REVIEW

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Corticoids Reduce Incidence of Oral Mucositis during Antineoplastic Treatment? A Systematic Review and Meta-Analysis of Randomized and Nonrandomized Clinical Trials

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Abstract

Background: Oral mucositis (OM) is a serious complication of antineoplastic therapy and its clinical presentation can range from small erythematous lesions to large, debilitating ulcerative areas. This adverse effect results from the non-specificity of chemotherapeutic agents. This study aims to determine whether corticosteroid protocols reduce the incidence or severity of OM during antineoplastic treatment. **Materials and Methods:** This PROSPERO registered systematic review (CRD42023442448) searched PubMed, Scopus, Web of Science, LILACS, EBSCOhost, LIVIVO, Embase, and the gray literature. RoB-2 and ROBINS-I were used to assess the risk of bias (RoB), and a meta-analysis was performed evaluating the incidence or severity of OM. GRADE-pro analyzed the certainty of the evidence. **Results:** Of the 1795 articles, 5 RCTs and three n-RCTs were included, involving 718 patients, 255 men and 463 women distributed among 379 patients in the intervention groups and 339 patients in the control groups. High heterogeneity and low publication RoB were identified. The topical application of corticosteroids did not impair OM incidence ($p=0.860$). However, the systemic application of corticosteroids resulted in a reduction of 0.44 (CI95% = 0.29 to 0.66) times ($p<0.001$). There is no significant risk of publication bias ($p=0.881$). In the meta-analysis of OM severity, topical ($p=0.280$) or systemic ($p=0.270$) application did not show a significant reduction in the MO scores; there was no significant heterogeneity ($p=0.940$, $I^2=0\%$), and leave-one-out analysis demonstrated that removing individual study results did not alter this outcome. GRADE showed moderate certainty for both OM incidence and severity. Inconsistency and imprecision were low to moderate, and the risk of publication bias was low. **Conclusion:** High doses of systemic corticosteroids demonstrate clinical benefits in controlling OM, while the topical use requires further investigation, particularly with high-potency formulations.

Keywords: Antineoplastic Protocols- Glucocorticoid- Oral Mucositis- Neoplasms

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Introduction

Oral mucositis (OM) is a serious complication of antineoplastic therapy and its clinical presentation can range from small erythematous lesions to large, debilitating ulcerative areas [1]. This adverse effect results from the nonspecificity of chemotherapeutic agents that act on organs and tissues with high rates of cell replication, such as epithelial tissue [2]. Approximately 40% of patients undergoing chemotherapy and 90% of patients undergoing head and neck radiotherapy develop OM [3], leading to subsequent candidiasis, dysphagia, dysgeusia, nutritional deficits, interruption of antineoplastic treatment, and a decrease in quality of life [2, 4, 5].

The development of OM results from a cascade of events culminating in the death of basal and suprabasal epithelial cells of the oral epithelium, release of damage-associated molecular patterns (DAMPs), reactive oxygen species, pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and robust activation of transcription factors such as nuclear factor-κB (NF-κB) [3]. The release of pro-inflammatory cytokines promotes damage to both connective tissue and endothelium and minimizes tissue oxygenation [6]. During the ulcerative phase of OM, there is typically an increase in the inflammatory response due to secondary infections, thereby increasing tissue damage

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resulting from this injury [3, 7], making the control of mucositis a significant challenge [8].

Despite evidence-based clinical practices for the treatment and/or prevention of OM [1], the use of anti-inflammatories has been suggested as a low-cost approach for preventing and treating OM [9, 10], given that more effective treatments such as low-level laser therapy require trained staff and expensive equipment [11].

The use of corticosteroids has been suggested as tools for the prevention and treatment of OM given its highly inflammatory pathogenesis. It has recently been reported that a mouthwash containing prednisolone reduces the incidence of these damages in breast cancer patients who experienced grade 2–3 oral mucositis in the preceding cycle [12]. Additionally, in a retrospective study evaluating the effectiveness of dexamethasone in docetaxel-induced OM and dysgeusia, it was observed that high doses of dexamethasone significantly reduced docetaxel-induced OM [13].

Corticosteroids are one of the oldest and most widely used classes of drugs worldwide for the treatment of numerous inflammatory and immune-related diseases. This drug can inhibit the aggregation of inflammatory cells, including macrophages and white blood cells at the site of inflammation, and inhibit phagocytosis, the release of lysosomal enzymes, and the synthesis and release of inflammatory chemical mediators, which can reduce and prevent the tissue response to inflammation, thereby reducing inflammation expression [13].

Therefore, considering the effectiveness of corticosteroids in controlling numerous inflammatory disorders and since oral mucositis is a condition strongly associated with acute inflammation, the objective of this study is to conduct a systematic review with the following research question: In patients undergoing antineoplastic treatment, does the use of corticosteroids reduce the incidence or severity of oral mucositis?

Materials and Methods

Protocol

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [14]. This study design did not require Ethics Committee approval or signed patient consent forms. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42023442448.

Search Strategy

The search planning was based on PICOS, which is an acronym for population (P), intervention (I), comparison group (C), outcome (O), and study design (S). Thus, the elements used to compose the main research question were patients under antineoplastic treatment (P); use of corticoids (I); placebo use / no use of corticoid / use of corticoid in a low dose (C); incidence and/or severity of OM (O); controlled clinical trials (S).

Eligibility Criteria

Inclusion Criteria

Controlled clinical trials were included and evaluated the use of any formulation of corticoid compared to placebo, no use of corticoid or use of corticoid in a low dose. There were no study restrictions on age, gender, language, education, or year of publication.

Exclusion Criteria

Articles were excluded if they met at least one of the following criteria: (1) literature reviews; (2) letters to the editor; (3) personal opinions of the author; (4) book chapters; (5) meeting abstracts; (6) cross-sectional studies; and (7) laboratory studies.

Database

This research involved eight online databases: PubMed, Scopus, Web of Science, LILACS, EBSCOhost, LIVIVO, Embase, and Cochrane Library. In addition, the gray literature was reviewed and included the ProQuest and OpenGrey databases and the first 100 most relevant articles from Google Scholar through December 2023, with time restrictions.

Study Selection

A two-stage selection process was performed with two reviewers (authors' initials AB and GBA) and one judge (JV). First, the titles and abstracts of potential studies were obtained from electronic databases and imported into Rayyan® (Qatar Computing Research Institute, Doha, Qatar) application software for the inclusion and exclusion criteria [15]. In the second phase, the full texts of the articles were independently evaluated based on the eligibility criteria adopted in this systematic review. Any disagreement in both phases was resolved when the two authors reached an agreement. If they could not reach a consensus, a second judge (CENM) participated in the final decision. No language restrictions were performed.

Data Collection Process

A dental oncologist (CENM) participated in the data collection phase, and a statistician (PGBS) cross-checked all the extracted information. Similarly, any persistent disagreements between the two authors were discussed with a third researcher (MMFB). After each medical consultation with the multi-professional team immediately before chemotherapy, the professionals assigned toxicity grades for mucositis, which were recorded in the toxicity scale tool and exported to a standard Microsoft Excel spreadsheet containing the number and date of care and the severity grade of the adverse effect.

Data Items

Of the selected studies, the following information was recorded: (1) year of publication; (2) methodological design; (3) participants (sample size, sex, and age); (4) groups; (5) corticoid protocol; (6) antineoplastic treatment; (7) start and duration of intervention; (8) evaluation days; (9) oral mucositis scale used; and (10) outcomes of interest to the systematic review.

Risk of bias (RoB) in individual studies

The risk of bias was independently assessed by two authors (MMFB and CENM). The revised Cochrane risk of bias tool for randomized trials (RoB-2) [16] was used to access RoB in randomized clinical trials (RCTs), and the Cochrane Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) method bias was used to assess RoB in non-randomized clinical trials (n-RCT) [17]. In addition, RevMan Software (Review Manager, version 5.3, Cochrane Collaboration, Copenhagen, Denmark) generated the RoB summary numbers.

Meta-Analysis

The incidence (categorical data) of any episode of OM was assessed by a meta-analysis using the combined relative risk of OM with the method of inverse variance and random effects. I^2 and Tau^2 coefficients calculated heterogeneity, and sensitivity analysis was performed by leave-one-out analysis by removing study-by-study results to check the weight of each study in the meta-analyses. In addition, the risk of publication bias was analyzed by Funnel Plot Begg tests. All analyses were performed with Revman software, adopting 95% confidence in this review.

Evidence Analysis

The evidence quality assessment followed the recommendation and grading (GRADE) approach [18]. The GRADE profiler summarized the quality of evidence using the GRADE pro-GDT software (http://gdt.guidelinedevelopment.org). Depending on the importance of study design, RoB, consistency, frankness, heterogeneity, precision, publication bias, and others reported by the studies included in the systematic review, the quality of evidence could be downgraded by one or two levels for each aspect. In addition, it could be upgraded by one or two levels according to the quality of its evidence.

Results

Study Screening and Selection

Out of a total of 1,795 articles, eight clinical trials were included in this study.; of these, 1,691 were from databases, 879 from Pubmed, 519 from Scopus, 14 from Web of Science, 144 from Lilacs, 48 from EBSCO, 31 from Livivo, 22 from Embase, and 34 from Cochrane Library. From grey literature, there were 104 records, 4 from ProQuest, and the first 100 Google Scholar searches. No one record was rescued from OpenGrey

A total of 1,717 articles were excluded for not meeting eligibility criteria because they were duplicates and for other reasons, leaving 37 articles to be read in their entirety. Of these, 31 articles were excluded due to the absence of a control group (n=20), not evaluated oral mucositis (n=10), and one was a absctract from a congress/symposium. So, one article was removed after complete analysis because it was a protocol registration of a clinical trial and six articles were finally included. After rescue of their references, two articles were rescued totalling eighth clinical trials (Figure 1).

Descriptive Analysis of the Clinical Trials

Of the 8 articles included, 5 were RCTs and 3 were non-RCT, of which 8 were conducted in Japan, one in Iran, one in China, one in Brazil, and one in Uruguay. Regarding blinding, only three studies were double-blind.

Regarding the intervention group, three studies used systemic administration of corticosteroids (prednisone (n=1) or dexamethasone (n=2) and five used local application of corticosteroids (dexamethasone elixir (n=2) or ointment (n=1), clobetasol (n=1), Triamcinolone acetonide mucoadhesive (n=1)). The control group of studies using systemic administration of high doses of dexamethasone was low dose of dexamethasone (n=2) and systemic administration was placebo (n=1). The control group of studies using local application of corticosteroids were oral care (n=2), dexamethasone elixir (n=1), Chlorhexidine mouthwash (n=1) or Licorice mucoadhesive films (n=1) (Table 1).

The eight included studies comprised a total of 718 patients, including 255 men and 463 women distributed among 379 patients in the intervention groups and 339 patients in the control groups. The mean/median age ranged around 50 years old, and the corticosteroid application protocols are presented in Table 1.

Regarding the antineoplastic protocols, four studies investigated patients undergoing head and neck radiotherapy, with or without concurrent chemotherapy, three studies worked with patients undergoing chemotherapy for breast cancer treatment, and one study worked with patients with myeloproliferative diseases. The corticosteroid administration protocols varied from single administration (when given systematically) to oral rinses or administration in the early days post-antineoplastic treatment (when locally applied). Three studies used the CTCAE scale, three studies used the WHO scale, one study used the RTOG scale, and one study used a proprietary scale (Table 2).

Regarding the primary outcome, all studies reported a significant reduction in the incidence or severity of oral mucositis in the intervention groups. Concerning the secondary outcomes, one study reported a reduction in the number of interruptions of RT sessions, one study reported a reduction in pain scores, and one study reported a reduction in the use of opioid medications (Table 3).

Risk of Bias (RoB) in RCTs and non-RCT

The risk of bias in RCTs was predominantly moderate to high. In the criteria bias due to the measurement of outcome and bias in selection of reported results Kawashita et al. [4], Kuba et al. [12] and Noce et al. [22] showed a high risk of bias. Regard bias arising from the randomization process Leborgne et al. [19] showed a high risk of bias (Figure 2a and Figure 3a). In NRCT the risk of bias was predominantly moderate. No on study showed a high risk of bias in analyzed parameters, but bias in measurement of outcomes and selection of reported results 100% of studies showed unclear parameters (Figure 2b and Figure 3b).

Table 1. Study Design of Randomized Clinical Trials Evaluating Corticoid Treatment Protocols to OM.

	Country	Blinded	Rando-mization	Antineoplastic treatment	Intervention	Control	Sex (M/F)		Age	Control	Intervention method
							Intervention	Control	Intervention		
Ghalayani et al., [20]	Iran	Double blinded	Yes	Patients with head and neck radiotherapy	Triamcinolone acetonide mucoadhesive films	Licorice mucoadhesive films	12/18	12/19	Mean ± SD = 58.53 ± 8.89	Mean ± SD = 57.33 ± 10.05	Topical application of mucoadhesive films four times daily (applied upon the upper lip mucosal surface).
Saito et al., [10]	Japan	No	No	Women with breast cancer and chemotherapy	High doses of dexamethasone	Low doses of dexamethasone	0/88	0/43	Median = 55 Range = 26–73	Median = 50 Range = 32–66	Administration of 9.9 mg of dexamethasone infusion on day 1 and 8 mg orally on days 2-4 vs.6.6 mg infusion on day 1 and 4 mg orally on days 2-4
Li et al., [21]	China	No	No	Patients with nasopharyngeal carcinoma treated with radiotherapy	Dexamethasone-lidocaine-vitamin B12 mouth rinse	Chlorhexidine mouthwash	45/22	46/20	>49: 41/67	>49: 39/66	Dexamethasone solution (20mg in 4ml solution) plus lidocaine hydrochloride solution (2mg in 20 ml) Vitamin B12 solution (2mg in 4ml) shaken with 250 ml normal saline, used before three meals and before going to bed respectively vs chlorhexidine mouthwash
Noce et al., [22]	Brazil	Double blinded	Yes	Patients with chronic graft-versus-host disease	Clobetasol topic	Dexamethasone elixir	6-Aug	8-Oct	Median = 53.00 Range = 29-60	Median = 45.50 Range = 27-66	Mouth rinse of with 5 mL of clobetasol propionate .05% administered with nystatin 100,000 IU/mL vs. 5 mL of dexamethasone 0.1 mg/mL administered with nystatin 100,000 IU/mL
Kuba et al., [12]	Japan	No	Yes	Women with breast cancer and chemotherapy	Dexamethasone elixir	Oral care	0/59	0/58	Median = 52 IQ = 44-61	Median = 54 IQ = 44-62	10 mL of dexamethasone-based elixir (0 .1 mg/mL; directions for use: swish for 2 minutes and spit, 4 times daily) beginning on day 1 of the first cycle of chemotherapy
Saito et al., [13]	Japan	No	No	Women with breast cancer and chemotherapy	High doses of dexamethasone	Low doses of dexamethasone	0/47	0/45	Median = 53 Range = 27-73	Median = 51 Range = 30-66	Administration of 8 vs 4 mg orally on days 2-4 after chemotherapy
Kawashita et al., [14]	Japan	No	Yes	Patients with head and neck radiotherapy or radiochemotherapy	Dexamethasone and pilocarpine ointment	Oral care	29/13	26/19	>69 = 22/42	>69 = 17/45	Pilocarpine hydrochloride plus a 0.1% dexamethasone ointment applied over areas with redness or pseudomembrane formation four times a day, after meals and before bedtime.
Leborgne et al., [19]	Uruguay	Double blinded	Yes	Patients with head and neck radiotherapy or radiochemotherapy	Prednisone	Placebo	26-Jun	32/2	Median = 60 Range = 40-79	Median = 64 Range = 42-92	Prednisone 40 mg orally daily

IQ, interquartile interval

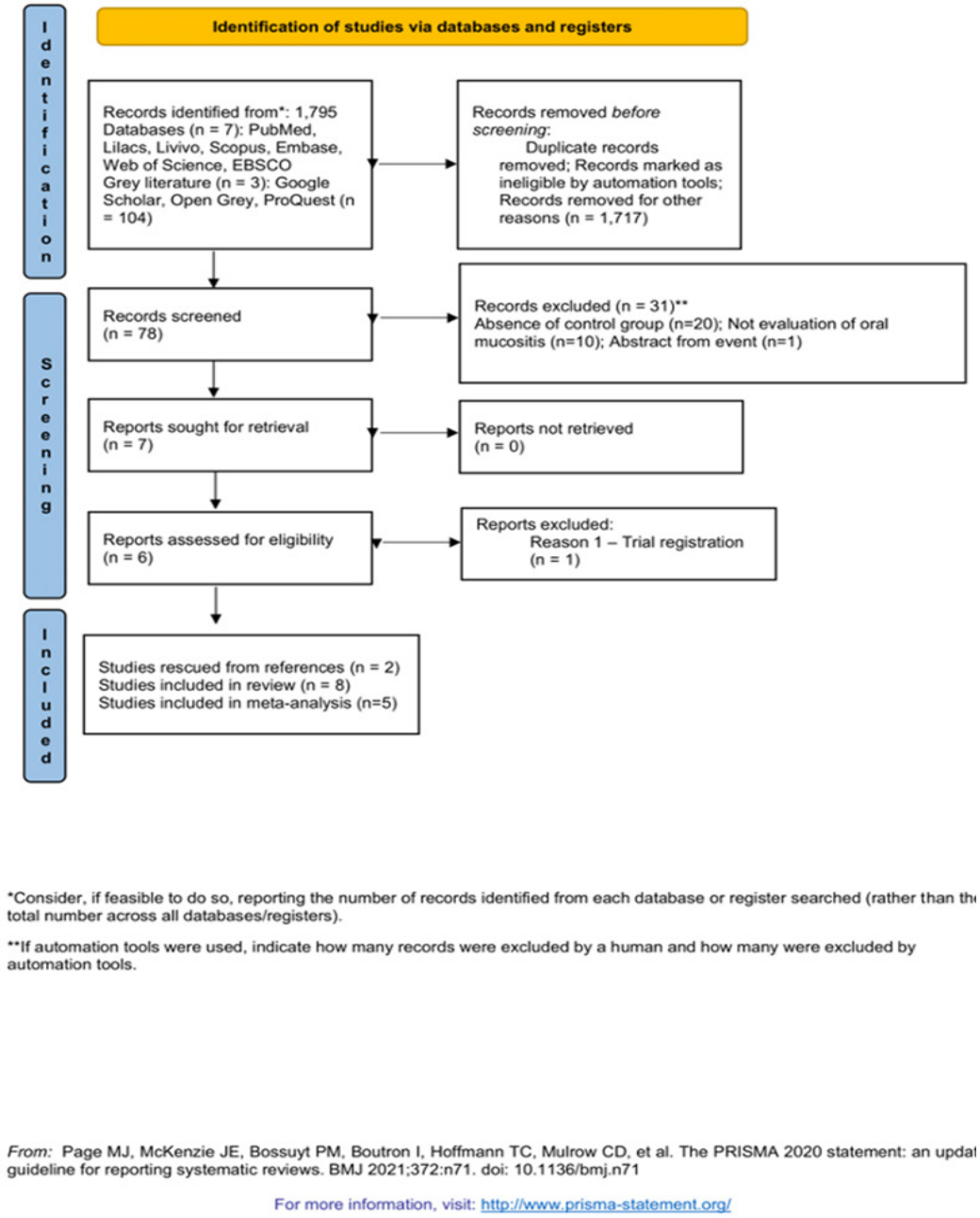

Figure 1. PRISMA 2020 Flow Diagram for New Systematic Reviews which Included Searches of Databases and Registers Only

Meta-analysis

Systemic corticosteroids reduce the incidence of oral mucositis

Of the eight studies included in the SR, only five provided data for meta-analysis: Ghalayani et al. [20], Kawashita et al. [4], Li et al. [21], Noce et al. [22], and Leborgne et al. [19]. Two meta-analyses could be performed, one assessing the incidence of OM and one evaluating the mean OM scores. In both, the meta-analysis was divided into two subgroups, one using corticosteroids locally and one applying corticosteroids systemically.

In the meta-analysis of incidence, 316 episodes in the intervention group and 272 in the control group could be included. Topical application of corticosteroids did not demonstrate a significant benefit in reducing the incidence of OM (p=0.860), with no significant heterogeneity (I^2 = 20%, p=0.280). In the one-of-out analysis, the removal of data from Ghalayani et al. [20] favored the intervention group with a reduction of 0.20 [95% CI = 0.06 to 0.65] times in the incidence of OM (p=0.008). In the subgroup of systemic application of OM, there was a reduction of 0.44 [95% CI = 0.29 to 0.66] times (p<0.001) with two studies published by the same team (Saito et al. [10] and Saito et al. [13] (Figure 4a). The Begg test did not show significant publication bias (p=0.881) (Figure 5a).

In the severity meta-analysis, 254 episodes of OM in the intervention group and 263 episodes in the control groups were evaluated. Topical (p=0.280) or systemic (p=0.270) application did not show a significant reduction in OM scores (Figure 2a). There was no significant heterogeneity (p=0.940, I^2=0%), and the one-of-out analysis showed that the removal of individual study

Table 2. Characterization of Treatment and Clinical Outcomes of Clinical Trials Evaluating Corticoid Treatment Protocols to Prevent OM.

	Specific treatment	Start of intervention	Evaluation days	Oral mucosites scale
Ghalayani et al., [20]	RT was delivered in a two-dimensional cobalt-based technique. It was irradiated with 56–60 Gy in 28–30 fractions, daily 200 cGy per fraction. The head and neck RT did take 5–6 weeks	Both treatment modalities were stopped in case of complete response, but continued for another period of 7 days in case of improvement without the complete resolution.	Weekly, from after the occurrence of WHO grades 2-3 mucositis to 4 weeks or until complete remission.	WHO scale oral mucositis
Saito et al., [10]	Patients under anthracycline-containing chemotherapy regimens	Infusion's day and days 2-4 after infusion	In 1st chemotherapy cycle	Common Terminology Criteria for Adverse Events version 5.0
Li et al., [21]	60-70Gy of radical intensity-modulated RT for primary tumor and cervical metastatic lymph nodes Treatment (IMRT: 69.96Gy/2.12Gy/33F, 1 time/day, 5 times/week) with or without platium or nitozumab	From day 17 of RT until 2 weeks after the end of RT.	Weekly after start of intervention	American Society of radiation oncology (RTOG) scores of oral mucositis
Noce et al., [22]	Myeloproliferative diseases treated with hematopoietic stem cell transplantation	Patients were instructed to use the solution for 1 minute timed by a clock, 3 times a day, for 28 days	At baseline and after 28 days of treatment	Modified oral mucositis rating scale: (1) total remission to (3) no remissionn..
Kuba et al., [12]	Epirrubicin plus cyclophosphamide or taxanos plus cyclophosphamide for breast cancer	Mouth rise for 2 minutes and spit, 4 times daily) beginning on day 1 of the first cycle of chemotherapy.	In each day of chemotherapy cycle	WHO scale oral mucositis >0
Saito et al., [13]	Patients under docetaxel or docetaxel + cyclophosphamide without or with trastuzumab chemotherapy regimens	Infusion's day and days 2-4 after infusion	In 1st chemotherapy cycle	Common Terminology Criteria for Adverse Events version 5.0
Kawashita et al., [4]	63Gy (interquartile interval = 60-60Gy) of RT plus platium, cetuximab, taxane or tegafur–gimeracil–oteracil potassium derived chemotherapy	After mucositis installation	Daily after oral mucositis installation	CTCAE version 4.0 scale oral mucositis >2
Leborgne et al., [19]	64–65 Gy in 26–29 elapsed days (1.6Gy/section) without resorting to programmed treatment breaks in a 60Co or 6 MV photons	Prednisone on day 8-28 of treatment through day 28. From day 29-33 the dose was tapered to 20 mg and from day 34 -43 to 20 mg.	Daily from day 1 of the beginning of RT through day 90	WHO scale oral mucositis >0

WHO, World Health Organization

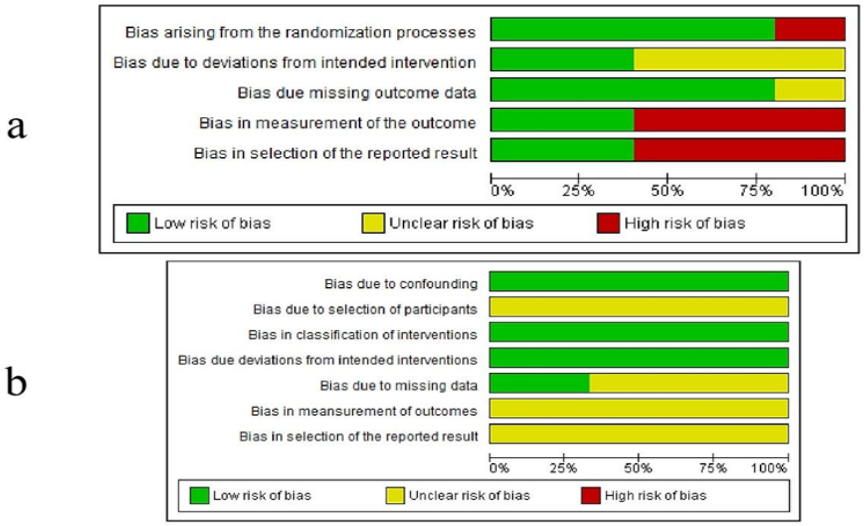

Figure 2. RoB RCT and NRCT Group

results did not alter this outcome (Figure 4b). The Egger test did not demonstrate significant publication bias (p=0.210) (Figure 5b).

Analysis of the certainty of evidence
GRADE

According to the GRADE criteria-based evaluation, the certainty was moderate. Such incidence as severity of OM showed moderate certainty of the evidence due moderate to high risk bias. Inconsistency and imprecision were low to moderate and risk of publication bias was low [3].

Discussion

Oral mucositis (OM) is a serious inflammatory, painful, and ulcerative collateral complication that occurs as a result of antineoplastic treatment. The inflammatory effect can negatively impact oral intake, including dietary intake and oral medications, oral hygiene maintenance, and patients' quality of life [23]. Considering the pathogenic mechanisms of OM, several strategies have been suggested to enable the use of corticosteroids as a promising preventive method [11].

Due to OM pathogenesis involving inflammation, the use of corticosteroids such as topical dexamethasone has been suggested in combination with systemic therapy [12, 22]. Similarly, in a randomized, double-blind clinical trial comparing topical clobetasol and dexamethasone for the treatment of symptomatic oral chronic graft-versus-host disease (cGVHD), it was demonstrated that the use of clobetasol led to a symptomatic improvement in OM 2.5 times more frequently than the use of topical dexamethasone. It was hypothesized that clobetasol would provide a better response than dexamethasone due to its potency [22]. Given its greater potency, clobetasol was chosen as the test group in the meta-analysis, and dexamethasone as the control group.

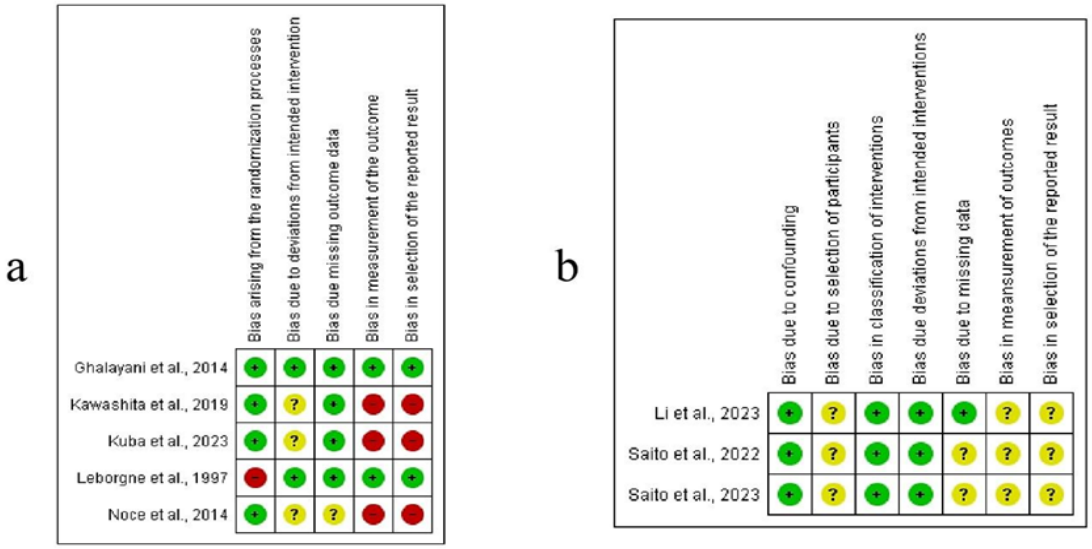

Figure 3. RoB RCT and NRCT Individual

Ghalayani et al. [20] compared the efficacy and safety of mucoadhesive films containing triamcinolone acetonide with licorice mucoadhesive films in the treatment of oral mucositis (OM) in patients with head and neck cancer undergoing radiotherapy or postoperative adjuvant treatment. Triamcinolone mucoadhesive films were superior in managing OM during radiotherapy, consistent with the study by Hosseini et al. [24], a triple-blind randomized clinical trial, which demonstrated the efficacy of a mouthwash combined with vitamin E, triamcinolone, and hyaluronic acid in patients with radiotherapy-induced OM.

In a retrospective study, where 113 patients with Nasopharyngeal Carcinoma undergoing radiotherapy were selected, divided into two groups (DLVBM group: 4ml of dexamethasone solution, 20ml of lidocaine hydrochloride solution, 4ml of vitamin B12 solution shaken with 250ml of normal saline solution; CCM group: mouthwash composed of chlorhexidine) [21], it was observed that the dexamethasone-treated group showed a significant reduction in oral pain and weight loss, being considered more effective in pain relief and prevention of RT-induced OM. Confirming this finding, in 2019, Kuba et al. [12] when evaluating 120 patients undergoing chemotherapy for breast cancer (allocated in a 1:1 ratio for the use of dexamethasone-based elixir (10mL, 0.1mg/mL); or standard oral care, for OM prevention), observed that the dexamethasone-based elixir reduced the incidence and severity of OM.

Fernández-Sala et al. [25], using a mouthwash with dexamethasone as a treatment for OM patients, described that all patients experienced a significant reduction in the severity of the adverse effect after starting the dexamethasone mouthwash formulation.

Similarly, in a double-blind, placebo-controlled randomized trial where head and neck cancer patients were randomly assigned to receive 40mg/day of prednisone or placebo, a 15% reduction in total treatment time and a lesser weight loss compared to the prednisone group were observed. This finding suggests that corticosteroids used during radiation therapy may influence the reduction of clonogenic cells in the mucosa [19].

Kawashita et al. [4], evaluating the combination of pilocarpine hydrochloride and topical dexamethasone ointment, along with standard oral care, showed that the use of these treatments during radiotherapy significantly reduced the incidence of grade 3 oral mucositis. However, the topical use of dexamethasone was found to be less effective in patients undergoing chemoradiotherapy, disagreeing with previous studies suggesting that oral dexamethasone may reduce oral mucositis in patients treated with everolimus and exemestane.

Despite the majority of studies indicating a clinical benefit in using corticosteroids for preventing OM, the heterogeneity among the studies and different comparison groups make it difficult to find a common denominator. These findings were reflected in the meta-analysis, which showed that, in a global context, the use of corticosteroids does not bring significant clinical benefit when compared to different control groups. However, when administered systemically, there appears to be an improvement in the

Table 3. GRADE-pro Analysis of Certain of Evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
Nof studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticoids	Non corticoids	Relative (95% CI)	Absolute (95% CI)		
Oral mucositis incidence												
5	Randomised and non-randomised trials	Serious	Not serious	NOT serious	Very serious	All plausible residual confounding would reduce the demonstrated effect dose response gradient	128/316 (40.5%)	155/272 (57.0%)	RR 0.77 (0.59 to 1.01)	RR 0.77 (0.59 to 1.01)	Moderate	IMPORTANT
Oral mucositis severity												
4	Randomised and non-randomised trials	serious	Serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	264	263	-	SMD 0.05 SD higher (0.12 lower to 0.22 higher)	Moderate	IMPORTANT

CI, confidence interval; RR, risk ratio; SMD, standardised mean difference

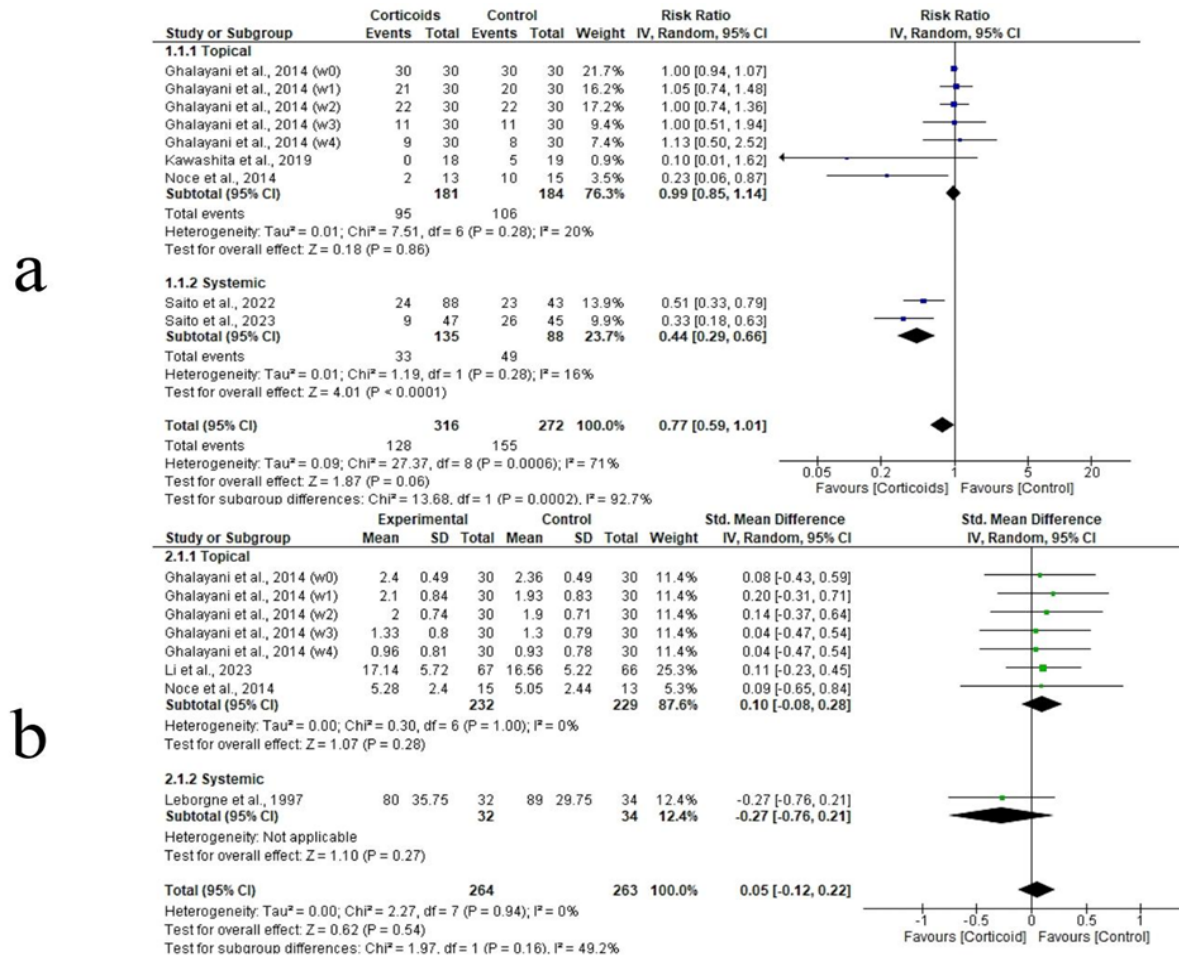

Figure 4. Forest Plot (a and b)

clinical condition of patients with OM.

When it comes to systemic administration, the two studies conducted using high doses of oral dexamethasone compared to low doses, in which breast cancer patients undergoing chemotherapy with anthracyclines had a lower incidence of oral mucositis (27.3%) when receiving higher doses of dexamethasone (9.9mg on day 1 and 8mg orally on days 2 to 4), compared to those who received lower doses (53.5%) [10]. Similar results were documented by the same group in 2023 when they evaluated patients on docetaxel regimens, showing a lower incidence of oral mucositis in the high-dose group (19.2%) compared to the low-dose dexamethasone group (57.8%). Such findings suggest a beneficial relationship between higher doses of dexamethasone and the reduction of oral mucositis in this patient subgroup.

Thus, it seems that systemic administration of corticosteroids reduces the inflammatory events responsible for the development of OM, especially when chemotherapy involves anthracyclines, while there is still no standard for topical application in patients with head and neck tumors. In Wistar rats subjected to oral mucositis models with 5-Fluorouracil, the use of dexamethasone topically exhibited characteristics consistent with the

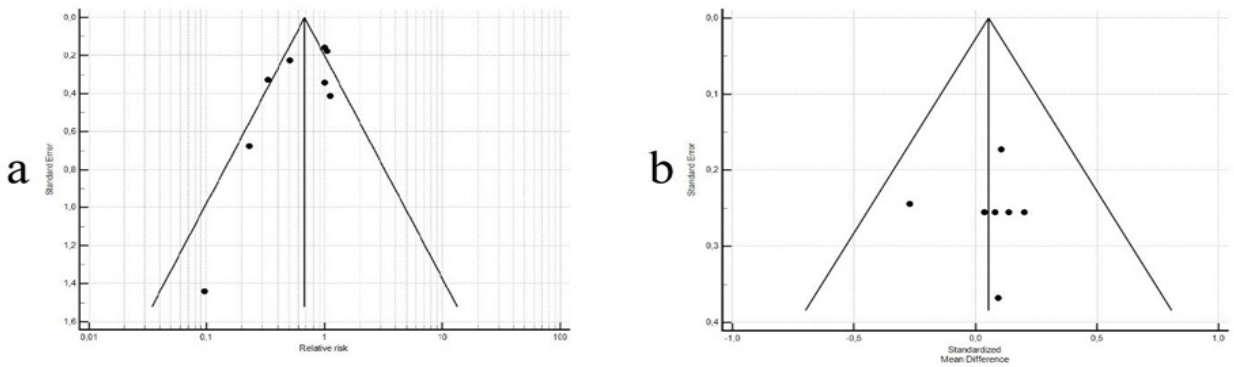

Figure 5. a, Begg test; b, Egger test

healing phase of mucositis and high efficacy in controlling this condition [26]. Corticosteroids administered topically have been shown to prophylactically reduce the incidence and severity of oral mucositis in patients who have undergone the use of drugs such as exemestane and everolimus [27].

As a limitation of the present study, we can mention that several included studies are from the same research group, especially the trials with systemic corticosteroids, which may reduce external generalizability. Furthermore, the heterogeneity of the studied formulations and corticosteroid formulations used is observed; additionally, new corticosteroid formulations, such as nanoparticulates and combination administration, were not evaluated; the vast majority were low-potency corticosteroids. However, when considering the control group as non-use of corticosteroids, use of low doses of corticosteroids, and corticosteroids of low potency, there is naturally an increase in the heterogeneity of the results. Additionally, the studies do not consistently and standardizedly assess the grades of mucositis, and oral use has a potential that needs to be further explored, leading to moderate to high RoB analysis, thus reducing the quality of GRADE and its strength of recommendation.

In conclusion, despite the described limitations, controlling the inflammatory process with corticosteroids appears to be a promising low-cost approach in managing OM. High doses of systemic corticosteroids show some clinical benefit in controlling OM, and topical use needs to be further explored with high-potency drugs (such as clobetasol) and good bioavailability in designs with adequate control groups to arrive at a formulation with appropriate concentrations for OM control.

Author Contribution Statement

Paulo Goberlânio de Barros Silva: Analysis of bioestathitics. Ana Beatriz Silva Marques Araújo: Carried acquisition of data, wrote the article and were responsible analysis and interpretation of data. Jennifer Vianna Barbosa: Were responsible analysis and interpretation of data. Giulianna Aparecida Vieira Barreto: Carried acquisition of data and wrote the article. Gabriella Julião Alves Costa: Were responsible analysis and interpretation of data. Marcela Maria Fontes Borges: Was responsible for critical revision of the manuscript for important intellectual content, review text and writing of the paper. Cássia Emmanuela Nóbrega Malta: Elaborated the concept and design of the study, revised the text and read and approved the final version.

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Conflicts of interest

The authors have no conflicts of interest.

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