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REVIEW

Efficacy of bioadhesives in the management of oral mucositis in patients undergoing radio-chemotherapy for treatment of head and neck cancer—a systematic review and meta-analysis

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Abstract

Background Management of head and neck cancers requires a multidisciplinary approach where surgery followed by radio and chemotherapy is the mainstay of treatment. The above-mentioned treatment can cause mucositis, a severely debilitating side effect. This can have a significant impact on quality of life. A recent advancing mode of drug delivery is the bioadhesive system. This interacts with mucosa by adhering to it and thereby improving the efficacy of the therapeutic agent delivered.

Aim and objective The purpose of this systematic review is to evaluate the effectiveness of bioadhesives in reducing oral mucositis and relieving pain associated with mucositis in head and neck cancer patients receiving radio-chemotherapy.

Materials and method Studies assessing the effectiveness of bioadhesives for the treatment of radiation-induced oral mucositis were retrieved from specialized databases (PubMed/MEDLINE, Scopus, ProQuest, Google Scholar, LILACS, OpenGrey) as well as institutional repositories. Data on incidence, pain reduction, resolution, and improvement of oral mucositis using bioadhesive were compiled. A Cochrane tool was used for randomized controlled trials and a JBI tool for non-randomized controlled trials and observational studies to assess the quality of included studies. Based on the eligible study data, a meta-analysis was conducted with STATA version 16, 2019 software, and 95% confidence intervals and p values greater than 0.05.

Results A total of 15 studies were included which assessed the effectiveness of bioadhesives in managing mucositis and its associated pain. Studies included in the review described either reduction, resolution, or incidence of oral mucositis respectively. A total of three meta-analyses were conducted to assess the incidence of oral mucositis and the pain associated with it, as well as the reduction in incidence. Bioadhesives showed statistically significant differences in the incidence of severe mucositis ($p = 0.04$). A meta-analysis comparing bioadhesives efficacy in reducing mucositis and pain associated with it found no statistically significant differences ($p = 0.36$).

Conclusion Bioadhesives are emerging as a novel drug delivery method for treating radio-chemotherapy-induced oral mucositis because of their rapid absorption and easy application. Regardless of its benefits, clinical trials comparing it with conventional treatment methods are necessary to assess its efficacy in treating oral mucositis.

Keywords Stomatitis · Head and neck neoplasms · Radiotherapy · Chemotherapy · Adhesives (MeSH) bioadhesives

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Introduction

Head and neck cancers (HNC) are the sixth most common cancer, with more than 800,000 diagnosed cases 2016 [1]. More than 90% of malignant tumors arise from the mucosal epithelium in the oral region known as squamous cell carcinomas (OSCC) while others include salivary minor glands, melanomas, and lymphomas. The development of oral cancer is primarily associated with smoking tobacco including smokeless tobacco and heavy alcohol consumption [2]. HNC has a 5-year survival rate of less than 50% after diagnosis, making it a disfiguring disease with a poor prognosis [3].

Locally advanced HNC often requires radiotherapy and concurrent systemic treatment (platinum-based chemotherapy) or surgery followed by radiotherapy with or without systemic therapy [4]. The cytotoxic effects of these therapies are not only limited to tumor cells but also act on normal tissues with high cell turnover [5]. The following adverse events have an impact on a patient's quality of life: oral mucositis (OM), hyposalivation, loss of taste, dental caries, osteoradionecrosis, and trismus.

Ninety percent of HNC patients receiving standard radiotherapy and chemoradiotherapy will develop oropharyngeal mucositis [6]. Lesions occur commonly in non-keratinized oral mucosa, such as lip and buccal mucosa, lateral and anterior mucosa of the tongue, the floor of the mouth, and the soft palate [7]. Radiation therapy-induced OM depends on the dose administered, the fraction of the dose administered, the volume of the tissue treated, and the type of radiation used. Infections like HIV, collagen vascular disease, alcohol-based mouth rinses, and smoking habits can all contribute to the development of OM [8–10].

After radiation therapy, radio-induced OM typically lasts between 2 and 6 weeks [11, 12]. Radiation doses of 10 Gy cause hyperkeratinized lesions, and doses of 20 Gy cause erythema as an early sign of OM. A dose equal to or greater than 30 Gy leads to pseudomembrane-covered ulcers susceptible to super-infection due to bacterial colonization [11, 12]. Chemotherapy-induced OM is typically more aggressive than radiotherapy-induced OM. Erythema appears 5–8 days after treatment, followed by edema and ulceration 2 days later [11]. The symptoms of OM from both radiotherapy and chemotherapy can decrease the quality of life (QOL) of patients with HNC. OM can lead to great discomfort, pain, inability to eat, and secondary infections.

According to the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO), the treatment for oral mucositis consists primarily of pain control, nutritional support, oral decontamination, palliation of dry mouth, and therapeutic interventions [13]. It has become paramount in clinical practices to design therapeutic interventions aimed at reducing the intensity or preventing OM. These interventions include a variety of agents such as cryotherapy [14], growth factors [15], anti-inflammatory agents [16], antioxidants [17], and photobiomodulation (low-level laser therapy) [18]. Although many treatment options exist to prevent and treat mucositis, there is no gold-standard protocol [19].

Oral mucoadhesive drug delivery is a promising alternative to conventional systems as it acts by the efficiency and residence time of the active compound at the absorption site through interaction with mucous layers. Oral mucoadhesive systems provide higher bioavailability and are ideal for preventing first-pass metabolism, allowing for direct and painless administration, and limiting undesirable systemic effects. There are various forms of these drugs available, such as tablets, semisolids, which are usually dissolved in aqueous or non-aqueous solutions, and liquids that can be applied orally throughout the buccal cavity [20].

This systematic review evaluated the efficacy of bioadhesives in reducing OM and relieving pain associated with oral mucositis in patients undergoing treatment for HNC. This systematic review will address the following questions.

1. Can bioadhesives aid with pain relief in patients with OM caused by radio/chemotherapy for HNC?
2. Do bioadhesives prevent/protect patients who are undergoing HNC therapy from developing OM?

Methodology

Eligibility criteria

By establishing inclusion and exclusion criteria, the population, intervention, comparison, outcome, and study design (PICOS) strategy was used to define the eligibility criteria as described in Table 1. Studies, where interventional

Table 1 PICOS criteria for inclusion and exclusion of studies with a description of each

PICOS	*Inclusion criteria*	*Exclusion criteria*
Population	Clinicopathologically confirmed case of HNC patients treated by chemo-radiotherapy and those with oral mucositis above 18 years of age are included	Oral mucositis in patients with neoplasms other than head and neck cancer of belonging to below 18 years of age
Intervention	Bioadhesives in the form of wafers, tablets, pastes, etc.	Conventional gels, tablets, and mouthwashes
Comparison	Standard treatment measures such as mouthwashes, analgesics, or matched placebo	–
Outcomes	Primary outcome: reduction of OM and pain associated with it; incidence of OM; resolution of OM Secondary outcome: adverse effects	–
Study design	Interventional studies with or without control that are either randomized or non-randomized and observational studies	Case-control studies, cohort studies, case reports, letters to the editors, comments, and review articles

trials were conducted with or without controls, either non-randomized or randomized, observational studies, and publications pertaining to the above-mentioned study design in scientific journals and gray literature that describe the patients undergoing chemotherapy and radiotherapy for HNC with OM treated with a bioadhesive.

Information sources

An extensive search was conducted in the following databases and repositories for articles relevant to the title and research question until 31st July 2022. Search engines such as PubMed/Medline, Google Scholar, ProQuest, Scopus, OpenGrey, Tamil Nadu Dr. MGR Medical University repository, Rajiv Gandhi University of Health Sciences repository, and KLE Academy of Higher Education and Research repository were sought. A literature search was performed on the topic by two independent researchers, JP and VK, with studies restricted to the English language. Literature saturation was also ensured by searching reference lists of included studies.

Search strategy

A combination of Boolean operators "AND" and "OR" specific to databases is used to match the medical subject headings (MeSH) and text words related to head and neck cancer, radiotherapy, chemotherapy, and oral mucositis with bioadhesives as separate search term. According to respective databases, the following filters were applied: PubMed–Human; Scopus–Full text; LILACS–All text; ProQuest–Full text and peer-reviewed/dissertations and thesis + scholarly articles + English language.

Selection process

The included studies were assessed by two observers, JP and VK, to determine whether they met the eligibility criteria. The full-text articles were read thoroughly, and any disputes were resolved by a third reviewer, VJ. In order to remove duplicates and manage references and bibliographies, Mendeley desktop application version 1.19.8 was used.

Data collection process and data items

The review team developed standardized data extraction sheet in Microsoft Excel (2007) format that were used independently by JP and VK to collect data from each study. Data items like author name, year of publication, sample size, age group, study design, control group, interventional group, reduction of mucositis and mucositis pain assessed using various grades or scales, the incidence of mucositis, resolution of mucositis, and adverse effects reported were recorded.

Study risk of bias assessment

Risk of bias assessment for included studies was done by JP and VJ. The Cochrane Handbook of Randomized Controlled Trials Tool was used in the RevMan application for studies using randomized controlled trials [21]. The Joanna Briggs Institute (JBI) critical appraisal checklist developed by the Faculty of Health Sciences at the University of Adelaide was used to assess bias in non-randomized controlled trials [22] and observational studies [23]. To resolve any disagreement, a third reviewer (VK) was consulted.

Effect measures

The standardized mean difference (SMD) of reduction in oral mucositis and pain associated with it was utilized as the main effect measure. This meta-analysis included the studies which provided mean and standard deviation values for weekly or overall reduction between control and treatment groups. According to data provided regarding the incidence of mucositis in both control and treatment groups, the relative risk (RR) was calculated. Meta-analysis for incidence of non-severe oral mucositis (WHO grades 0, 1, 2 and RTOG/EORTC grades 1, 2) and severe oral mucositis (WHO grades 3, 4 and RTOG/EORTC grades 3, 4) was carried out. The other relevant data were described and used for narrative synthesis.

Synthesis methods

The meta-analysis was conducted with STATA (Software for statistics and data science by StataCorp LLC, Texas, USA version 16, 2019) provided that at least 2 studies fell under the particular analysis category.

I-squared (I^2) statistics were utilized to assess heterogeneity between the included studies with a 95% confidence interval (95% CI). In the meta-analysis, the incidence of mucositis, reduction of mucositis, and pain associated with mucositis were compared between the intervention (bioadhesives) and control group. Studies' consistency can be affected by variations in participants, outcomes, interventions, or evaluation methods of interventions, resulting in heterogeneity. Therefore, a fixed-effect model that represents a typical intervention effect or a random-effect model that presents the average intervention effect will be used in the meta-analysis.

Reporting bias assessment

A funnel plot analysis was used to assess publication bias. The substantial bias in meta-analysis is assessed by analyzing how the studies are distributed either symmetrical or asymmetrical within the inverted funnel, where they are expected to lie without heterogeneity and reporting biases.

Certainty assessment

To determine whether the true effect is within a particular range or relative to the threshold, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used. Using the GRADE [24] approach, we assessed the certainty of the evidence, formulated recommendations, and checked the applicability in evidence-based medicine.

Results

The search strategy yielded 97,842 results from 7 databases and 2 university repositories. A total of 49 articles were selected after screening all the titles, excluding those that had other study designs, titles unrelated to the present review, articles with inappropriate outcome measures, articles that were published in other categories (case report, case series, etc.), and articles not written in English. It was found that 24 articles were non-retrievable. After removing the duplicates, the total was reduced to 25 articles. The abstracts of 25 articles were read, of which 7 articles were excluded (2 animal studies that examined mucoadhesiveness and drug release properties in mice; one study used frozen pig buccal mucosa; two in vitro studies were conducted—one using various incubation mixtures to evaluate bioadhesiveness of chitosan and melatonin and another using rheometers, tension tests, and saliva samples of an admixture paste to evaluate viscosity, adhesiveness, and elution; 2 studies were review articles), resulting in 18 articles. A full-text screening of 18 articles excluded 3 articles related to other neoplasms including HNC. Based on the results of this systematic review, 15 articles met the eligibility criteria, and 8 studies were included in the meta-analysis (Fig. 1).

Study characteristics

Based on the search strategy, 15 eligible articles were included in this review (Table 2); 9 [25–33] were histopathologically confirmed cases of HNC, including oral squamous cell carcinoma, malignant lymphoma, and nasopharyngeal carcinoma.

A total of 11 studies [25, 29, 30, 32–39] mentioned the site of HNC as the tongue, buccal mucosa, oropharynx, nasopharynx, hypopharynx, and salivary gland, whereas 4 studies [26–28, 31] did not mention the site of the tumor. Based on the number of subjects included by site, 172 cases of oral cancer have been reported, 47 have been reported as tongue cancer, 38 have been reported as laryngeal carcinoma, 127 have been reported as oropharyngeal carcinoma, 20 hypopharyngeal carcinomas, and 38 have been reported as carcinoma of the nasopharynx.

In total, 763 patients participated in this study, including 302 in the control group and 461 in the intervention group. In these included studies, the age group of patients was in the range of 18–59 years where 487 were males and 189 were females. Based on the geographic location of the studies, 3 each were carried out in Japanese [32, 38, 39] population; 2 studies each were conducted in Iranian [27, 28] and Spanish [26, 29] populations; 1 study each in Chinese [33], Indian [30], Italian [34], Bulgarian [37], Brazilian [31], American [25], and British [35] population and a multicentric study [36] involving French, German, Spanish, and American population.

As part of the intervention group, bioadhesive barriers were provided as gel [25, 26, 29, 31, 34, 35], spray [33], adhesive film [27, 28, 32], tablet [36], mouthwash [25, 35, 38], and wafer [30]. As interventions, Episil® [33, 38, 39], Mucotrol™ [30], Tetracaine [33], MuGard [25], Melatonin [29], Clonidine [36], Propolis [31], Gelclair [35], Chlorhexidine [26], Triamcinolone acetonide [27, 28], MF-5232 [30], and CAM2028-Benzydamine [37] were used.

The site of the irradiation was mentioned in a single study [38]. There is a direct correlation between radiation doses and their duration in the development of OM. All the studies included the conventional or hyperfractionization method. A range of doses was given five times per week including 1.2 to 1.5 Gy [34], 1.8 Gy [31], 1.8 to 2.2 Gy [36], 2 Gy [27, 28, 32, 38], and 2 to 2.2 Gy [25, 29].

In order to deliver radiation to the tissues, a variety of radiation delivery techniques were employed. 3DCRT (three-dimensional conformal radiation therapy) was utilized in 3 studies [36, 38, 39]; IMRT (intensity-modulated radiation therapy) was utilized in 3 studies [36, 38, 39]; two-dimensional cobalt-based therapy was utilized in 2 studies [27, 28]; Brachytherapy was utilized in 1 study [32]; VMAT-SIB (Volumetric Modulated Arc Therapy-Simultaneous Integrated Boost) was utilized in 2 studies [29, 33]; External beam photon therapy was utilized in 3 studies [25, 30, 33]; conventional fractional therapy was utilized in 2 studies [26, 34].

In addition to radiotherapy, various chemotherapeutic agents were utilized in 11 studies [25–27, 29, 30, 32–34, 36, 38, 39]. Cisplatin was administered at 30 mg/m^2 [33, 34, 36, 38, 39], 50 mg/m^2 [30], and 100 mg/m^2 [26, 29]. Tegafur-gimeracil-oteracil-potassium was administered at 80 mg/m^2 [33, 38]. Cetuximab was administered at 400 mg/m^2/w and 250 mg/m^2/w [29, 38]. Peplomycin 5 mg was administered intravenously [32]. UFT was administered

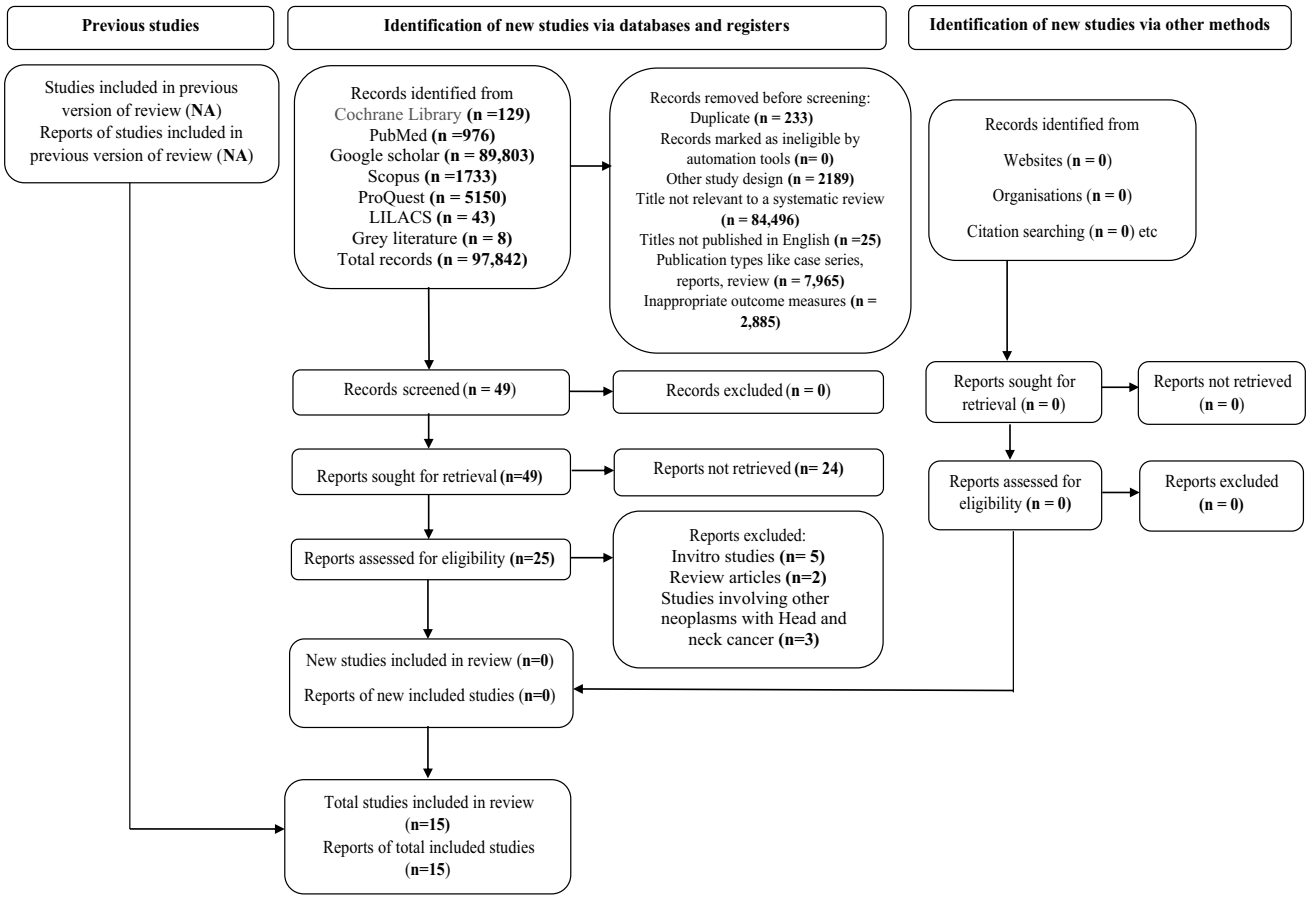

Fig. 1 PRISMA flowchart depicting study selection

at 200 mg/day [33]; 5-fluorouracil [34] and carboplatin [34, 39] were also administered. The primary outcomes were the reduction in pain associated with OM and the incidence or reduction of OM.

The safety of the interventions provided was evaluated based on their potential to cause local or systemic adverse effects in the studies that were included. In two studies, there were no adverse effects [32, 34]. Several local adverse effects have been reported, such as xerostomia [29, 33, 36], burning sensation [34, 40], mild inflammation, and stinging in the mouth [35].

There were several systemic adverse effects associated with the therapy, including nausea [25, 29, 33, 36, 37, 39], vomiting [25, 29, 33, 36, 37], dysphagia [36], diarrhea [25, 29, 36], constipation [25, 29, 36]; blood-related disorders such as neutropenia [25, 29, 33, 36], leukopenia [36], thrombocytopenia [33], and anemia [29]; metabolic disorders such as dehydration [38] and weight loss [36]; and infectious complications, such as oral candidiasis [36], fungal infection [36], and other infections [26, 36].

According to various studies, compliance with bioadhesives is measured in terms of tolerability and factors contributing to discontinuation. Several studies stated that the application of the product was difficult [31, 34, 38]; there were also reports of dysgeusia [34, 38] and a dislike of the smell [38] product. Lack of compliance and patient decision resulted in discontinuing the treatment [29]. Some studies did not measure patients' compliance with the treatment provided [26–28, 30, 33, 35, 39].

Risk of bias in studies

JP and VJ independently assessed the quality of included studies. In case of disagreement, VK acted as a moderator whenever there was a disagreement.

Quality assessment of randomized controlled trials

A total of 15 studies were included, of which 10 were randomized controlled trials [25–30, 35–37, 39]. In order to perform Cochrane's tool for randomized controlled trials, RevMan software was used (version 5.4.1). It consists of the following domains.

Table 2 Study characteristics of included studies

S. no.	Author	Study design	Sample size			Control	Intervention	Oral mucositis assessment	Pain assessment	Primary outcome measures	Secondary outcome measures	Results
			Male	Female	Total							
Studies that assessed the incidence of oral mucositis												
1	Allison et al., 2014 [25]	Randomized double-blinded, placebo-controlled trial	66	12	78	Sham-control (SC) consisted of flavored saline bicarbonate rinse	Mucoadhesive hydrogel (MuGard)	WHO		OM resolution, mouth and throat soreness (MTS) at week 4 and end of RT	Delay to the onset of Oral Mucositis Daily Questionnaire (OMDQ), adverse effect, opioid use	Ulcerative and severe mucositis were noted in 63% and 44% of the control group compared to 43% and 27% in the intervention group, respectively.
2	Giralt et al., 2020 [36]	Randomized placebo-controlled II trial	138	45	183	Placebo	Mucoadhesive Clonidine 50 µg, 100 µg tablet	WHO		Incidence of severe oral mucositis (SOM) assessment up to 6 weeks	Duration and time to onset of SOM	SOM was noted in 45% vs. 60% of the intervention group compared to placebo. Non-severe mucositis was noted in 55% vs. 40% of the intervention group to placebo.
3	Noronha et al., 2014 [31]	Interventional phase II trial (post only design)	19	5	24	–	Mucoadhesive propolis gel	WHO	–	Oral mucositis prevention	Evaluation of candidiasis and product acceptability	Incidence of mucositis was not seen in 20 patients (83.33%) with 2 patients each developed grade 1 (8.33%) and grade 2 (8.33%) mucositis.
4	Lozano et al., 2021 [29]	Randomized double-blinded, placebo-controlled trial	19	5	24	Placebo	3% melatonin gel	RTOG, NCI, and RTOG-NCI scale	–	Incidence and duration of ulcerative and severe oral mucositis	Safety and adverse effects	SOM incidence was lower in the intervention group compared to the control group (53 vs. 64%; $p = 0.36$). UOM was not significantly reduced among both the groups (88 vs. 92%; $p = 0.71$).

Table 2 (continued)

S. no.	Author	Study design	Sample size			Control	Intervention	Oral mucositis assessment	Pain assessment	Primary outcome measures	Secondary outcome measures	Results
			Male	Female	Total							
Studies that assessed reduction of oral mucositis												
5	Naidu et al., 2005 [30]	Randomized double-blinded, parallel-controlled trial	16	14	30	Placebo	MF 5232 (Mucotrol™)	WHO, RTOG, and objective scoring system	–	Reduction in mucositis	Patient compliance and adverse effects	Significant reduction in mean WHO and RTOG grading scores in both the groups ($p = 0.007$; $p = 0.031$).
Studies that assessed resolution of oral mucositis												
6	Kabasawa et al., 2022 [38]	Non-randomized clinical trial	–	–	65	Mouthwash containing sodium gualenate hydrate, sodium bicarbonate, and 0.2% lidocaine	Episil®	CTCAE	–	–	–	Median days for resolution of OM was 47 days. Other outcome measured was pain relieving effect within 6 hours noted in 16 out of 26 patients in the intervention group.
Studies that assessed pain reduction in oral mucositis												
7	Barber et al., 2007 [35]	Randomized controlled trial	11	9	20	Sucralfate and mucaine	Gelclair	NCI	VAS	General pain and pain on speaking for 24 hours	Swallowing assessment at 1, 3, and 24 h	There was no significant difference in pain reduction between both the groups across various time intervals (p=0.236).
8	Hadjieva et al., 2014 [37]	Randomized crossover trial	32	6	38	CAM2028-control	CAM2028-benzydamine	WHO	Likert scale	Pain intensity difference baseline to 6 h after administration	Pain intensity difference at other time intervals and peak pain	Statistically there was no significant difference noted for mean pain rating and pain intensity difference at any time point among both the groups.

Table 2 (continued)

S. no.	Author	Study design	Sample size			Control	Intervention	Oral mucositis assessment	Pain assessment	Primary outcome measures	Secondary outcome measures	Results
			Male	Female	Total							
9	Sanchez et al., 2015 [26]	Randomized double-blinded clinical trial	5	2	7	Placebo	Bioadhesive Chlorhexidine gel 0.2%	WHO	VAS	Reduction of pain and mucositis	Drug tolerance	Integrity of oral mucosa and pain post intervention at 1 hour was higher in the study group with no statistically significant differences.
10	Alterio et al., 2006 [34]	Interventional phase II trial (post only design)	36	14	50	–	Tetracaine oral gel	RTOG, EORTC	Verbal scale	Degree of pain relief	Weight loss, necessity of increasing drug administration	Degree of reduction of pain was described in terms of grade ranging from 1 to 4. Pain relief was found to be 21%, 23%, 29%, and 27% for grades 1 to 4, respectively.
11	Soutome et al., 2021 [39]	Crossover randomized controlled trial	–	–	15	Dexamethasone ointment (Dexaltin®)	Episil®	–	–	Pain	Adverse events	Pain improvement ratio was 85.7% for control compared to 71.4% for the intervention group with no statistically significant differences ($p = 0.682$).
Studies that assessed both reduction of oral mucositis and pain associated with it												
12	Pakravan et al., 2019 [27]	Randomized double-blinded clinical trial	35	25	60	Standard oral care plus placebo	Standard oral care with triamcinolone acetonide mucoadhesive film	WHO	VAS	Reduction of pain and mucositis	–	Significant decrease in mean grade of mucositis and pain in both the control and intervention groups ($p<0.001$).
13	Parichehr Ghalayani et al., 2017 [28]	Randomized double-blinded clinical trial	37	23	60	Standard oral care plus licorice root	Standard oral care with triamcinolone acetonide mucoadhesive film	WHO	VAS	Reduction of pain and mucositis	–	Significant decrease in mean grade of mucositis and pain in both the control and intervention groups ($p<0.05$).

Table 2 (continued)

S. no.	Author	Study design	Sample size			Control	Intervention	Oral mucositis assessment	Pain assessment	Primary outcome measures	Secondary outcome measures	Results
			Male	Female	Total							
Studies that assessed both incidence of oral mucositis and pain associated with it												
14	Oguchi et al., 1998 [32]	Non-randomized clinical trial	31	21	52	Topical anesthetics and/or systemic analgesics (non-AD)	600 mg of hydroxy-propyl-cellulose in an adhesive film	Modified RTOG	Modified RTOG	Severity of acute radiation-induced oral mucositis	Pain relief at rest and while eating	Oral mucositis was observed in 88% vs. 92% in the intervention and control groups. Pain is also noted in 84% vs. 88% in the intervention and control groups.
15	Jinlong Wei et al., 2021 [33]	Retrospective single-center study	42	8	50	10 ml Kangfuxin oral gargle (Kangsu™)	Episil®	RTOG	Likert scale	Pain relief	Nutritional status	High-level mucositis (III, IV) was found in 20% of the treatment group compared to 48% in the control group. Also, low-level oral mucositis (I, II, III) was found in 80% of the treatment group compared to 52% of the control group.

Selection bias

All the included studies [25–30, 35–37, 39] showed adequate randomization methods resulting in a low risk of bias. Regarding allocation concealment, three types were used: sealed envelopes [26], an open-labeled method [39], and a code system [36], while allocation concealment was not clearly mentioned in 3 studies [25, 30, 35] and allocation concealment was not carried out in 4 studies [27–29, 39].

Performance bias

In 8 studies [25–30, 36, 37], both participants and personnel were blinded, whereas blinding only participants was carried out in a study [35], thereby revealing a low risk of bias in 9 out of 10 included studies. There was no blinding in the study [39], leading to a high risk of bias.

Detection bias

Except for one article where the outcome assessment was blinded [36], we judge that the outcome measurement was unlikely to be influenced by the lack of blinding of outcome assessment in 3 studies [27, 28, 37]. Six studies [25, 26, 29, 30, 35, 39] have not mentioned blinding of outcome assessment thereby indicating a high risk of bias.

Attrition bias

There was no reported risk of bias in any of the included studies because all participants completed the clinical trial [25–30, 35–37, 39].

Reporting bias

Considering all of the included studies reported every planned outcome including primary as well as secondary outcomes, the results were adjudged to be low in bias [25–30, 35–37, 39].

Other bias

There was a low risk of bias in all the included studies due to the lack of other sources of bias [25–30, 35–37, 39].

The overall risk of bias

The overall risk of bias was low for 1 study [36], unclear risk of bias for 1 study [37], and high risk of bias (because of selection bias, performance bias, and detection bias) for 8 studies [25–30, 35, 39]. Review of authors' judgments about each risk of bias item appears as percentages in Fig. 2, illustrated as a graph of risk of bias. Figure 3 presents the summary of bias judgments made by the review authors about each included study's risk of bias item.

Quality assessment of non-randomized controlled trials and observational studies

Critical appraisal tool from the Joanna Briggs Institute (JBI) was used for non-randomized controlled trials [22] and observational studies [23]. Positive responses that were under 49% were considered to have a high risk of bias and low quality; those between 50% and 69% were considered to have a moderate risk of bias and moderate quality, and those above 80% were considered to have a low risk of bias with high quality. Considering the above-mentioned criteria, three non-randomized controlled trials [32, 33, 38] and two observational studies [31, 34] are of high quality as depicted in Table 3.

Results of synthesis

It was found that 8 articles were eligible for meta-analysis. Meta-analysis was conducted using standardized mean difference for 2 studies and risk ratios for the remaining 6 studies. The random-effect method and the fixed-effect method will give identical results when there is no heterogeneity among the studies. Since there is considerable heterogeneity, a random-effect meta-analysis will award relatively more weight to smaller studies than a fixed-effect meta-analysis. This systematic review used a random-effect model, as heterogeneity was not considered. There is evidence that triamcinolone acetonide mucoadhesive films reduce OM grading more effectively than placebo in two randomized controlled trials [27, 28]. Despite the high heterogeneity and no statistically significant differences, the experimental group demonstrated a significant reduction in OM ($p = 0.36$; SMD = 0.49; 95% CI = −0.55, 1.52; $I^2 = 87\%$) as depicted in Fig. 4.

In another meta-analysis, triamcinolone acetonide mucoadhesive films were compared to a placebo for relieving pain associated with OM [27, 28]. Results indicated a favorable outcome for the experimental group as depicted in Fig. 5, yet no statistically significant difference was found between the experimental and control group ($p = 0.36$; SMD = 0.77; 95% CI = −0.87, 2.40; $I^2 = 94\%$).

Six studies were reviewed to determine whether experimental groups containing various bioadhesives had greater success in detecting severe OM compared to control groups [21, 26, 29, 32, 33, 36] which demonstrated statistically significant differences with considerable heterogeneity (p=0.04; RR=1.23; 95% CI=1.01, 1.49; I^2=57%) as shown in Fig. 6.

Reporting biases

For studies that assessed the incidence of OM, a funnel plot was generated using fixed effects, which indicated some asymmetry caused by the small study effects or by publication bias, as shown in Fig. 7.

Certainty of evidence

According to the GRADE method, when comparing bioadhesives with placebos and matched controls, the overall probability of the evidence was moderate. Based on Table 4, it shows that bioadhesives can serve as an alternative to conventional treatment methods by showing a close match with the estimated effect, which proves that bioadhesives are an effective alternative. The quality of the evidence was assessed for each study, and three studies [27, 28, 31] were found to have high certainty of evidence. Eight studies [20–25, 32, 33] were rated as moderate in the certainty of evidence because of bias, i.e., allocation concealment not mentioned [20, 22–25], detection bias [20–25], and measurement of outcome [32, 33]. A low certainty of the evidence was reported in four studies [26, 29, 30, 34] as shown in Table 5.

Fig. 3 Risk of bias summary using Cochrane's risk of bias assessment tool for randomized controlled trials

Discussion

The incidence of oral cancer is among the top ten most common cancers in the world, with late clinical detection, a poor prognosis, specific biomarkers for the disease, and costly therapeutic alternatives [39]. Combining radiation therapy and chemotherapy is the most widely used intervention for the management of oral and HNC. It is well known that these treatments improve the QOL and extend the life expectancy of the patients; however, they are often associated with adverse effects [40]. One of the most painful and debilitating adverse effects of radiation and chemotherapy is OM [41, 42]. In severe cases, OM also causes unrelenting pain, inability to eat or drink, weight loss, and reduced QOL [43, 44]. This is caused by oxidative damage, which releases reactive oxygen species (ROS) that cause inflammatory cytokines to activate causing DNA damage and resulting in cell death [45].

Mucositis is managed with an intensive oral care protocol, antimicrobial, anti-inflammatory, cytoprotective agents, dietary supplements, biostimulants, and natural and homeopathic agents [46–49]. In order to increase the effectiveness of a variety of therapeutic agents, a new method of localized drug delivery was developed in the form of bioadhesives

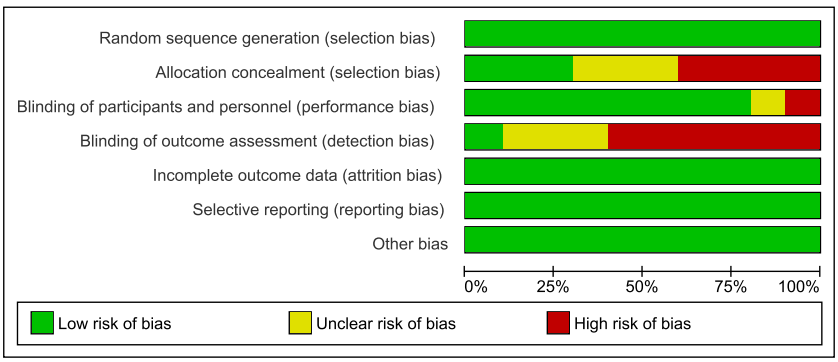

Fig. 2 Risk of bias graph presented as percentages across all included studies using Cochrane's risk of bias assessment tool for randomized controlled trials

Table 3 Assessment of risk of bias of included studies utilizing the Joanna Briggs Institute (JBI) critical appraisal tool for non-randomized controlled trials and observational studies

S.no	Author name	1	2	3	4	5	6	7	8	9	Overall	Quality
1	Kabasawa et al., 2020 [38]	✚	✚	✚	✚	✚	✚	✖	✚	✚	88%	High
2	Oguchi et al., 2020 [32]	✚	✚	✚	✚	✚	✚	✚	✚	✚	100%	High
3	Wei et al., 2020 [33]	✚	✚	✚	✚	✚	✚	✚	✚	✚	100%	High
4	Alterio et al., 2009 [34]	✚	✚	✚	✚	✖	✖	✚	✚		75%	High
5	Noronha et al., 1987 [31]	✚	✚	✚	✚	✖	✖	✚	✚		75%	High

Each number represents the question to be answered with yes, no, unclear, and not applicable with green color representing answer yes and red color representing answer no

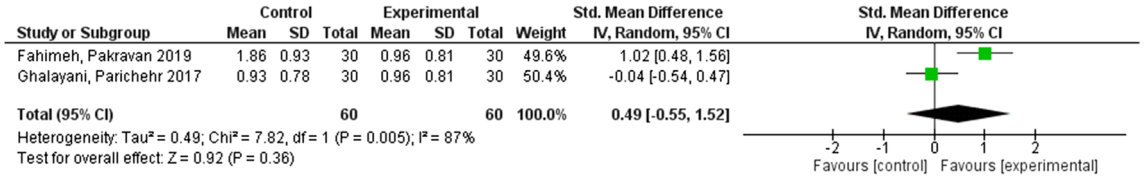

Fig. 4 Forest plot analysis of mucositis reduction reveals heterogeneity ($I^2 = 87\%$) with experimental (bioadhesives) favored values as the pooled effect estimate (black diamond) is away from the line of no effect (black line) is toward the right side

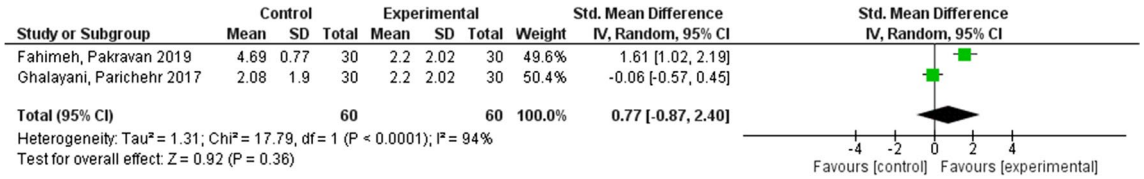

Fig. 5 Forest plot analysis of pain reduction reveals heterogeneity ($I^2 = 94\%$) with experimental (bioadhesives) favored values as the pooled effect estimate (black diamond) is away from the line of no effect (black line) is toward the right side

or mucoadhesives that adhere to the oral mucosa upon application.

Current MASCC/ISOO guidelines do not address the efficacy of bioadhesive barrier-forming oral liquids. It is because there is insufficient proof that using these products reduces the severity of OM, although some of these oral care products provide comfort to patients [49]. A topical oral mucosal protectant such as Caphosol®, MuGard®, Oralife®, Gelclair®, and Episil® is suggested by the European Oral Care in Cancer Group and the UK Oral Mucositis in Cancer Group for mild to moderate OM [50, 51].

A gel formulation is a semisolid mucoadhesive that has several advantages, including rapid drug release, ease of preparation and administration, increased biocompatibility, and easy dispersal throughout the oral mucosa, allowing it to adhere to the oral mucosa and reducing the risk of irritative or allergic reactions [52]. Six of the 15 included studies [21, 25, 26, 29, 34, 35] used bioadhesive gel to treat OM. According to two studies [26, 35], the intervention was equally effective in managing OM and reducing pain as standard therapy. There was a consistent reduction in OM incidence in a phase II trial [29]. In the remaining studies [25, 34], bioadhesive gels were found to be safe in delaying the progression of OM and improving its symptoms.

Patches and films are semisolid preparation that comes in an elliptical shape and can range from 1 to 3 cm in size,

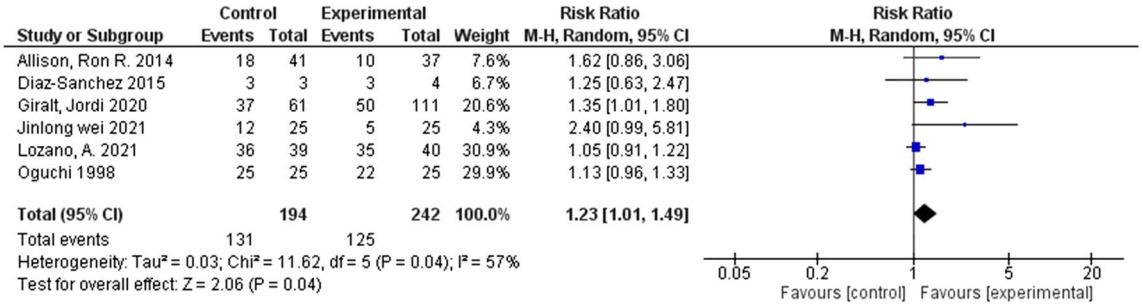

Fig. 6 Forest plot analysis of incidence reduction reveals heterogeneity ($I^2 = 57\%$) with experimental (bioadhesives) favored values as the pooled effect estimate (black diamond) is away from the line of no effect (black line) is toward the right side

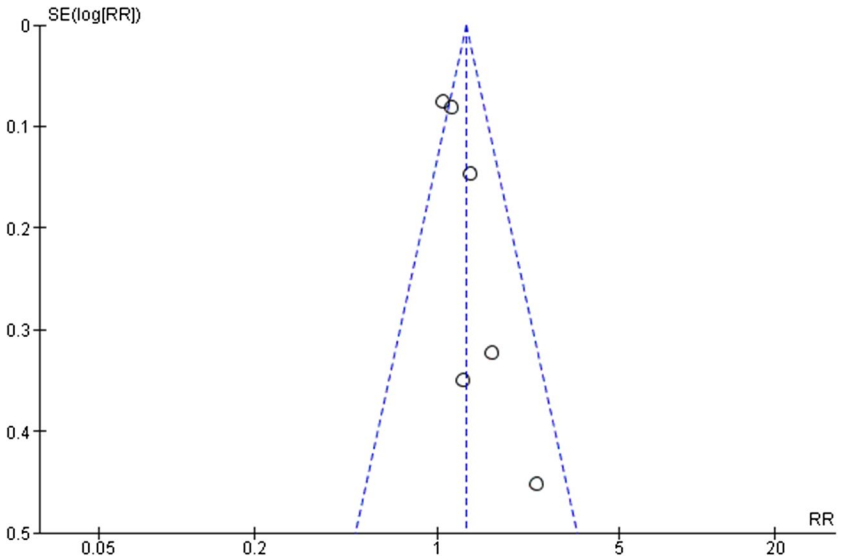

Fig. 7 Funnel plot analysis to evaluate reporting bias for studies assessing incidence of oral mucositis revealed. Each plotted point represents risk ratio plotted against standard error

and they are used to deliver drugs directly to the mucosal membrane [53]. There were three studies [27, 28, 32] that used mucoadhesive patches or films, two of which contained triamcinolone acetonide [27, 28]. Triamcinolone acetonide film was proven to be effective in reducing the OM grade and associated pain with it. Film-based adhesives were effective at relieving pain when topical anesthetics and antibiotics were combined in a water-soluble film [32].

Lipid-based solutions such as phospholipid and diglycerides can effectively relieve intraoral pain due to their unique bioadhesive properties [54]. The Episil® is a bioadhesive lipid-based solution containing soybean lecithin and diolein which forms a protective barrier within five minutes upon contact with oral mucosa, thereby having a local analgesic effect [38]. The results of three studies [33, 38, 39] utilizing Episil® showed that it effectively improved OM and the pain it causes. A study that used CAM-2028 [37] demonstrated clinically significant pain relief for up to eight hours.

Drug-loaded wafers can provide a mucoadhesive layer while providing prolonged and stable drug release [55]. A study [30] concluded Mucotrol™ (MF 5232), a polyherbal formulation containing *Polygonum cuspidatum*, *Angelica* sp., *Camellia sinensis*, *Cyamopsis tetragonolobus*, *Centella asiatica*, and *Aloe* sp. and glycyrrhizin. Beneficial activity in OM is owing to its antioxidant, analgesic, immunomodulatory, and wound healing properties.

Tablets are a solid form of mucoadhesive system that can be applied both topically and systemically. Bioadhesive polymers can be used to form a matrix for drug delivery that incorporates the active ingredient into the tablet [56]. According to a study [36], mucoadhesive tablet containing Clonidine which is known for its anti-hypertensive and anti-inflammatory activity showed a favorable effect on OM severity and course.

This systematic review included studies with a variety of study designs. According to the quality assessment, a study [36] had a low risk of bias and was of high quality. Similarly, a study [37] carried an unclear risk of bias as the participants, presenter, and outcome assessor were not blinded. The remaining 8 [25–30, 35, 39] out of 10 studies were judged

Table 4 GRADE method for the assessment of the certainty of evidence. Efficacy of bioadhesives are compared to placebo or matched controls for mucositis reduction, mucositis pain reduction, and incidence of mucositis in head and neck cancer patients treated by radio-chemotherapy respectively.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo or matched controls	With bioadhesives		Risk with placebo or matched controls	Risk difference with bioadhesives
Mucositis assessment											
120 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	60	60	–	–	SMD 0.77 higher (0.87 lower to 2.4 higher)
Mucositis pain assessment											
120 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	60	60	–	–	SMD 0.49 higher (0.55 lower to 1.52 higher)
Mucositis incidence											
436 (6 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias is strongly suspected	⨁⨁⨁◯ Moderate	125/242 (51.7%)	131/194 (67.5%)	RR 1.23 (1.01 to 1.49)	517 per 1000	119 more per 1000 (from 5 more to 253 more)

CI confidence interval, *SMD* standardized mean difference, *RR* risk ratio

to have a high risk of bias due to insufficient information regarding methods for assigning patients to experimental and control groups and the absence of blinding of participants, personnel, or outcome assessor. A total of three studies that were non-randomized [32, 33, 38] and two studies that were observational [31, 34] have been found to be of high quality. Therefore, studies included with their results can be considered for potential clinical significance.

The findings of this systematic review and meta-analysis have several strengths, including a comprehensive literature search, the inclusion of studies conducted using different bioadhesive systems, and the results of qualitative and quantitative synthesis. It is important to note, however, certain limitations apply to the results of this systematic review. Studies published in the English language were included in this review with results obtained in other languages being excluded leading to selection bias.

Limitations

The heterogeneity among the included studies is one of the limitations of this systematic review. There were heterogeneities noted in the study design, sample size, radiation delivery method, pain assessment tools, data presentation regarding OM, and adverse effects. It was important to note that different types of study designs were utilized in this systematic review. In most of the included studies, randomized or non-randomized controlled trials were used while only a few were observational studies. An evidence-based approach places randomized controlled trials at the top of the pyramid as the ideal study design for comparing the effectiveness of two different interventions, but studies other than these can have an impact on the outcome as well.

The limited sample size is another factor that should be considered as 2 out of 15 included studies used a sample size of 15 or fewer patients. It was also noted that experimental and control samples were distributed unequally, which could contribute to heterogeneity. Mucositis may be influenced by the method of radiation delivery to the patient. There are differences between radiotherapy methods in the included studies, which range from larger fields of treatment using conventional or cobalt machines to a smaller field using IMRT, which raises the question whether this is a confounding factor.

In this systematic review, the efficacy of various bioadhesive systems was compared. The treatment group contains various forms of bioadhesives, such as gels, wafers, and films, having a control group in a similar form to that of the intervention provided should be used for accurate comparison. Furthermore, differences in the duration of intervention and control contribute to heterogeneity.

Assessment of OM uses various scales like WHO, RTOG, and NCI, and assessment of pain due to OM was measured

Table 5 GRADE evidence profile (EP) for the 15 studies included in the systematic review

GRADE evidence profile (EP) for the 15 studies included in the systematic review						
Study	Limitation	Inconsistency	Indirectness	Imprecision	Risk of bias	Quality grading
Allison et al. [25]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment not mentioned and detection bias)	⊕⊕⊕◯ Moderate
Sanchez et al. [26]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (detection bias)	⊕⊕⊕◯ Moderate
Pakravan et al. [27]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment not mentioned and detection bias)	⊕⊕⊕◯ Moderate
Ghalayani et al. [28]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment not mentioned and detection bias)	⊕⊕⊕◯ Moderate
Lozano et al. [29]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment not mentioned and detection bias)	⊕⊕⊕◯ Moderate
Naidu et al. [30]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment not mentioned and detection bias)	⊕⊕⊕◯ Moderate
Noronha et al. [31]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Unclear (identification and measures to deal with confounding factors not mentioned)	⊕⊕◯◯ Low
Oguchi et al. [32]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	None detected	⊕⊕⊕⊕ High
Wei et al. [33]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	None detected	⊕⊕⊕⊕ High
Alterio et al. [34]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Unclear (identification and measures to deal with confounding factors not mentioned)	⊕⊕◯◯ Low
Barber et al. [35]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment, performance bias, and detection bias)	⊕⊕◯◯ Low
Giralt et al. [36]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	None detected	⊕⊕⊕⊕ High
Hadjieva et al. [37]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Unclear (detection bias)	⊕⊕⊕◯ Moderate
Kabasawa et al. [38]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	Unclear (measurement of outcomes of participants in comparison not carried out in a similar way)	⊕⊕⊕◯ Moderate
Soutome et al. [39]	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	High (allocation concealment, detection and performance bias)	⊕⊕◯◯ Low

using WHO, Likert, VAS, and RTOG scales, which may result in heterogeneity. In included studies, data were presented on the incidence of severe OM, reduction in OM, reduction or improvement of pain, and number of days until OM and pain associated with it resolved, as well as improvement of pain or OM with intervention. As a result, heterogeneity can be observed as different methods of measurement were used to present the data.

The studies included did not precisely describe how secondary outcomes, such as adverse reaction and interruptions of radiotherapy, were measured. The efficacy of the intervention as well as adverse effects of the treatment was not assessed through long-term follow-ups of the patients. Also, the clinical and oncological safety of the bioadhesives was not assessed.

A major limitation of this systematic review was the methodological quality of the studies that were included in it. Even though 6 out of the 15 studies included in this review were of high quality, selection, performance, and detection bias compromises the internal validity of results in remaining 9 studies, which subsequently makes it difficult to draw a robust conclusion from these studies.

Suggestions

Studies in the future should have a randomized controlled study design with improved sample size and similar forms of bioadhesives both in the treatment and control groups. In order to evaluate the effectiveness of bioadhesive systems for the reduction of mucositis or the relief of pain, two different bioadhesive systems utilizing the same intervention agent should be compared. For assessment of the recurrence of the lesion or adverse effects, a longer follow-up period of the patient's post-intervention or treatment duration is required.

In order to avoid heterogeneity, common assessment tools can be used to assess OM and pain associated with it. A single tool can be used for assessing the incidence of OM or reduction in OM for the purposes of evaluating the efficiency of bioadhesives in relation to pain associated with OM. As an alternative and promising therapeutic modality for the management of OM in patients with HNC, cost-effectiveness regarding the manufacturing of various adhesive systems and accessibility are factors that should be considered.

Implications for practice and research

The bioadhesive drug delivery system appears to be one of the most promising systems as it has shown positive preliminary results. Based on the data from included studies, it is predicted that the outcome of this study will be positive. This is due to the substantial reduction in the incidence of OM, associated pain, and the frequency of OM in the bioadhesive group compared to the placebo in this study. Moreover, the certainty evidence revealed a higher degree of certainty providing valuable insight regarding the potential use of these modalities in the treatment of OM and other oral mucosal lesions.

Conclusion

The findings of this multiendpoint systematic review indicate that bioadhesives can be used as an alternative treatment option for patients with OM caused by radiotherapy or chemotherapy in the treatment of HNC in most cases. Several clinical outcomes suggest that bioadhesives can considerably reduce pain and OM while being less likely to cause adverse effects compared to systemic therapy. However, due to the observed heterogeneity of the results, it is recommended to conduct further well-designed studies with long-term treatment and follow-up on the subjects.

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Author contributions Dr. Jayapriya T: conceptualization and protocol development, methodology, data collection and extraction, bias assessment, meta-analysis, and manuscript writing. Dr. Vaishali Keluskar: conceptualization, methodology, data collection and extraction, bias assessment, manuscript—review, and editing. Dr. Vasanti Lagali-Jirge: supervision, validation, visualization, bias assessment, manuscript—review, and editing. Dr. Sridhar M: data curation, supervision, writing review, and editing.

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Declarations

Ethics approval This is a systematic review and meta-analysis that involves assessment of studies, and hence, ethical clearance was not sought for.

Consent to participate This is a systematic review and meta-analysis does not involve any human or animal intervention, and hence, consent was not mandatory.

Consent for publication The authors declare that they are willing to publish this article and data will be shared upon reasonable request.

Competing interests The authors declare no competing interests.

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Other information Registration and protocol: Protocol for this systematic review was prepared before the start of the review and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) maintained by the Centre of Reviews and Dissemination, University of York, York, UK (Ref No. CRD42022340445), which can be accessed through (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022340445). The current systematic review was written in concordance with the preferred reporting items for the systematic review and meta-analysis (PRISMA) 2020 statement.