositis frequency (SC = 68%; MuGard = 43%)	○
Hawley (2014) [25]	Manuka honey ($n=54$)	Placebo gel ($n=52$)	RTOG, WHO	Unclear	At least 50	There was no statistically significant difference between the manuka honey and placebo arms	○

Table 3 (continued)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Rao (2014) [26]	Turmeric gargle ($n=39$)	Povidone-iodine gargle ($n=40$)	RTOG	Unclear	70	This study clearly suggests that when compared with the cohorts using povidone-iodine gargle, the group using turmeric as a mouthwash had delayed and reduced levels of radiation-induced oral mucositis and was statistically significant at all time points ($p < 0.001$ to $p < 0.0001$)	×
Lambrecht (2013) [27]	Calcium phosphate (CP) mouth rinse ($n=27$)	Standard treatment ($n=31$)	CTCAE ver. 3.0	IMRT	60–72	There was no significant difference in the grade, the time of onset or the duration of peak mucositis between the two treatment groups	○
Pawar (2013) [28]	SAMITAL®, a gel-like suspension of highly standardized botanical extracts ($n=17$)	Placebo ($n=10$)	WHO	Unclear	60	Mean scores for the severity of oral mucositis were significantly ($p < 0.05$ versus baseline) reduced from day 31 until the end of treatment in patients treated with SAMITAL®. No significant improvement was observed in the placebo group	×
Nakayama (2013) [29]	Polaprezinc oral rinse ($n=20$)	Azulene oral rinse ($n=24$)	CTCAE ver.3.0	Unclear	66	The grade of oral mucositis in polaprezinc group was significantly lower than that in the control group at 6 and 7 weeks ($p = 0.016$, $p = 0.018$)	×

Table 3 (continued)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Yen (2012) [30]	5 ml phenylbutyrate 5% mouthwash ($n=17$)	5 ml of placebo mouthwash ($n=19$)	RTOG, WHO	3D-CRT or IMRT	60–76	At RT doses of 5500–7500 cGy, phenylbutyrate significantly mitigated the severity of mucositis compared with placebo, based on the WHO score (severity ≧ Grade 3; $p=0.0262$)	×
Sharma (2012) [31]	Lactobacillus brevis CD2 lozenges ($n=93$)	Placebo ($n=95$)	NCI-CTC ver. 2.0	3D-CRT	70	Grade 3 and 4 mucositis developed in 52% of patients in the *L. brevis* CD2 arm and 77% in the placebo arm ($p<0.001$)	○
Bardy (2012) [32]	Manuka honey ($n=64$)	Golden syrup ($n=63$)	RTOG	Unclear	20–55	No significant difference in the severity and duration of oral mucositis	○
Tosaka (2011) [33]	Rebamipide ($n=31$) Polaprezinc–alginate sodium ($n=11$)	Sodium azulene sulfonate ($n=15$)	CTCAE ver. 3.0	Unclear	60–66	Occurrence rate of grade 1 mucositis and above Rebamipide: 48% Polaprezinc–alginate: 36% Sodium azulene sulfonate: 80% Polaprezinc–alginate significantly prevented mucositis compared with sodium azulene sulfonate ($p=0.0426$)	○ (only rebamipide)
Satheeshkumar (2010) [34]	Triclosan mouthwash ($n=12$)	Sodium bicarbonate ($n=12$)	WHO	Unclear	Unclear	Early reversal of mucositis and reduction in its severity	×

Table 3 (continued)

First author (year)	Intervention (no. of patients)	Control (no. of patients)	Assessment of oral mucositis	Radiation technique	Radiation dose (Gy)	Results	Meta-analysis
Maddocks-Jennings (2009) [35]	Manuka + kanuka (essential oil *Leptospermum Scoparium* + *Kunzea ericoides*) ($n=6$)	Placebo (gargling with water) ($n=6$) and control (usual care) ($n=7$)	RTOG	Unclear	Mean dose 53–62	Delayed onset of mucositis and reduction of associated symptoms (pain and oral symptoms, weight loss)	×
Madan (2008) [36]	Group 1: ($n=19$) 0.12% Chlorhexidine Group 2: ($n=19$) 1% Povidone-iodine Group 3: ($n=18$) Salt–sodium bicarbonate	Plain water ($n=20$)	WHO	External bilateral irradiation from cobalt-60 radioactive source	60	Patients in the povidone-iodine group had significantly lower mucositis scores when compared with the control group from the first week of radiotherapy. Their scores were also significantly lower when compared with the salt/soda and chlorhexidine groups from the fourth and fifth week, respectively, after radiotherapy	×
Cheng (2006) [37]	Chlorhexidine oral rinse ($n=7$)	Benzydamine oral rinse ($n=7$)	WHO	Unclear	54–68	No statistically significant differences in the mucositis grade	○
Naidu (2005) [38]	MF 5232 (Mucotrol®) ($n=11$)	Placebo group ($n=11$)	WHO	3D-CRT	Unclear	There was a significant reduction in mean mucositis scores with MF 5232—WHO score reduced from 3.0 to 1.8	○
Trotti (2004) [39]	Iseganan HCl oral solution plus standard-of-care oral hygiene (SOC) ($n=253$)	Placebo plus SOC ($n=171$) and SOC alone ($n=87$)	NCI-CTC ver. 2.0	Unclear	66–81.6	No reduction in the incidence of ulcerative oral mucositis	○

WHO World Health Organization oral mucositis grading scale, *CTCAE* Common Terminology Criteria for Adverse Events, *RTOG* Toxicity criteria of the Radiation Therapy Oncology Group, *NCI-CTC* National Cancer Institute Common Toxicology Criteria oral mucositis grading scale for radiation therapy, *3D-CRT* Three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy

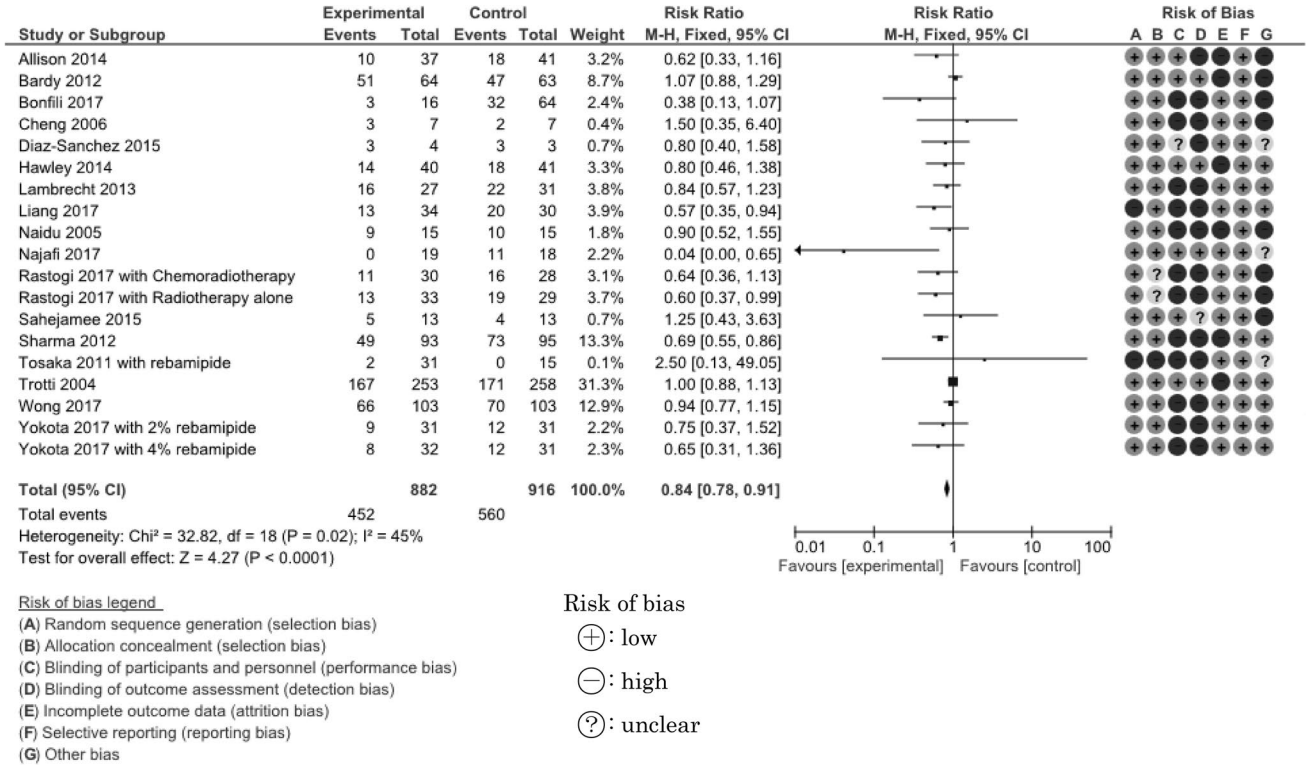

Fig. 2 Forest plot comparing the severity of mucositis in the intervention and control groups and a risk of bias summary: review of the authors' judgments about the risk of bias for each of the included studies

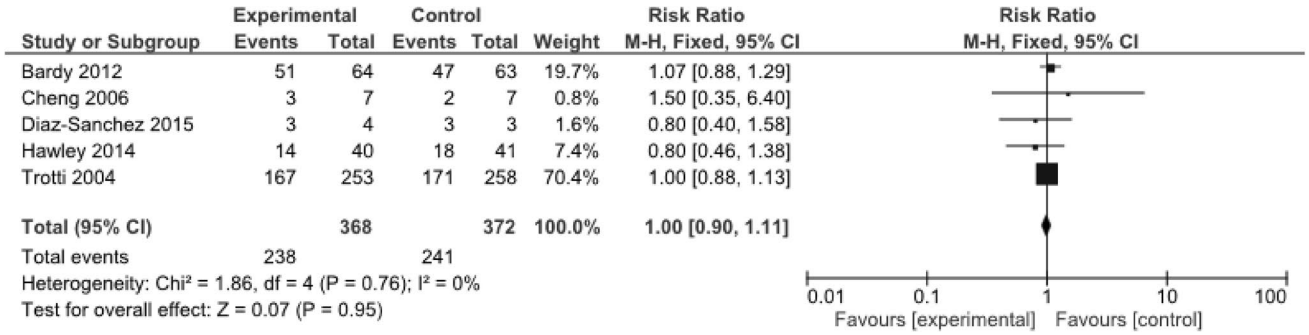

Fig. 3 Forest plot comparing the severity of mucositis in the intervention and control groups for antibacterial activity mouthwash

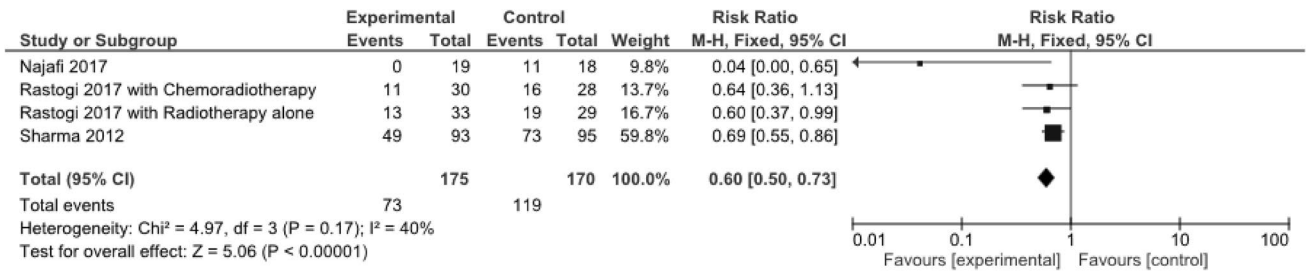

Fig. 4 Forest plot comparing the severity of mucositis in the intervention and control groups for anti-inflammatory mouthwash

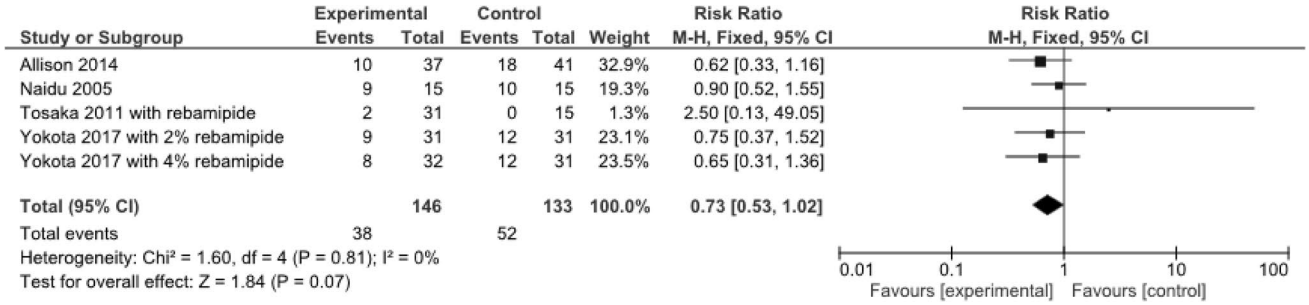

Fig. 5 Forest plot comparing the severity of mucositis in the intervention and control groups for mucosal protective effect mouthwash

Studies that reported a reduction in oral mucositis

Glycyrrhiza glabra extract [15]

Glycyrrhiza glabra (licorice) is a traditional pharmaceutical herb that has been reported to have an anti-inflammatory nature. The intervention group received 100 ml glycyrrhiza extract, while the placebo group received the same amount of water. Both solutions were of the same appearance and taste. Grade 4 oral mucositis was absent in both groups. Grade 3 mucositis occurred in 11 patients (61.1%), but only in the placebo group. Grade 1 mucositis occurred in 12 patients (63.15%) and grade 2 mucositis appeared in 7 patients (36.84%) in the intervention group. Conversely, in the placebo group, grade 1 mucositis occurred in 1 patient (5.55%), grade 2 mucositis in 6 patients (33.3%), and grade 3 mucositis in 11 patients (61.11%). When comparing the severity of oral mucositis between the intervention and the control groups, there was a significant difference ($p < 0.001$) indicating a beneficial effect of the intervention.

Platelet gel supernatant (PGS) [19]

Platelets have been reported to release several beneficial factors that promote tissue repair, angiogenesis, and inflammation. Patients belonging to the PGS group were instructed by the investigators to use PGS three times a day (i.e., 1 h before breakfast, lunch, and dinner), including weekends, and to refrain from any oral intake for 30 min after dosage intake. The control group, which underwent standard supportive treatment, showed a significant higher occurrence of oral mucositis (55%, 35/64) compared with the intervention group (13%, 3/16) ($p = 0.012$) especially for grades 3 and 4.

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) [21]

Granulocyte colony-stimulating factor is a hematopoietic growth factor promoting the proliferation and differentiation of neutrophils. Mouthwash containing saline and 2 µg/ml rhG-CSF was administered to the intervention group. Grade 3 or 4 oral mucositis occurred in 38.2% of the intervention group and in 66.7% of the control group. The incidence of grade 3 or 4 mucositis significantly decreased in the intervention group ($p = 0.02$).

Mucoadhesive hydrogel (MuGard) [24]

MuGard is a viscous liquid mucoadhesive hydrogel drug formulation. It acts by forming a palliative barrier over the damaged mucosa. Investigators evaluated the severity of oral mucositis on week four and the last day of radiotherapy (using the WHO grading scale). Grade 2, 3, and 4 mucositis occurred in 43% of the intervention group and 61% of the control group at week four. Also, grade 3 and 4 mucositis occurred in about 16% of the intervention group and 24% of the control group at week four. These results did not show statistically significant differences. Conversely, grade 2, 3, and 4 mucositis showed a statistically significant decrease in the intervention group on the last day of radiotherapy (MuGard: 43%, control: 68%, $p = 0.038$). With respect to grade 3 and 4 mucositis, there were no significant differences on the last day of radiotherapy between the two groups (MuGard: 27%, control: 44%, $p = 0.159$).

Turmeric [26]

Turmeric is the rhizome of the *Curcuma longa* Linn, a plant related to the ginger family that is commonly used as a medication agent. Turmeric is considered to have anti-inflammatory and wound-healing properties. The patients in the intervention group used a turmeric gargle six times per day, and the control group used a povidone-iodine gargle twice per day. Grade 3 or 4 oral mucositis (intolerable mucositis) occurred in 14 of 39 patients in the turmeric intervention group, while in the control group, this number was 34 of 40 patients. This difference was statistically significant indicating a beneficial effect of turmeric ($p < 0.0001$).

SAMITAL® [28]

SAMITAL® is a gel-like suspension containing a multicomponent and multi-acting botanical formulation. Patients were administered four oral doses of SAMITAL® or placebo every 5 h daily for around 50 days (corresponding to the approximate length of the radiotherapy). Mean scores for oral mucositis went from 2.94 ± 0.43 to 2.00 ± 0.35, which was a significant decrease from baseline ($p < 0.05$). For the control group, no improvements were observed (scores remained around 3.0).

Polaprezinc oral rinse [29, 33]

Polaprezinc prevents inflammation of the gastric mucosa and is often prescribed as a drug to treat gastric ulcers. However, it has also been used orally to treat mucositis. Nakayama et al. reported that the oral mucositis grade in the intervention group was significantly lower than that in the control group at 6 and 7 weeks ($p = 0.016$, $p = 0.018$), and the incidence of grade 3 and above mucositis was 15.0% in the intervention group and 41.7% in the control group at 6 weeks [29]. Additionally, Tosaka et al. reported that the occurrence rate of grade 1 mucositis and above was about 36% in the polaprezinc–alginate sodium group and about 80% in the control group, and a significant group difference was observed ($p < 0.05$) [33].

Phenylbutyrate [30]

Phenylbutyrate (an antitumor histone deacetylase inhibitor) is thought to increase the efficacy of radiotherapy by inhibiting tumor growth and protecting normal tissues from radiotherapy-induced damage. Phenylbutyrate was given as a gel product to be used as a mouthwash. At cumulative doses of 5500–7500 cGy, the intervention group showed a statistically significant decrease in the severity of mucositis ($p = 0.0262$). At cumulative radiotherapy doses of 6000–7000 cGy, significantly lower mucositis scores were observed in patients who received phenylbutyrate (mean score 0.7) compared with those who received placebo (mean score 1.2; $p = 0.0485$).

Lactobacillus brevis CD2 lozenges [31]

The *Lactobacillus brevis* CD2 (*L. brevis* CD2) strain contains arginine deiminase and sphingomyelinase, which have prospective anti-inflammatory properties. The percentage of grade 1/2 and grade 3/4 oral mucositis incidence was lower in the intervention group (19% and 52%, respectively) than in the control group (15% and 77%, respectively). This difference was statistically significant ($p < 0.001$).

Triclosan mouthwash [34]

Triclosan is a broad-spectrum antibacterial drug. The patients in the intervention group were administered triclosan mouthwash, while those in the control group were given sodium bicarbonate mouthwash. Grade 4 oral mucositis occurred in 1 out of 12 patients (8%) in the intervention group and in 10 out of 12 patients (83%) in the control group. The severity of mucositis was statistically lower in the intervention group ($p < 0.001$).

Manuka and kanuka honey [35]

Manuka (or *Leptospermum scoparium*), an essential oil, and kanuka (or *Kunzea ericoides*) are both members of the myrtle family. The patients in the intervention group were given a 1:1 mixture of manuka and kanuka honey, while the placebo group was administered a bottle of sterile water in combination with typical dental care. Maddocks-Jennings et al. evaluated the effects of gargling on radiation-induced mucositis using a solution containing a mixture of manuka and kanuka honey during radiotherapy. The intervention group showed a delayed onset of oral mucositis and experienced reduced pain and oral symptoms when compared with the placebo group. However, the mean score of maximum mucositis grade was not statistically significant between the intervention and the placebo group.

Povidone-iodine, salt–sodium bicarbonate, chlorhexidine [36]

The patients were allocated to four groups: (1) povidone-iodine, (2) salt–sodium bicarbonate, and (3) chlorhexidine as the intervention groups, with (4) plain water acting as the control group. There were significant differences in the average mucositis scores among all four groups with the lowest score for the povidone-iodine group and comparable scores for the salt–sodium bicarbonate and chlorhexidine groups. The highest score was for the control group indicating more severe mucositis. Furthermore, the onset of oral mucositis was statistically different among the groups ($p < 0.01$) with earlier onsets of mucositis for the control group.

MF 5232 (Mucotrol®) [38]

MF 5232 is a polyherbal wafer formulation that consists of sorbitol, *Cyamopsis tetragonolobus*, stearic acid, magnesium stearate, aloe, natural and artificial flavors, acesulfame K, extracts of glycyrrhizin, *Centella asiatica, Polygonum cuspidatum, Angelica* sp., and *Camellia sinensis*. Another

formulation made of sorbitol, stearic acid, magnesium stearate, natural and artificial flavors, and starch acted as a placebo. This formulation had the same color, shape, texture, taste, and smell as MF 5232. There was a significant reduction in mean oral mucositis score by the WHO scale (3.00 ± 0.63 to 1.81 ± 0.75; $p = 0.007$) in the intervention group, while there was no significant reduction in the mean scores in the placebo group. Furthermore, the mean score from the Radiation Therapy Oncology Group (RTOG) oral mucositis scale showed a significant reduction in the intervention group (from 2.77 ± 0.44 to 1.77 ± 0.83, $p = 0.031$), while there was no significant reduction in the placebo group.

Studies that reported no reduction in oral mucositis

Rebamipide [16, 33]

Rebamipide was initially developed to alleviate gastritis and gastric ulcers. Additionally, it has shown potential to inhibit inflammatory reactions. Rebamipide 2% or 4% liquid solution was administered to the intervention group, and a similar liquid formulation without rebamipide was administered to the placebo group. Grade 3 or 4 oral mucositis occurred in around 29% and 25% of subjects in the rebamipide 2% and 4% groups, while this number was around 39% for the placebo group. This result was not statistically significant ($p = 0.2399$). Additionally, in terms of the onset time of grade 3 or 4 mucositis, there were no significant differences between the intervention and placebo groups [16]. Additionally, Tosaka et al. reported that the incidence of grade 1 mucositis and above was 48% in the rebamipide group and 80% in the control group but, although this number was high, there was no reliable statistical difference between the two groups [33].

Calcium phosphate (Caphosol®) [18, 27]

Caphosol® is a liquid containing concentrated calcium phosphate. It has similar constituents to human saliva. Wong et al. reported that there was no difference in the incidence of severe oral mucositis between the intervention and control groups (64.1% versus 65.4%, respectively; $p = 0.839$) [18]. Wong et al. used only standard oral care such as saline mouthwash, aspirin mouthwash, and toothbrushing with fluoride toothpaste by dental practitioners as a control group. Furthermore, Lambrecht et al. reported that 16 patients (59%) in the intervention group versus 22 patients (71%) in the control group had a peak mucositis of grade 3 or more ($p = 0.25$). There was no significant difference between mucositis grades among the two groups [27].

Triamcinolone [20]

Triamcinolone is a form of synthetic glucocorticoid and has anti-inflammatory properties. The intervention group received standard oral care plus triamcinolone, and the control group received standard oral care plus licorice. Standard oral care included mouthwashing frequently with boiled water, regular toothbrushing and flossing, scaling, and plaque and tartar elimination. There were no significant differences between the two groups during the radiotherapy. This does not unequivocally mean that there is no beneficial effect of triamcinolone as, in fact, there was no neutral control group. That is, this paper reported that both triamcinolone and licorice mucoadhesive film showed decreased pain scores during the course of the radiotherapy treatment. The lack of a neutral (placebo) control group, however, restricts the claims this paper can make.

Chlorhexidine [22, 37]

Diaz-Sanchez et al. reported (using standard WHO criteria) that the integrity of the mucosa showed no significant differences between intervention (bioadhesive chlorhexidine gel 0.2%) and placebo groups ($p > 0.05$) [22]. Cheng et al. compared the effectiveness of two different types of mouthwashes. One group used chlorhexidine gluconate 0.2% mouthwash and the other group benzydamine hydrochloride 0.15% mouthwash [37]. There were no significant differences between the two groups. These results contrast with the findings of Madan et al. [36], which showed a beneficial effect of chlorhexidine.

Aloe vera [23]

Aloe vera is a plant considered to be effective for wound healing. Sahebjamee et al. divided patients into two groups. One group was allocated to use aloe vera mouthwash containing pure aloe vera gel and the other group used 0.15% benzydamine mouthwash. Grade 4 mucositis was shown in both groups with no statistically significant differences in mucositis grade between the two groups ($p = 0.35$). Note that benzydamine was used as an intervention agent [17], which may explain the non-significant result between the two groups in Sahebjamee et al.'s study [23].

Manuka honey [25, 32]

Bardy et al. reported that no significant differences were seen in the severity of oral mucositis (WHO grade) in manuka honey and placebo groups [32]. Furthermore, Hawley et al. similarly concluded that there was no significant difference between the manuka honey and placebo groups [25]. These results conflict slightly with those of Maddocks-Jennings et al.,

who reported a delayed onset of oral mucositis and reduced pain and oral symptoms using manuka in combination with *Kunzea ericoides* (kanuka) [35].

Iseganan [39]

Iseganan hydrochloride is an antimicrobial peptide. Trotti et al. divided patients into three groups: (1) iseganan mouthwash plus standard oral care (SOC), (2) placebo mouthwash plus SOC, and (3) SOC alone. There were no statistically significant differences between the three groups in the occurrence of oral mucositis (according to WHO grade).

Study reporting mixed results in the reduction of oral mucositis

Benzydamine [17]

Benzydamine, which is typically used as a hydrochloride salt for pain relief and as an anti-inflammatory treatment measure, was investigated in this study. Patients were randomly allocated into four groups depending on treatment type: group A (control) or group B (intervention) in patients undergoing radiation therapy, and group C (control) or group D (intervention) in patients undergoing chemoradiotherapy. All groups received saline mouth rinses, and groups B and D received additional 0.15% benzydamine rinses. Group B (intervention) had a lower rate of grade 3 mucositis than group A (control), 62.1% vs 36.4% ($p=0.038$). Oral mucositis grades in group C and D were not statistically significant different from each other, 64.3% vs. 43.3% ($p=0.091$), although the 21% difference was sizeable.

Limitations of this systematic review

This systematic review has several strengths including the comprehensive literature search, the inclusion of a large number of studies, and the thoroughness of the quantitative meta-analysis. The findings of this systematic review, however, should be interpreted in the context of the following two limitations: (1) the restriction of the search to the English and Japanese languages with respect to the published literature, and (2) that large variations were evident across studies with regard to sample size, selection of the studies, administration of the intervention, radiation dose, radiation technique (2D or 3D-CRT, IMRT), and controls as well as duration of the interventions, and the assessment methods.

Conclusion

The meta-analysis performed in this study suggests that radiation-induced oral mucositis in head and neck cancer patients can be controlled by several kinds of oral care given before and during radiotherapy. The use of mouthwash that includes an anti-inflammatory agent may contribute significantly to alleviating oral mucositis in patients undergoing radiotherapy for head and neck cancer. However, as some of the studies showing alleviation of mucositis had small sample sizes, further investigations using the same mouthwash in larger samples seem warranted to corroborate this conclusion.

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Compliance with ethical standards

Conflict of interest Masaru Konishi, Rinus Gerardus Verdonschot, Kiichi Shimabukuro, Takashi Nakamoto, Minoru Fujita, and Naoya Kakimoto declare that they have no conflict of interest.

Human rights statements All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent was obtained from all patients for being included in the study.

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