Review Article

A systematic review of interventional studies on oral care of palliative patients

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Background: To study and review the effectiveness of oral care interventions for palliative patients for amelioration of clinical conditions affecting oral cavity.

Methods: Following PRISMA standard, a systematic evaluation of articles published between 2000 and 2021 was undertaken utilising five databases on interventions studies. This comprehensive review consists of randomised controlled trials (RCTs) and specific types of non-randomised studies (NRS) examining oral care interventions for palliative patients. Three independent authors screened search records, identified related studies, extracted data and evaluated risk of bias. The key findings of each study were summarised according to the research questions and data that generated during the data extraction procedure.

Results: Out of the 67 identified studies, seven were included in this review (five RCTs and two NRSs) involving head-and-neck cancer, oral cancer, oral mucositis, xerostomia and individuals with malignant disease. Interventions studied were: Ziziphus honey, artificial saliva, CAM2028-Benzydamine, morphine mouthwash, ketamine mouthwash, bethanechol tablets and caphosol with regular oral-care. The durations of interventions in the included studies were largely short-term (six weeks or less). Overall, six studies revealed good results in support of the intervention, with magnitudes of effect ranging from 13.2–10,110.0%. However, just four researches found significant changes, with magnitudes of effect ranging from 50.0–10,110.0%. Although two of the trials have not revealed significant changes in the results, investigations have indicated a reduction in oral conditions in the group with interventions. Only one trial has not indicated an improvement in oral conditions in the groups which received the interventions.

Discussion: By assessing the efficacy of available oral hygiene interventions for palliative patients, this systematic review can help palliative team finds the viable strategies to apply in controlling oral problems among hospice patients. Even though only four of the seven research found a statistically significant difference, most studies found great effectiveness in favour of intervention.

Keywords: Oral health; oral disease; oral condition; palliative patients; cancer

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Introduction

Oral palliative care is the treatment of patients who have a progressive, far-advanced disease, such as cancer, and whose oral cavity has been affected, either directly or indirectly, by disease or treatment (1,2). Medications used to treat palliative illnesses, such as chemotherapy, frequently led to oral problems in these individuals. They have xerostomia, candidiasis, mucositis, stomatitis, ulceration, loss of masticatory function, taste issues, and sore/dry lips, which can affect their appetite, taste, chewing, swallowing, nutrition, speaking, social interactions, and sleeping (1,3). These patients' oral disorders have a significant impact on the quality of their remaining lives.

Despite the fact that the implications of oral disorders for palliative patients are well established, the challenges of providing oral care for these patients have been recognised (2). Most commonly oral discomfort is of less importance for the patients themselves in comparison with their devasting disease complaints and often missed to inform treating physicians (4). Furthermore, changing demographics and improved medical illness management are putting growing pressure on dental professionals to gain a better understanding of oral symptoms of systemic diseases and how to treat them. Oral therapies for palliative patients, according to the World Health Organization (WHO), must show benefit and provide the best possible quality of life (QoL) and mouth comfort (4). While there has been an increase in the number of high-quality systematic reviews of oral health interventions for the general population (5), no systematic study evaluating the effectiveness of oral health interventions for palliative patients has been published.

The primary goal of this systematic review was to examine and analyze the existing evidence on the effectiveness of oral care interventions for palliative patients in improving clinical states or diseases of the mouth.

This comprehensive assessment of oral hygiene therapies for palliative patients will enable us to draw conclusions regarding the efficacy of the interventions now available. Furthermore, the review can assist both non-dentist palliative care physicians and dental practitioners in determining the most effective ways for managing oral diseases among palliative patients in the context of health. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-215/rc).

Methods

Sources of data

We searched five electronic computer-indexed databases: PubMed, Ovid, EBSCOhost, ScienceDirect, and Google Scholar, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (6). These databases were chosen because they are exhaustive and yield articles that are most pertinent to our subject. We restricted our search to articles published between 2000 and 2021 to ensure that we included the most recent research on the subject. We used the medical subject headings (MeSH) and the free search terms "oral" OR "oral condition" OR "oral disease" OR "dental disease" OR "mouth disease" OR "mouth condition" OR "oral cancer" OR "oral mucositis" OR "mucositis" OR "stomatitis" OR "candidiasis" OR "cheilitis" OR "xerostomia" OR "periodontal disease" OR "halitosis". The search took place from 2000 and 2021. Additionally, we combed through the bibliographies or references of the selected publications in order to identify additional research that were missed during the searches.

Selection of studies

The inclusion criteria stated that studies must be (I) in full-text; (II) in the English language; (III) research studies only—to confirm that the retrieved articles had undergone the research process; (IV) published between 2000 and 2021—to include the most up-to-date research studies on the topic; (V) The primary intervention was preventive or curative; (VI) The intervention must have emphasized oral care promotion among palliative patients; (VII) The study should have included a comparison to one of the following: usual care, no care, or a similar alternative intervention; (VIII) Outcome measurements must be clinical or behavioural; nevertheless, any legitimate instrument employed in the included research, including questionnaires, observational outcomes, interviews, observational measures or self-reported outcomes were accepted.

Grey literature, review articles, and pieces in the form of abstracts, letters, commentaries, newsletter articles, or editorials were omitted.

The number of records found and excluded at each phase is depicted in *Figure 1*. The initial combined search resulted

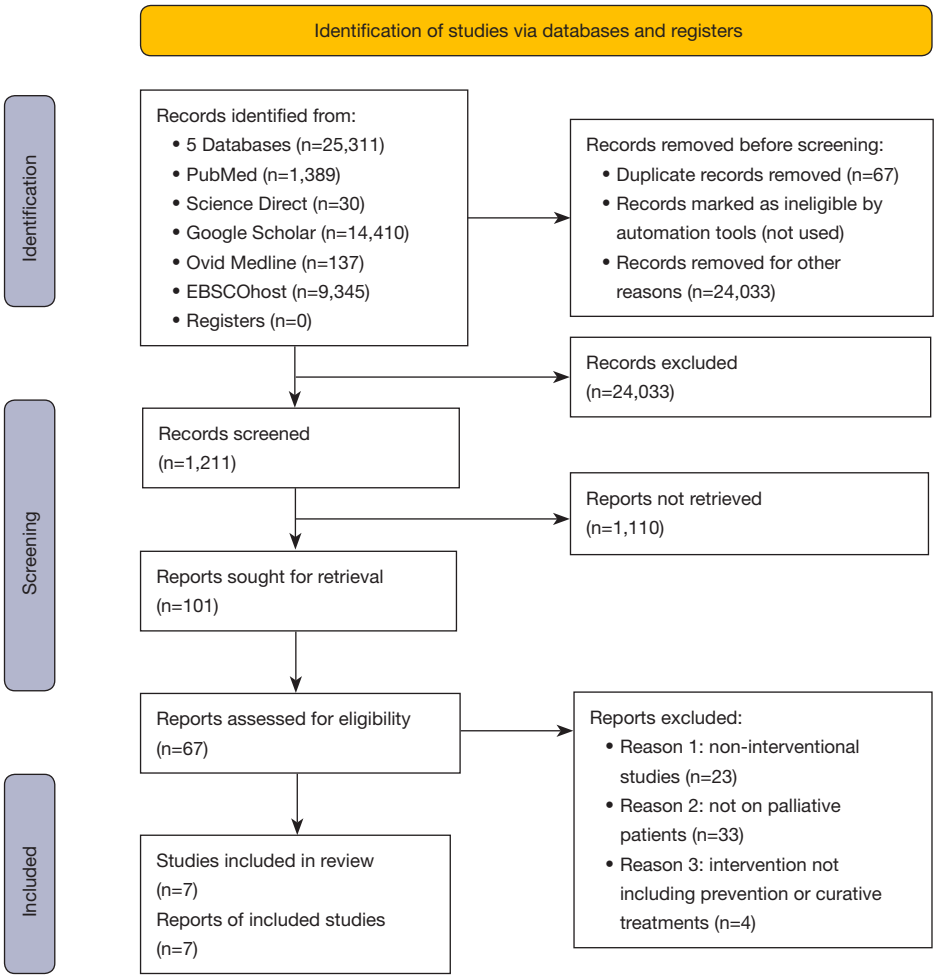

Figure 1 Search approach for identifying and selecting studies pertaining to oral palliative care interventions (PRISMA Flowchart).

in the identification of 25,311 articles. After removing duplicates and irrelevant articles, two reviewers (D.T.R, J.S.D) independently examined the remaining 1,211 articles and then classified into inclusion or exclusion. Subsequent to the independent evaluation, the two reviewers met to discuss preliminary findings and came to an agreement on which research to include. We rejected 1,144 papers from the 1,211 that were reviewed due to the following reasons: title and abstract screening, lack of relevance to our study population and research goals, poor sample size, and non-interventional studies. As a result, we ended up with a total of seven papers for additional study.

Extraction of data

The study's details were extracted into a table using the data extraction technique. D.T.R. and T.T. discussed each article in detail in order to establish agreement on the study's details. The following data were retrieved for each study: author(s), year of publication, study title, study design, objectives, sample population, sample age range, sample size (both at baseline and final assessment), intervention descriptions (including personnel delivering or supporting the intervention), intervention setting, duration of intervention, outcomes measured, evaluation tools used, and type of analysis used. The major findings or outcomes of each study were then extracted and summarized, along with any significant findings (P=0.05).

Additionally, in addition to giving the results of the outcomes directly in the articles, we generated an estimation of the interventions' relative influence on the results using a method previously described in the literature (7). In each group, we performed the following calculations: The final outcome evaluation result (FR) was

subtracted from the initial outcome result (IR), divided by the IR, and multiplied by 100: [(FR – IR)/IR] × 100. When the study included a control group, we compared the intervention group's percentage results to the control group as described above. In this method, we calculated the extent of the intervention group's decreases or gains in outcomes relative to the control group in terms of percentage.

Study quality assessment

The quality of the included studies was then evaluated using the Downs and Black (8) instrument, which originally included 27 questions about the article's information quality, external validity, internal validity, and statistical power, and yielded a score between 0 to 28. The question of attempting to blind subjects to exposure was omitted from this evaluation because it does not relate to several of the interventions tested. As a result, the articles' scores may range from zero to twenty-seven. According to criteria employed in another review (9), we (D.T.R and T.T) rated each study as excellent [24–27], good [20–23], decent [15–19], or poor or limited [14 or below] in terms of evidence quality.

Risk of bias in included studies

Additionally, D.T.R. and T.T. separately assessed the risk of bias for each study, resolving discrepancies. We kept track of the rationales for our decisions. According to the Cochrane Handbook for Systematic Reviews of Interventions, we assessed bias in randomised controlled trials (RCTs) and non-RCTs (NRCTs) in the following domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias (10). Each study was classified as having a high risk of bias, a low risk of bias, or an unknown risk of bias. The overall risk of bias within a study was determined by the number of low, unclear, and high ratings: if the study received at least one rating of high risk of bias, it was rated as high risk of bias overall; if all the ratings were of low risk of bias, the study was graded as low risk of bias overall; and if the study received a mix of low and unclear ratings, it was rated as uncertain risk of bias overall (11).

Results

Outcomes of the search

The five databases yielded 25,311 articles, and additional 19 were discovered from external sources, of which 67 were eliminated as duplicates. The remaining publications' titles and abstracts were then evaluated, and 24,033 were removed as being irrelevant. The remaining papers were then independently examined and rated for eligibility using the inclusion and exclusion criteria by two reviewers (D.T.R, J.S.D). After the independent evaluation, preliminary findings were discussed between the two reviewers and came to an agreement on which research to include. We rejected 60 of the 67 studies assessed for the following reasons: they did not match the criteria for an interventional trial. As a result, we ended up with a total of seven papers for additional study.

The study's characteristics

This review includes a total of seven papers. *Table 1* (12-18) summarizes the major characteristics of seven studies reporting on oral palliative care interventions.

Five of the studies included were RCTs and two were non-randomised studies (NRS). In terms of RCTs, two were parallel-group studies (12,14), one was a double blinded study (13), while the other two were cross-over trials (15,16). Two of the NRS were NRCTs (17,18). The five RCTs were reported to have taken place between 2011 and 2015. However, the duration of both NRS studies was unknown (17,18).

We classified intervention studies into three types: brief (six weeks or less), medium (six weeks to 12 months), and long term (more than 12 months). The interventions in the included studies were mostly brief (six weeks or less) in duration (n=6) (12,13,15-18), with one being only moderate in duration (between six weeks and 12 months) (14). None of the studies involved a sustained intervention (more than 12 months).

The studies had recruited participants based on the number at the baseline; this number ranged between 30 and 220 for RCTs and 30 to 50 for NRS. Three RCTs (13,15,16) enrolled fewer than 50 individuals, whilst the other two RCTS included more than 50 participants (12,14). The studies were conducted in six different countries: Pakistan (12), the United Kingdom (14,15), Bulgaria (16), Iran (13), India (17), and the United States of America (18), with the majority of them taking place in hospitals (18).

In terms of participant characteristics, all studies included males and females, ranging in age from 23 to 87 years, and involving patients with head and neck cancer (12,13,14,16), oral cancer (histopathological diagnosis-carcinoma of the buccal

Table 1 Characteristics of included studies (n=7)

Author/year	Title of study	Study design	Study objective(s)	Study population	Age of study population	Sample size		Intervention descriptions	Intervention setting	Intervention duration
						Baseline	Final			
Amanat *et al.*, 2017	The effect of honey on radiation-induced oral mucositis in head and neck cancer patients	RCT: parallel group	To determine the impact of honey on clinically scoring values of oral mucositis	Head and neck cancer patients who planned for external beam radiotherapy (fractioned and hyper-fractioned radiation therapy), with a total radiation dose of 60–70 Gy (in 5–6 weeks)	Age range not reported	82	79	• 82 patients were divided into TWO groups (i.e., control and intervention group by simple random sampling. Patients in both groups were treated with a total dose of 60–78 Grays	Hospital: Radiation Oncology Department of Mayo Hospital, Lahore, Pakistan	4–6 weeks
					Median age (control): 50.2 years	Control group (n=41): 27 males, 14 females	40 controls	• In intervention group, patients were instructed to take 20 mL of Ziziphus honey, 15 min before and after the radiotherapy, and before sleeping in the night. They were instructed to swallow slowly to smear the layer of honey on the oral and pharyngeal mucosa		
					Median age (intervention): 49.9 years	Intervention group (n=41): 33 males, 8 females	39 interventions	• In control group, patients were given 20 mL of 0.9% of saline (rinsing), 15 min before and after radiotherapy, and before sleeping in the night—They were instructed to keep saline for at least 5 min duration and then to spit it out		
Davies, 2000	A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer	Prospective RCT: open, cross over study	To compare a mucin-based artificial saliva (Saliva Orthana™) with a low-tack, sugar-free chewing gum (Freedent™) in the management of xerostomia in patient volunteers with advanced cancer	Patients with xerostomia, malignant disease, and an estimated prognosis of more than 2 weeks	Age range, 32–87 years	43	1st phase: 30	• Patients received 5 days' intervention with one product, then nothing for 2 days ('washout period'), then 5 days' intervention with the other product before breakfast, before lunch, before dinner and before bedtime, and also at times whenever needed for dry mouth	Hospitals: King's College Hospital, London, and was continued at St Christopher's Hospice, London, United Kingdom	12 days (including 2 days' washout)
					Mean age: 66 years	23 females, 20 males	1st and 2nd phases: 26	• The patients were given instructions on how to use the artificial saliva: they were told to shake the bottle before use, to use enough artificial saliva to cover their whole mouth, to spray around their mouth, and to use their tongue to help spread the artificial saliva around their mouth. Similarly, for chewing gum: they were told to use one or two pieces at a time, to chew for at least 10 min, to chew gently, and to chew using both sides of their mouth		
Hadjieva *et al.*, 2014	Treatment of oral mucositis pain following radiation therapy for head-and-neck cancer using a bio adhesive barrier-forming lipid solution	RCT: cross-over, double-blind, placebo-controlled, single-dose, proof-of-concept trial	To compare the analgesic effect of CAM2028 plus benzydamine (CAM2028-benzydamine) with unmedicated CAM2028 (CAM2028-control) for the intervention of oral mucositis in patients with head-and-neck cancer over an 8-hour period. To evaluate the safety and tolerability of a single dose of the new formulation	Patients with head-and-neck cancer having symptomatic oral mucositis (WHO Value II or above at screening and pain scores of at least six on an 11-point Likert scale at screening and on each day before intervention with study medicine. Also, at their 3rd to 4th week of radiation therapy	Age range, 32–73 years	38 (32 males: 6 females)	32	• Generally, after undergoing radiation, patients were administered a single dose of CAM2028-control or CAM2028-benzydamine (containing benzydamine 28.2 mg/mL) 2 days apart	Hospitals: five oncology centres in Bulgaria	5 days

Table 1 (*continued*)

Table 1 (*continued*)

Author/year	Title of study	Study design	Study objective(s)	Study population	Age of study population	Sample size		Intervention descriptions	Intervention setting	Intervention duration
						Baseline	Final			
					Median age: 52 years			• Day 1: each patient was randomly assigned to one of 2 sequences: CAM2028-benzydamine • Day 3: followed by CAM20208-control or CAM2028-control followed by CAM2028-benzydamine. Procedures: One mL of either the study medicine was applied to the oral mucosa using a syringe, and patients were instructed to swirl the medicine around in the mouth for approximately 15 seconds and then spit out any residual medicine. The procedure was repeated after 5 minutes • Day 5: Final evaluation		
Sarvizadeh *et al.*, 2015	Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer	RCT; Double blinded	To evaluate the effectiveness of topical morphine compared with a routine mouthwash in managing cancer treatment-induced mucositis	Head and neck cancer Patients with severe mucositis due to chemotherapy, radiotherapy or chemo-radiotherapy	Age range not reported	Participants (n=30)	N=28	Patients were randomized into the morphine and magic mouthwash groups, 15 in each by random table numbers		
					Median age (morphine group): 52.1	Morphine group (n=15): 5 male and 10 female	Morphine group (n=15)	The morphine group used the mouthwash of 2% morphine solution (20 mg morphine sulphate diluted in 100 mL of water)		
					Median age (magic mouth wash group): 47.5	Magic mouth wash group (n=13): 5 male and 8 female	Magic mouth wash (n=13)	The magic group used a mouthwash containing a mixture of 240 mL magnesium aluminium hydroxide (Alborz Co., Iran), 25 mL 2% viscous lidocaine (SinaDaru Co., Iran), and 60 mL diphenhydramine (Emad Co., Iran)		
							2 patients died after first assessment	Patients were administered with 10 mL every 3 hours is administered six times a day Total treatment period was 6 days		
Kavitha *et al.*, 2017		NRS: Interventional study	To determine the efficacy of Bethanechol in patients with xerostomia following chemo-radiation therapy for oral cancer	Oral cancer patients (histopathologically diagnosed as carcinoma of buccal mucosa, gingivo-buccal sulcus, anterior 2/3rd of the tongue, floor of the mouth, gingiva and hard palate) with xerostomia post-chemoradiation therapy	Age range, 30–65 years	50	50 (30 intervention group; 20 control group)	Patients with xerostomia were divided into TWO groups:	Department of Oral Medicine and Radiology, Madha Dental College and Hospital, Chennai, Tamil Nadu, India	3 weeks
					Mean age: 47.74 years		Intervention group: 19 males: 11 females	• In intervention group (i.e., those with normal liver and renal function), patients were administered 25 mg Bethanechol (tablets), orally 3 TDS on empty stomach, 1 h before or 2 h after food to prevent nausea and vomiting for 3 weeks		
							Control group: 12 males: 8 females	• In control group, patients were administered placebo capsules containing wheat flour, orally 3 TDS 1 h before or 2 h after food for 3 weeks		

Table 1 (*continued*)

Table 1 (*continued*)

Author/year	Title of study	Study design	Study objective(s)	Study population	Age of study population	Sample size		Intervention descriptions	Intervention setting	Intervention duration
						Baseline	Final			
Shillingburg *et al.*, 2017		NRS: Open-label, prospective, interventional study	To assess the reduction in pain intensity of stomatodynia and odynophagia compared to baseline assessment. Also, to assess patient-reported onset and duration of impact, reduction in both narcotic analgesic use and topical lidocaine use, and improvement in patient-reported sleep quality, safety, and tolerability	Patients with grade 3 or 4 oral mucositis (according to the WHO scale and as a result of chemotherapy)	Age range, 23–67 years	30 (17 females, 13 males)	29	Patients were treated with ketamine mouthwash 20 mg/5 mL four times daily and every 4 h as needed	An institution, USA	9 days
					Median age: 44 years			Patients were asked to swish the solution for at least 30 s		Median: 4 days
								Patients were also requested to avoid oral intake for at least 30 min after each ketamine dose		
								Patients were removed from the study on the day when their mucositis had resolved to less than value 3 (removal from the study was permitted by request from either the patient or physician or due to lack of efficacy, defined as no decrease in pain scores for three consecutive days)		
Wong *et al.*, 2017		RCT; non-blinded, parallel-group	To determine the efficacy of Caphosol mouthwash in the management of radiation-induced oral mucositis in patients with head and neck cancer	Patients with head and neck cancer (except thyroid and larynx) undergoing radical (chemo) radiotherapy (in a radical setting with Karnofsky's performance status >70%)	Mean age (SD): 58.8 (10.6) years	220	215 (108 Intervention group: 107 control group): 161 males, 54 females	Patients were randomised (1:1) to the use of Caphosol plus standard oral care (intervention) or standard oral care regimen (control) using random permuted blocks method	Hospital: Royal Marsden Hospital, London, United Kingdom	8 weeks
					Mean age (SD) for intervention group: 57.8 (11.7) years		Intervention group: 85 males and 23 females	Patients were stratified by radiotherapy technique (unilateral versus bilateral) and type of therapy (chemo-radiotherapy versus radiotherapy only)		
					Mean age (SD) for control group: 59.9 (9.3) years		Control group: 76 males and 31 females	In intervention group, patients started using Caphosol from the 1st week of radiotherapy. Caphosol was used as a mouthwash 4 times a day but the frequency could be increased up to 10 times a day at the physician's or patient's discretion		
								Patients used Caphosol for a total duration of 7 weeks; 6 weeks during radiotherapy and 1 week after completion		
								Depending on the symptoms, patients had access to other symptom treatment options available in the control arm. If patients did not tolerate Caphosol, it could be stopped immediately and the reasons for discontinuation were recorded		
								In control group, patients received standard intervention for oral mucositis that included normal saline mouthwash at least 4 times a day, aspirin mouthwash 3 times a day and tooth brushing with fluoride toothpastes prescribed by a dental hygienist		

RCT, randomised controlled trial; NRS, non-randomised study; TDS, times daily.

Table 2 Evaluation of the quality of the interventions, according to the criteria of Downs and Black

Authors (year)	Reporting	External validity	Bias*	Confounding	Power	Sum
	(0 to 10)	(0 to 3)	(0 to 6)	(0 to 6)	(0 to 1)	(0 to 26)
Amanat *et al.* [2017]	9	2	5	5	0	21
Davies [2000]	10	2	4	4	0	20
Hadjieva *et al.* [2014]	9	2	4	4	0	19
Sarvizadeh *et al.* [2015]	10	3	5	6	1	25
Kavitha *et al.* [2017]	10	0	4	3	0	17
Shillingburg *et al.* [2017]	10	0	4	3	0	17
Wong *et al.* [2017]	9	2	3	5	1	20
Average (SD)	9.6 (0.5)	1.6 (1.1)	4.1 (0.7)	4.3 (1.1)	0.3 (0.5)	19.9 (2.9)

*, Question 14 of the Downs and Black instrument was excluded.

mucosa, gingivobuccal sulcus, anterior 2/3rd of tongue (15). Sarvizadeh *et al.* and Wong *et al.* gave mean ages only (13,14), but Amanat *et al.* (12) supplied median ages only.

Table 2 summarizes the quality assessment of the studies. The average total score was 19.9 points (SD =2.9) using the Downs and Black instrument (8). The minimum score was 17 points (17,18), and just one study received a perfect score of 25 points (13). Three studies were deemed to be of high quality (12,14,15), while the remaining three were deemed to be of acceptable quality (16-18). The review of the instrument's items revealed more methodological issues with external validity and power.

Characteristics of the interventions

Interventions on oral palliative care of the included studies and its related findings are summarised in *Table 3*.

Six interventions in the included studies assessed each of the following comparisons:

- Comparison 1: Honey (Ziziphus honey) versus 0.9% of saline (12).
- Comparison 2: Artificial saliva (Saliva Orthana™) versus chewing gum Freedent™ (15).
- Comparison 3: CAM2028-benzydamine versus CAM2028-control (16).
- Comparison 4: Morphine mouthwash versus 'magic' solution (13).
- Comparison 5: Bethanechol tablets versus placebo capsules (17).
- Comparison 6: Caphosol plus standard oral care versus only standard oral care (14).

The following intervention was evaluated in one of the studies included:

The efficacy of oral ketamine mouthwash on severe mucositis pain (18).

Because stakeholder involvement can have an effect on the outcome of an intervention, it was deemed necessary for this review to capture the nature of stakeholders participation in the interventions. Only two studies (12,18) reported involving dental professionals (dentists and/or dental hygienists) in the interventions, whereas the remaining three (n=3) did not (12,13,15,17). Two further research did not specify whether dental practitioners were involved (14,16). Dental practitioners were primarily responsible for initiating oral hygiene training, doing clinical measurements during the intervention, and providing continuous support.

On the other hand, several studies included radiotherapists (12,14), radiologists (17), and radiation oncologists (13). Additionally, physicians (13,14,18), pharmacists (13,18), biochemists (17), anatomists (12), and oral and maxillofacial surgeons participated as stakeholders (12). Two studies (15,16) indicated that stakeholders other than those directly participating in the research were unclear or absent (15,16).

Table 3 summarizes the outcome measures used in the interventions. The following clinical outcomes were assessed in the RCTs: the incidence or severity of oral mucositis and its duration, pain intensity, pain intensity difference (PID), the incidence and duration of severe pharyngeal mucositis, the incidence and duration of severe dysphagia, the incidence and duration of severe radiation-induced pain, quality of life, patient satisfaction, drug effect maintenance, and treatment efficacy. Meanwhile, the

Table 3 Overall summary of interventions on oral palliative care and its related findings

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
Amanat *et al.*, 2017	Comparison: honey (Ziziphus honey) versus saline	With or without dental professional involvement: With dentists	Grades of oral mucositis (based on RTOG Grading System)	Assessment: Examination on oral cavity was done every week up to 6 weeks in both control and honey-treated groups	There was a significant reduction of oral mucositis in intervention group as compared to control group	Strengths & weaknesses: The study was unicentric in nature and patients were heterogeneous regarding cancer intervention (fractioned and hyper-fractioned radiation therapy), age, and tumour location. There is disparity in assessment and management of oral mucositis due to complex multi-factors related to the patients and intervention to the complex multifactorial patient and intervention factors related to oral mucositis
	• Patients in both groups were treated with a total dose of 60–78 Grays	Other stakeholder involvement: Radio therapist, anatomist, oral and maxillofacial surgeon		Timing of outcome assessment: Week 1, 2, 3, 4, 5 and 6	At the end of 6th week, the difference of Grades 3 and 4 was statistically significant among control and intervention groups (P value of Grade 3 mucositis: 0.016 and P value of Grade 4 mucositis: 0.032)	Modifications to the interventions: None reported
	• In intervention group, patients were instructed to take 20 mL of Ziziphus honey, 15 min before and after the radiotherapy, and before sleeping in the night—instructed to swallow slowly to smear the layer of honey on the oral and pharyngeal mucosa			Statistical analysis: Chi-square test	Honey demonstrated potential in reducing the severity of RTOG Value 3 and 4	Adverse effects: None reported
	Mechanism of action of honey: Radiotherapy rays are absorbed by the oral mucosal cells which leads to its inflammation. Honey is a prophylactic agent that has numerous beneficial health properties including its ability to facilitate healing. It has a powerful impact on the proliferation of B-lymphocytes and T-lymphocytes and also in the activation of macrophages. It inhibits inflammatory process by inhibiting cyclooxygenase pathway because it is the main pathway of inflammation. Certain enzymes, phytochemical agents (methylglyoxal and methyl syringate), low pH, defensin, a peptide, and high osmolarity are distinct mechanisms involved in the bactericidal activity of honey					Bias: Detection bias (blinding of outcome assessment) but with UNCLEAR RISK—All clinical measures were reported by the lead author but no mention on blinding Attrition bias: but have a LOW RISK as participants who did not complete the intervention was fully documented—"One patient in control group in 3rd week and 2 patients in intervention group refused to continue their radiotherapy intervention." p. 318
	• In control group, patients were given 20 mL of 0.9% of saline (rinsing), 15 min before and after radiotherapy, and before sleeping in the night—instructed to keep saline for at least 5 min duration and then to spit it out					
Davies, 2000	Comparison: artificial saliva (Saliva Orthana™) versus chewing gum Freedent™	With or without dental professional involvement: Without	1. The efficacy of both Saliva Orthana™ and Freedent™	Assessment:	27 received artificial saliva (Saliva Orthana™), 32 received the chewing gum Freedent™, and 26 received both interventions	Strengths & weaknesses: Small sample size, high attrition rate
	1. Patients received 5 days' intervention with one product, then nothing for 2 days ('washout period'), then 5 days' intervention with the other product before breakfast, before lunch, before dinner and before bedtime, and at times whenever needed for dry mouth	Other stakeholder involvement: N/A	2. The side-impact profile of both Saliva Orthana™ and Freedent™	1. The efficacy was measured using a combination of visual analogue scales (100 mm) [where the visual analogue scales were administered at the beginning and end of each intervention period, and the anchor points were 'worst imaginable dryness' (0 mm) and 'no dryness' (100 mm)]	1st Phase: The mean initial VAS score was 32.0 mm in the artificial saliva group and 32.5 mm in the chewing gum group. There was no statistically significant difference between these scores (unpaired *t*-test: P=0.95)	Modifications to the interventions: None reported

Table 3 (*continued*

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
	2. The patients were given instructions on how to use the artificial saliva: they were told to shake the bottle before use, to use enough artificial saliva to cover their whole mouth, to spray around their mouth, and to use their tongue to help spread the artificial saliva around their mouth			2. Efficacy was also measured using a questionnaire (at the end of each intervention period). e.g., 'Do you reckon the intervention has helped your dry mouth?', 'Would you like to continue with the intervention after the study?' and 'Did you notice any problems with the intervention?"	2nd Phase: The mean initial VAS score was 40.7 mm in the artificial saliva group and 31.9 mm in the chewing gum group. Again, there was no statistically significant difference between these scores (unpaired t-test: P=0.34)	Adverse effects: Nausea in two patients, and irritation of the mouth in three patients
	Mechanism of action of Saliva Orthana™: The artificial saliva used in this study was the mucin-based Saliva Orthana. It is a naturally occurring mucin and known to have very good rheological properties which makes them useful for protection against desiccation and environmental insult, impactive lubrication and shown to have anti-microbial impact			3. Meanwhile, the side-impact profile of the two products was also assessed by using the questionnaire.	Statistical analysis of the data revealed no evidence of either a period impact, or a carry-over impact (unpaired *t*-test: P=0.11)	Bias: Attrition bias (incomplete outcome data), but have a LOW RISK as participants who did not complete the intervention was fully documented and missing data was resolved using imputation method—"Only 70% of the subjects completed the first phase of the study, while only 60% of the subjects completed both phases of the study. The reasons for subjects withdrawing from the study were deterioration in condition (12%), death (9%), side-impacts (7%), spontaneous improvement in xerostomia (7%), and personal reasons (5%)." p. 5.
	3. Similarly, for chewing gum: they were told to use one or two pieces at a time, to chew for at least 10 min, to chew gently, and to chew using both sides of their mouth			Statistical analysis: Chi-square test	The mean change in VAS score was +22.4 mm with the use of artificial saliva and +30.1 mm with the use of chewing gum. There was no statistically significant difference between these results (paired t-test: P=0.49). The 95% CI for the difference between these results was from –15.9 to 30.4 mm Although none of these results reached statistical significance, patients with cancer reckon that chewing gum is an acceptable intervention, although both Saliva Orthana™ and Freedent™ can both cause side-impacts 69% of the patients preferred the chewing gum to the artificial saliva, as it is more usefulthan artificial saliva The chewing gum scored better than the artificial saliva on every measure of efficacy, therefore, chewing gum has a useful role in the management of xerostomia in patients with advanced cancer	Performance/intervention bias (blinding of participants and assessors)—HIGH RISK—Cross-over trials; not possible to blind participants or assessors.
Hadjieva *et al.*, 2014	Comparison: CAM2028-benzydamine versus CAM2028-control	With or without dental professional involvement: Unclear	1. Pain intensity difference (PID) (from baseline—6 h)	Assessment: Pain intensity (11-point Likert scale (0=no pain, 10=worst possible pain) over the following 8 h after administration of CAM2028-control/CAM2028-benzydamine	With both interventions, patients reported a mean 40% decrease in pain intensity at 6 h (the primary study end point), i.e., from a baseline of 6.5 (CAM2028-benzydamine) or 6.4 (CAM2028-control) to 4.6	Strengths & weaknesses: Short intervention duration
	• Patients were administered a single dose of CAM2028-control or CAM2028-benzydamine (containing benzydamine 28.2 mg/mL) 2 days apart	Other stakeholder involvement: Unclear	2. PID at other time intervals	Timing of outcome assessments: Baseline, 5 min, 1 h, 6 h, and 8 h	Both interventions resulted in significant pain relief within 5 min of application that was evident during the entire 8 h assessment period	Modifications to the interventions: None reported

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
	• Day 1: each patient was randomly assigned to one of two sequences: CAM2028-benzydamine		3. Peak pain (maximum Likert score on each intervention day)	Statistical analysis: ANCOVA	The mean AUC of pain intensity over time, however, did not differ between the two interventions	Adverse effects: Two patients reported nausea or vomiting on CAM2028-benzydamine, 1 on CAM2028-control, and 1 on both interventions. Upper respiratory tract infection and haemoptysis each occurred in 1 patient who received the CAM2028-benzydamine
	• Day 3: followed by CAM20208-control or CAM2028-control followed by CAM2028-benzydamine. Procedures: One mL of either the study medicines was applied to the oral mucosa using a syringe, and patients were instructed to swirl the medicine around in the mouth for approximately 15 secs and then spit out any residual medicine. The procedure was repeated after 5 min		4. AUC of the PID		There was no difference in pain relief between the two interventions at any time point	Bias: Attrition bias (incomplete outcome data/missing data)—but have a LOW RISK as missing pain score data was resolved by the last observation carried forth (LOCF) method, and also as participants who did not complete the intervention was fully documented—"Three patients were not included in the per-protocol set because they had a baseline pain score lower than 6 on the second intervention visit (when all three were scheduled to receive CAM2028-benzydamine) and three others had minor protocol violations in recording their pain scores", p. 4
	• Day 5: Final evaluation		5. Primary efficacy endpoint		Nevertheless, CAM2028-benzydamine and CAM2028-control were both efficacious in reducing pain in patients with oral mucositis related to radiation therapy for head-and-neck cancer	
	Mechanism of action of CAM2028-benzydamine: CAM2028-benzydamine acts as a lipid-based drug carrier system for local and extended delivery of benzydamine in the oral cavity. After application to the oral mucosa, phospholipid and triglyceride lipid components of the formulation spread in the oral cavity and self-assemble with a minute volume of aqueous fluid at the mucosal surface to create a bio-adhesive liquid crystalline lining safeguarding the sore and inflamed mucosa. The liquid crystalline film formation happens by molecular self-assembly of the lipid components and ambient water molecules found in saliva. The film attaches to the palate, the inside of the cheeks, gums, and the rim of the tongue. Other effect of bio-adhesive lipid formulation may include lubrication and mechanical protection of the sore mucosa and possibly a moistening advantage				Analgesic impacts of both medicines were immediate, clinically significant, and persistent for up to 8 h	
Sarvizadeh *et al.*, 2015	Comparison: morphine mouthwash versus 'magic' solution	With or without dental professional involvement: Without	1. Mucositis severity	Assessment:	There was a decrease in mucositis severity in both of the morphine (P<0.001) and magic (P=0.049) groups	Strengths & weaknesses: The study was unicentric in nature and heterogeneous regarding cancer intervention (although it seems that cancer intervention type might not have direct impacts on this intervention response), small sample size and short intervention period
	• In intervention group, patients received morphine mouthwash containing morphine sulfate 2% (20 mg morphine sulfate diluted in 100 mL of water), 10 mL for every 3 h, 6 times a day	Other stakeholder involvement: Radiation oncologist, pharmacist, physician	2. Patients' satisfaction	1. Grading of mucositis severity (0 = a healed mucositis and no signs or symptoms, 1 = mild soreness, but not problem in eating; 2 = painful erythema, edema, or ulcers, but able to eat; 3 = severe painful erythema, edema, or ulcers and having problem in eating; and 4 = whether there was a requirement for parenteral or enteral support)	However, at the 6th day, more reduction was observed in mucositis severity in the morphine compared with magic group (P=0.045)	Modifications to the interventions: None reported

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
	• Mechanism of action of morphine mouthwash: The opioid analgesics, of which morphine is the prototype, produce their analgesic impacts by binding to opiate receptors in the central nervous system and the peripheral terminals of afferent nerves. Opioid receptors are expressed on oral epithelial cells and morphine modulates the proliferation of inflammatory cells and modify the time course of the intensity of pain, which in turn help in the wound healing process		3. Drug impact maintenance	2. Patient satisfaction (satisfied, tolerable or intolerable)	Drug impact maintenance was similar between the two groups, but volunteers in the morphine group were more satisfied by their interventions than those in the magic group (P=0.008)	Adverse effects: Mild oral burning/itching during oral rinse
	• In control group, patients received magic solution (containing mixture of 240 mL magnesium aluminium hydroxide (Alborz Co., Iran), 25 mL 2% viscous lidocaine (SinaDaru Co., Iran), and 60 mL diphenhydramine (Emad Co., Iran)), 10 mL for every 3 h, 6 times a day			3. Drug impact maintenance (< 1 h, 1–2 h or >2 h)	Topical morphine is more helpful and more satisfactory to patients than the magic mouthwash in reducing severity of cancer intervention-induced oral mucositis	Bias: Performance/intervention bias (some patients were enrolled into this trial while still under cancer intervention, whereas others had just finished the intervention course)—UNCLEAR RISK
	• Patients were instructed not to swallow the solution and to hold it for at least two minutes			Timing of outcome assessments: Baseline, 3rd day and 6th day of the intervention		Performance/intervention bias (short intervention period—unable to find long-term benefits or harms of such therapy)—UNCLEAR RISK
	• Both groups received same dietary and oral hygiene instructions and care			Statistical analysis: Baseline characteristics between the two groups: Independent sample *t*-test and Chi-square test. Change in the severity of mucositis: Friedman test in each group and by Mann–Whitney test between the two groups		Attrition bias: Reason was clearly explained "2 patients from the magic mouthwash group died before the second or third assessment", p.4.—LOW RISK
Kavitha, Mubeen & Vijayalakshmi, 2017	Comparison: bethanechol tablets versus placebo capsules	With or without dental professional involvement: Without	1. Subjective symptoms of oral dryness	Assessment:	Twenty-four (80%) patients in Bethanechol group and only 2 (10%) patients in control group showed subjective improvement in oral dryness at the end of 3rd week	Strengths & weaknesses: Use of subjective assessment (for e.g., subjective symptoms of oral dryness). This may vary greatly from one patient to another. Others include small sample size and short duration of intervention
	Patients with xerostomia were divided into TWO groups:	Other stakeholder involvement: Radiologist, Biochemist, clinicians	2. Salivary analysis:	1. Subjective symptoms of oral dryness were assessed using a self-reported questionnaire (designed by Eisbruch *et al.* and Meirovitz *et al.*):	A significant difference was found between two groups in whole resting (P<0.001) and stimulated saliva volume (P<0.001), pH (P<0.001) and amylase (P<0.001)	Modifications to the interventions: None reported
	• In intervention group (i.e., those with normal liver and renal function), patients were administered 25 mg Bethanechol (tablets), orally 3 times daily (TDS) on empty stomach, 1 h before or 2 h after food to prevent nausea and vomiting for 3 weeks		• Whole resting saliva volume	• Difficulty in chewing due to dryness	No statistically significant difference in sodium potassium ratio with insignificant adverse impacts after 3 weeks of Bethanechol therapy.	Adverse effects: Three patients reported frequent urination as adverse impact (10%) and only 1 patient had sweating (3.3%), with overall percentage of adverse reactions of about 13.3% in patients treated with Bethanechol (insignificant); and none of the patients discontinued the drug during the three weeks of therapy
	Mechanism of action of bethanechol tablets: Bethanechol (saliva stimulant) is an acetylcholine analog possessing muscarinic and nicotinic-cholinergic activity that helps to increase the whole resting and stimulated saliva with minimum side impacts in xerostomia patients.		• WSS volume	• Difficulty swallowing solid foods due to dryness	Overall, 25 mg Bethanechol (TDS) has shown subjective improvement in oral dryness in 24 (80%) patients with significant improvement in whole resting and WSS volumes, pH and salivary amylase with insignificant adverse effects	Bias: Performance/intervention bias & detection bias: All clinical measures were reported by the lead author but no mention on blinding—UNCLEAR RISK

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
	• In control group, patients were administered placebo capsules containing wheat flour, orally 3 TDS 1 h before or 2 h after food for 3 weeks		• Amylase • pH • Sodium potassium ratio	• Mouth or throat dryness while not eating • Difficulty in talking due to dryness • Frequency of your sleeping problems due to dryness • Frequency of sipping liquids to aid swallowing food and for oral comfort 2. Salivary analysis was performed using enzymatic colorimetric assay and analysed using fully automated analyzer (CoBAS Integra 400) Timing of outcome assessments: Baseline, at the end of 1st, 2nd and 3rd weeks after Bethanechol and placebo therapy Statistical analysis: N/A		Selection bias: No mention on randomization—HIGH RISK Reporting bias: One of the important aspects of the methodology was not reported, i.e., type of statistical analysis utilized—LOW RISK
Shillingburg *et al.*, 2017	Patients were treated with ketamine mouthwash 20 mg/5 mL four times daily and every 4 h as needed	With or without dental professional involvement: With dental hygienist	1. Pain scores	Assessment:	A statistically significant reduction in pain scores of 2 and 3 points was obtained after 1 h and 3 days, respectively (P<0.0001, P=0.0003)	Strengths & weaknesses: Strength: The utilization of prospective study (the exposure has already been measured before the outcome has occurred, which allows for the assessment of temporal sequence. This allows for the calculation of incidence and the determination of the disease process/development)
	Patients were asked to swish the solution for at least 30 secs	Other stakeholder involvement: Pharmacist, physicians	2. Sleep quality	1. Pain scores - Patients were asked to score pain at rest and when swallowing. Pain scores were assessed on a numeric scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain	Pain scores were significantly ameliorated while swallowing, reduced 1 and 4 points at 1 h and 3rd day assessment, respectively (P=0.0006, P=0.0001)	Weaknesses: Inclusion of subjective measure and small sample size
	Volunteers were also need to observe no oral intake for at least 30 min after each ketamine dose		3. Food intake	2. Sleep quality was assessed on a 0 to 10 numeric scale, with 0 representing no sleep and 10 representing optimal sleep	Sleep quality significantly ameliorated from a median rating of 5 to 6 (P=0.006) after the first night and then sustained that improvement through day 3 (P=0.034)	Modifications to the interventions: None reported
	Volunteers were removed from the study on the day when their mucositis had resolved to less than value 3 (removal from the study was permitted by request from either the patient or physician or due to lack of efficacy, defined as no decrease in pain scores for three consecutive days)		4. Onset of impact	3. Food intake was classified as none, liquids only, soft food only, or normal diet	The onset of action was noted within 15 min of the dose in the majority of patients and reported to last for 1–3 h	Adverse effects: No adverse effects
	Mechanism of action of ketamine mouthwash: Ketamine is a sedative hypnotic with anesthetic and analgesic properties and with reported benefit in reducing severe pain when used topically. Ketamine works by selectively depressing the thalamo-neocortical system, non-competitively blocking Nmethyl-D-aspartate (NMDA) receptors, and having intrinsic sympathomimetic activity		5. Duration of impact	4. Onset of impact was reported as either no impact, 0–15 min, 16–30 min, 31–45 min, 46–60 min, or greater than 1 h	Tolerability of the solution was acceptable and several patients commented that the solution was preferable to the lidocaine-based solutions due to less burning and irritation	Bias: Intervention/performance bias: Comparing outcomes from subsequent assessments to baseline (prior to ketamine) removed inter-patient variability of pain scores—but have a LOW RISK, since no changes were made to the patients' current intensive systemic and local interventions at the time of ketamine intervention

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
			6. Oral mucositis severity	5. Duration of impact was reported as either no impact, less than 1 h, 1–2 h, 2–3 h, 3–4 h, or 4 or more hours	Ketamine mouthwashes resulted in clinically meaningful and statistically significant reduction in pain scores, have an acceptable safety profile, and can be a useful adjunctive intervention in the multi-modal management of severe mucositis	Detection bias: All clinical measures were reported by the lead author but no mention on blinding—UNCLEAR RISK
				6. The WHO oral mucositis severity value was recorded daily		Attrition bias: LOW RISK—Reason was explained "One patient (3%) withdrew from the study due to altered mental status, reported to be due to continuous intravenous narcotics and onset of sepsis and not deemed related to ketamine mouthwashes", p.218
				Timing of outcome assessments: At baseline, 1 h after the first dose of ketamine and then daily thereafter for up to 7 days		
				Statistical analysis: Wilcoxon's sum rank test and Fisher's exact test		
Wong *et al.*, 2017	Comparison: Caphosol plus standard oral care (intervention) versus standard oral care alone (control)	With or without dental professional involvement: Unclear	1. Incidence of severe oral mucositis (grade 3 or more) during and up to week 8 post-radiotherapy	Assessment: The scoring of radiation-induced side impacts was based on the NCI Common Toxicity Criteria scoring system (CTCAE) version 4.0. QoL was assessed using the EORTC QoL questionnaire, QLQ-C30 version 3.0 and QLQ-HN35	The incidence of severe oral mucositis did not differ between the intervention and control arms (64.1% versus 65.4%, P=0.839)	Strengths & weaknesses: Strength: The utilisation of prospective study
	Patients were randomised (1:1) to the use of Caphosol plus standard oral care (intervention) or standard oral care regimen (control) using random permuted blocks method	Other stakeholder involvement: Radiotherapist, physicians	2. Duration of severe oral mucositis	Timing of outcome assessment: At baseline, weekly basis during and up to 4 weeks following completion of radiotherapy. The final assessment fell on week 8 post-radiotherapy. The questionnaire was assessed at the following time points: pre-radiotherapy, week 4 during radiotherapy, week 4 and 8 post-completion of radiotherapy	The duration of severe oral mucositis did not differ between the intervention and control arms: 16.8±17.5 versus 17.5±21.9 days, respectively (P=0.692)	Weaknesses: High incompliance, no blinding
	Patients were stratified by radiotherapy technique (unilateral versus bilateral) and type of therapy (chemo-radiotherapy versus radiotherapy only)		3. Incidence and duration of severe pharyngeal mucositis	Statistical analysis: Chi-square test; Mann-Whitney U test was used to compare the duration of severity between the intervention and control groups; for QoL, changes from baseline measurements (%) at each time point were plotted and the differences between the two arms were visually inspected with 95% CI	No significant differences or benefit was observed for other secondary endpoints (P>0.05) in comparison to standard oral care	Modifications to the interventions: None reported
	In intervention group, patients started using Caphosol from the 1st week of radiotherapy. Caphosol was used as a mouthwash 4 times a day but the frequency could be increased up to 10 times a day at the physician's or patient's discretion		4. Incidence and duration of severe dysphagia		Overall, the study found Caphosol did not reduce the incidence or duration of severe oral mucositis during and after radiotherapy in head and neck cancer	Adverse effects: Treatment-induced nausea (mild)

Table 3 (*continued*)

Table 3 (*continued*)

Author/year	Intervention descriptions	Stakeholder involvement	Outcome measure(s)	Assessment and analysis	Findings	Notes
	Patients used Caphosol for a total duration of 7 weeks; 6 weeks during radiotherapy and 1 week after completion		5. Incidence and duration of severe radiation-induced pain			Bias: Intervention/Performance bias: Compliance with the recommended frequency of Caphosol was low (~20%) due to a subgroup of patients who either found it intolerable due to taste (partly precipitated by altered taste sensation secondary to intervention), nausea or perceived lack of benefit—HIGH RISK
	Depending on the symptoms, patients had access to other symptom control measures available in the control arm. If patients did not tolerate Caphosol, it could be stopped immediately and the reasons for discontinuation were recorded					Detection bias: No blinding of the physicians assessing the patients, this may have influenced the way patients completed their QoL questionnaires—HIGH RISK
	Mechanism of action of Caphosol: Caphosol is an aqueous solution of concentrated calcium phosphate, which is licensed for use in conditions resulting in dryness of the mouth and throat. As its composition is similar to natural saliva, it is postulated that it could help to maintain healthy oral mucous membranes during intervention by modulating the inflammatory process and promoting tissue repair					Selection or allocation bias: A higher number of patients underwent induction chemotherapy prior to radiotherapy in the control arm (46.7% versus 36.1%), also while patients were stratified by radiotherapy technique and type of therapy, they were not further stratified by primary site of disease—HIGH RISK
	In control group, patients received standard intervention for oral mucositis that included normal saline mouthwash at least 4 times a day, aspirin mouthwash 3 times a day and tooth brushing with fluoride toothpastes prescribed by a dental hygienist					Attrition bias: Reason was provided “5 patients were excluded due to either ineligible or withdrew at the start”—LOW RISK and “unlikely to have impacted on ou tcomes”, p.209

RTOG, Radiation Therapy Oncology Group; VAS, visual analog scale; RCT, randomised controlled trial; NRS, non-randomised study; TDS, times daily; PID, pain intensity difference, PID = the change in the Likert pain scale from baseline to 6 h after administration; QoL, quality of life; WSS, whole stimulated saliva.

outcomes assessed for the participants in the NRS were: severity of oral mucositis, subjective oral dryness, salivary analysis (whole resting saliva volume, whole stimulated saliva volume, amylase, pH, and sodium potassium ratio), subjective pain scores at rest and swallowing, sleep quality, and food intake.

In terms of timing, the majority of studies reported outcomes at many time points that were within the same time frame: short or medium term. We chose the longest time points for each study that were consistent across time periods.

Meanwhile, we analyzed the risk of bias in the included studies using established risk of bias criteria for RCTs and NRCTs (Higgins *et al.*, 2017). Three of the seven RCTs and NRCTs assessed had an overall high risk of bias (14,15,17), one had a low risk of bias (16), and the remaining three had an unclear risk of bias overall (14,15,17).

Interventional effects

Overall, six trials found support for the intervention (12,13,16-19), with effect sizes ranging from 13.2% to 10,110.0%. *Table 4* shows the results of four studies that found significant differences in oral conditions and disorders at the conclusion of their interventions (12,13,17,18), with magnitudes of effect ranging from 50.0% to 10,110.0%. Although two of the trials did not provide statistically significant differences in outcomes (15,16), the studies did demonstrate an improvement in oral conditions in the intervention groups. Only one study found no change or reduction in oral health in the groups that received interventions (14).

Honey (Ziziphus honey) versus 0.9% saline comparison

Amanat *et al.* demonstrated a substantial decrease in oral mucositis in the treatment group against the control group (12). At the end of the sixth week, the difference between Grades three and four was statistically significant between the control and treatment groups (P=0.016 for Grade three mucositis and P=0.032 for Grade four mucositis, respectively). In general, honey had a favorable effect on the severity of Radiation Therapy Oncology Group (RTOG) Grade three and four cancers. Additionally, the study stated that it is really encouraging to observe that patients with head and neck cancer who suffer from severe mucositis as a result of radiotherapy might have their symptoms significantly reduced simply by choosing this realistic and affordable choice.

Comparing synthetic saliva (Saliva Orthana™) to chewing gum (Freedent™)

Davies (15) observed that there was no statistically significant difference between the findings obtained with fake saliva and chewing gum (unpaired *t*-test: P=0.95 for the first phase; P=0.34 for the second phase). Additionally, data analysis indicated no evidence of a period or carry-over effect (unpaired *t*-test: P=0.10). Despite the fact that none of the findings attained statistical significance, cancer patients believe that chewing gum is an acceptable treatment. 69.0% of patients preferred chewing gum over artificial saliva due to its effectiveness, while both Saliva Orthana™ and Freedent™ may produce negative effects (e.g., nausea and irritation of the mouth in two and three patients respectively). Overall, chewing gum outperformed artificial saliva on all efficacy measures; thus, chewing gum may be beneficial in the management of xerostomia in patients with advanced cancer.

Comparative analysis of CAM2028-benzydamine and CAM2028-control

According to Hadjieva *et al.* (16), both treatments resulted in a mean 40% reduction in pain intensity at 6 hours (the primary trial end point), i.e., from 6.5 (CAM2028-benzydamine) or 6.4 (CAM2028-control) to 4.6. Additionally, both therapies produced significant pain alleviation after 5 minutes of application, which lasted throughout the 8-hour assessment period. The mean area under the curve (AUC) of the PID across time, on the other hand, did not differ between the two treatments, indicating no change in pain reduction among the two interventions at any point of time. Additionally, the two therapies did not differ in terms of any other measure of pain. This suggests that pain reduction was comparable between the two CAM2028 treatments, implying that benzydamine had no additional effect on pain reduction in oral mucositis when compared to the CAM2028-control. Both CAM2028-benzydamine and CAM2028-control were effective in lowering pain in patients with oral mucositis secondary to head and neck cancer radiation therapy, and their analgesic effects were immediate, clinically significant, and lasted up to 8 hours.

Morphine mouthwash versus 'magic' solution

Sarvizadeh *et al.* (13) demonstrated a reduction in the

Table 4 Results of the interventions for clinical outcomes in oral health and its relative impact of intervention (%)

Author(s), year	Index	Control group	Intervention group	P	Relative impact of intervention (%)
Amanat *et al.* [2017]	RTOG—Grade 3 mucositis	I: Zero	I: Zero	0.016	–50.0
		F: 4	F: 2		
	RTOG—Grade 4 mucositis	I: Zero	I: Zero	0.032	–100.0
		F: 3	I: 0		
Davies [2000]	Mean change in VAS score	I: NI	I: NI	0.49	34.4
		F: 22.4	F: 30.1		
Hadjieva *et al.* [2014]	Pain intensity	I: Average 6.4 (SD =0.72)	I: Average 6.5 (SD =0.80)	NI	–13.2
		F: Average 4.4 (SD =2.09)	F: Average 4.2 (SD =2.03)		
Sarvizadeh *et al.* [2015]	Mucositis severity value	I: 3.5	I: 3.5	0.045	–72.1
		F: Average 2.46 (SD =1.26)	F: Average 1.71 (SD =0.60)		
Kavitha *et al.* [2017]	Whole resting saliva volume	I: Average 0.10 (SD =0.02)	I: Average 0.10 (SD =0.02)	<0.001	1,200.0
		F: Average 0.11 (SD =0.02)	F: Average 0.23 (SD =0.03)		
	Whole stimulated saliva volume	I: Average 0.54 (SD =0.05)	I: Average 0.54 (SD =0.06)	<0.001	10,110.0
		F: Average 0.55 (SD =0.05)	F: Average 1.56 (SD =0.25)		
Shillingburg *et al.* [2017]	Pain scores (at rest)	I: –	I: Median 6	0.0003	–50.0
		F: –	F: Median 3		
	Pain scores (when swallowing)	I: –	I: Median 9	0.0001	–55.6
		F: –	F: Median 4		
Wong *et al.* [2017]	Incidence of severe oral mucositis	I: NI	I: NI	0.839	–1.99
		F: 65.4%	F: 64.1%		
	Duration of severe oral mucositis	I: NI	I: NI	0.692	–4.0
		F: Average 17.5 (SD =21.9)	F: Average 16.8 (SD =17.5)		

RTOG, Radiation Therapy Oncology Group; VAS, visual analog scale; I, initial assessment; F, final assessment; NI, not informed.

severity of mucositis in both the groups [morphine (P<0.001) and magic (P=0.049)]. However, on the sixth day, the morphine group had a greater reduction in mucositis severity than the magic group (P=0.045). Additionally, while the two groups maintained equal pharmacological effects, the morphine group patients were more satisfied with treatments (P=0.008). Thus, the study concluded that topical morphine is more effective and more acceptable to patients in lowering the severity of cancer treatment-induced oral mucositis than magic mouthwash.

Bethanechol tablets versus placebo capsules

Kavitha *et al.* (17) observed that at the conclusion of the third week, 24 (80%) patients in the Bethanechol group and just two (10%) individuals in the control group

demonstrated subjective improvement in mouth dryness. Between the two groups, a significant difference in total resting (P<0.001) and stimulated saliva volume (P<0.001), pH (P<0.001), and amylase (P<0.001) was observed. After three weeks of Bethanechol medication, there was no significant statistical difference in sodium potassium ratio and no significant untoward effects. Overall, the study found that 25 mg Bethanechol (TDS) significantly improved subjective oral dryness in 24 (80%) patients, in addition to entire resting and WSS volumes, pH, and salivary amylase, with no adverse effects.

Caphosol in combination with standard oral care versus standard oral care alone

Wong *et al.* (14) found no statistical difference in the incidence of severe oral mucositis among the intervention (64.1%) and control (65.4%) groups (P=0.839). Similarly, there was no difference in the duration of severe oral mucositis between both the groups (intervention and control groups: 16.8–17.5 versus 17.5–21.9 days) (P=0.692). Additionally, no significant differences or benefits were identified in contrast to normal oral care for additional secondary endpoints (e.g., severe pharyngeal mucositis, severe dysphagia, severe radiation-induced discomfort, or QoL). Caphosol did not significantly decrease the incidence or length of severe oral mucositis occurrence during or following radiotherapy for head and neck cancer, the study concluded.

The effect of oral ketamine mouthwash on the pain associated with severe mucositis

Shillingburg *et al.* (18) showed a two- and three-point reduction in pain scores after one hour and three days, respectively (P=0.0001, P=0.0003). Additionally, it was revealed that pain scores improved dramatically during swallowing, decreasing by one and four points after one hour and three days, respectively (P=0.0006, P=0.0001). Additionally, following the first night, patients had a better-quality of sleep dramatically increased from a median rating of five to six (P=0.006) and subsequently remained stable through day three (P=0.034). Additionally, the majority of patients indicated that the commencement of effect occurred within 15 minutes after the dose and lasted for one to three hours. The solution was well tolerated, and some patients stated that it was superior to lidocaine-based solutions owing to the lack of irritation and burning sensation. Overall, the study concluded that ketamine mouthwashes helped in lowering the pain scores for stomatodynia and odynophagia, improved sleep quality, and decreased oral lidocaine application in severe oral mucositis patients. Additionally, it has a favorable safety profile (i.e., no adverse effects) and may be used as an additional treatment in the multimodal care of severe mucositis associated with chemotherapy.

Adverse effects of interventional procedures

Studies that tested Ziziphus honey (12) and ketamine mouthwash (18) reported no recorded harmful effects associated with its use. Other studies had reported adverse effects such as mild oral burning/itching during oral rinse (with morphine mouthwash) (13), frequent urination (with bethanechol tablets) (17), nausea (with Saliva Orthana™ (15), CAM2028-Benzydamine (16), and caphosol plus standard oral care) (14), vomiting (with CAM2028-Benzydamine) , mouth irritation (with Saliva Orthana™), sweating (with bethanechol tablets), and (with CAM2028-Benzydamine).

Discussion

This is the only review that we are aware of that has conducted a systematic and complete analysis of published intervention studies on oral problems in palliative patients. Our review included six comparisons of various types of oral therapies (14-17) and one research of an individual intervention (18) in palliative care. Although practically all interventions improved oral conditions (n=6), only four studies out of seven revealed meaningful improvements at the conclusion of their interventions. Among these four investigations, one was deemed to have exceptional methodological quality (13), another to have fair methodological quality (12), and the remaining two to have decent methodological quality (17,18).

The majority of studies were rated as having a good or moderate quality. The only factors that contributed to this classification were the following: the design type; an insufficient description of the validity of the outcomes; a lack of sample calculations and analytic concerns. For example, some studies have relied on subjective assessment using self-reported questionnaires, which have poor validity and can result in significantly different conclusions from patient to patient (17,18). This, however, can result in unreliable data. The outcome of clinical interventions are measured usually by clinical assessment of the patients for its

benefits although it is highly influenced by subjective nature of the patient unless suing biomarkers for confirmation of the efficacy of clinical trials (19). Despite the subjective character of the assessments, we deemed those researches to be valuable contributions to the review; the outcomes were scored according to the quality of assessment.

In terms of intervention effectiveness, it can be shown that estimates of the amount of effects differed significantly across all trials, ranging from 4.0% to 10,110.0%. They are, however, extremely difficult to compare, as the most effective type of intervention remains unknown, as interventions, patients, research methodologies, and study outcomes vary significantly among studies. Future reviews should concentrate on people with certain forms of cancer or oral diseases. This would significantly add to the body of knowledge in the field of oral palliative care. Not only that, a simple proportional and average comparison of groups does not guarantee the relevance of the data stated in the studies. It was discovered that the studies lacked an assessment of the therapies' rates of change and relative effects on the outcomes. The relative effects of the interventions, as determined by us, are just estimations of the degree of the effect in percentage terms. The right calculation of relative risk must always take into account the rates of change in the groups, which vary according to the number of persons who began and completed the study, as well as the time period of follow-up (7). We propose that future research may incorporate these computations into their analysis of their findings, resulting in more accurate estimations of the interventions' impact. Notably, the methodological features of the studies (sample size and duration of follow-up) are also critical in determining whether the studies had a greater positive effect on clinical outcomes. Certain methodological difficulties, such as insufficient sample size and a follow-up period of less than twelve months, could have contributed to the lack of outcome (10).

Although direct comparisons between the included studies are difficult due to the wide range of intervention types, methods, measures, and analyses used, this review provides information on the interventions available to treat oral conditions in palliative patients and their relative effectiveness, which can assist non-dentist palliative care physicians and dental professionals. We discovered that using honey, morphine mouthwash, Bethanechol pills, and ketamine mouthwash significantly improved the patients' oral problems. Given that several studies reported adverse events, more pharmacological drug trials are recommended to determine if it is likely to extend drug effect maintenance despite the fact that overall dosage is decreased, therefore avoiding potential side effects.

This systematic review does have a number of limitations. Among the review's shortcomings are the absence of all available databases and difficulties of conducting statistical synthesis via meta-analysis due to the methodological variability and diverse target populations of existing managements. Additionally, because some studies had a short follow-up period, consideration should be given to following patients for a longer duration in order to determine the long-term advantages or risks of such therapy, as well as to determine whether any short- or medium-term benefits are sustained. For example, ketamine has been known to cause laryngospasm on occasion, which can be challenging in a patient with mucositis, but no such cases arose throughout the trial (18). This could be because the trial was conducted over a brief period of time, preventing them from detecting the intervention's harmful effect. Additionally, as previously stated, the review was limited by the small sample size of the included studies; future studies should consider a larger sample size and a longer follow-up period to ensure appropriate randomization, for detecting marginal differences between the groups, and to identify factors related with improved response to the interventions studied. Despite these shortcomings, this study possesses a number of strengths. The review's strengths include the systematic selection and evaluation of peer-reviewed articles, as well as the incorporation of a standardized approach for interventional studies' methodology quality assessment.

Conclusions

This systematic review of oral hygiene interventions for palliative patients enables us to draw conclusions about their effectiveness, which can inform both non-dentist palliative care physicians and dental professionals about the most effective strategies for managing oral conditions in palliative patients. In general, the majority of studies examining clinical outcomes associated with oral palliative care have indicated substantial effectiveness in favor of interventions, however only four of the seven papers revealed a statistically significant difference.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-215/coif). The authors have no conflicts of interest to declare.

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