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REVIEW ARTICLE

Topical interventions to prevent acute radiation dermatitis in head and neck cancer patients: a systematic review

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Abstract
Purpose The purpose of the study is to evaluate the effects of pharmacological and non-pharmacological topical controls in the prevention of radiation dermatitis.
Methods Relevant clinical trials were identified through electronic searching databases CINAHL, CENTRAL, LILACS, PubMed, Scopus, and Web of Science. Handsearching and gray literature searches were also performed to find additional references. Primary outcomes of interest were the development of radiation dermatitis and the time of occurrence of radiation dermatitis.
Results Thirteen randomized clinical trials were included in this review. The trials were published in Chinese, English, or French, from 1980 to 2015. Pharmacological interventions used in the trials were trolamine, *aloe vera*, allantoin, Lianbai liquid, sucralfate, Na-sucrose octasulfate, olive oil, hialuronic acid, and dexpanthenol. Non-pharmacological topical controls were usual care/institution routine, aqueous cream, mild soap, water thermal gel, placebo, and no intervention.
Conclusions There was no strong evidence that indicates differences between topical pharmacological interventions or non-pharmacological topical controls in the prevention of acute radiation dermatitis among patients with head and neck cancer undergoing radiotherapy.

Keywords Radiodermatitis · Head and neck cancer · Skin care · Radiotherapy

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Introduction

Acute radiation dermatitis is a radiation that induces injury to the epithelium and underlying structures of the skin, characterized by erythema, dry or moist desquamation, and even ulceration [1, 2]. Its onset commonly occurs within 2–3 weeks following the radiotherapy commencement [2], and it is usually observed at skin dose levels of 20–40 Gy [3]. About 80–90% of all patients with head and neck cancer undergoing radiotherapy develop radiation dermatitis [3], whereas severe skin reactions occur in approximately 25% of these patients [4].

Several factors may potentially affect skin toxicity. Radiotherapy-related factors such as total dose, fractionation, radiation energy, volume of treated regions [5], treatment duration, boost application, and treatment site have been suggested [3]. Patient-related factors depend on age, comorbid conditions, skin phototype, and genetic predisposition [5]. Furthermore, the combination of radiotherapy and chemotherapy increases skin reactions, resulting in severe xerosis, inflammation, skin thinning, and necrosis of the upper dermis and epidermis [6]. Patients with head and neck cancer are commonly treated with radical radiotherapy or chemoradiotherapy [7], which increases the likelihood to have exacerbated acute skin toxicity [5, 7].

Radiotherapy side effects tend to have early onset. Although mostly mild, they can become severe and significantly impair quality of life [6]. These reactions may lead to dose reduction or discontinuation of therapy, which, in turn, could be detrimental to the treatment outcome [6], particularly in head and neck cancer patients [8]. There is no evidence-based standard approach for the prevention and treatment of radiation dermatitis, although several medications have been proposed such as topical agents, dressings, and radioprotectors [5].

Previous systematic reviews have evaluated the prevention of radiation dermatitis in several irradiated areas, either simultaneously or separately [9–15]. However, to the best of our knowledge, no review has specifically assessed the use of topical interventions in the prevention of acute radiation dermatitis in head and neck cancer patients. Therefore, the main goal of this systematic review was to answer the focused question "*In patients undergoing radiotherapy for head and neck cancer, what is the effect of pharmacological topical interventions compared to non-pharmacological topical controls in the prevention of acute radiation dermatitis?*"

Material and methods

The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist [16].

Protocol and registration

The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) [17], registration number CRD42015020823.

Terminology definition

Prevention of acute radiation dermatitis was defined as to prevent a reaction from occurring (yes or no) [18] and prevention of grades 1 (erythema and dry desquamation) and 2 (bright erythema and moist desquamation) according to the Radiation Therapy Oncology Group (RTOG) criteria of acute radiation dermatitis or to the Common Terminology Criteria for Adverse Events (CTCAE) criteria for dermatitis radiation [19, 20]. Pharmacological topical interventions were considered as products that contain both the active ingredient and the vehicle, whereas non-pharmacological topical controls were considered as those that contain only the vehicle (or base) or it is placebo/usual care/no medication [21].

Eligibility criteria

Only original prospective studies in which the objective was to investigate the effects of the use of pharmacological topical interventions (compared to non-pharmacological topical controls) in the prevention of acute radiation dermatitis in patients with head and neck cancer undergoing external beam radiotherapy were included. Studies that compared topical interventions and used prevention of acute radiation dermatitis as an outcome were eligible. There were no restrictions to the year of publication or language of the study. Age of the participants, gender, previous or concurrent therapies, health status, or dosage of treatment were also not restricted.

Studies were excluded for the following reasons: (1) cobalt therapy; (2) studies that compared exclusively non-topical interventions; (3) therapeutic and not preventive interventions; (4) studies that compared two or more products containing active ingredient; (5) insufficient data on the effect of the intervention; and (6) reviews, letters, conference abstracts, personal opinions, book chapter, retrospective study, descriptive study, case reports, or cases series.

Information sources and search strategy

Studies were identified using a search strategy adapted for each electronic database, with the aid of a health sciences librarian: CINAHL EBSCO, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, PubMed, SCOPUS, and Web of Science (Appendix 1). The hand search was performed on the reference lists from the selected articles for any additional references that might have been missed in the electronic search. In addition, a gray literature search was

performed using Google Scholar and ProQuest Dissertations and Theses databases.

After obtaining all references, duplicates were excluded by using appropriate software (EndNoteBasic®, Thomson Reuters, USA). All the electronic database searches were conducted on March 27, 2016.

Study selection

Study selection was conducted in two phases. In phase 1, two investigators (E.B.F. and P.E.D.R.) independently screened the titles and abstracts of potentially relevant studies and selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, the same reviewers independently read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. Any disagreements, either in the first or second phases, were resolved by discussion and mutual agreement between the two reviewers. In case a consensus could not be reached, a third author (C.I.V.) was involved to make a final decision. Studies that were excluded after full-text assessment and the reasons for their exclusion are listed in Appendix 2.

Data collection process and items

Two investigators (E.B.F. and P.E.D.R.) independently collected the data from the selected articles: study characteristics (author(s), year of publication, setting, objectives, methods), population characteristics (sample size, age), intervention characteristics (groups, follow-up period, primary outcomes, radiation dermatitis criteria, and statistical analysis), and outcome characteristics (results and main conclusion). The third author (C.I.V.) cross-checked all the retrieved information to make a final decision. If the required data were not complete, attempts were made to contact the authors to retrieve any pertinent missing information.

Risk of bias in individual studies

To assess the risk of bias of the included randomized controlled trials (RCT), it was applied the Cochrane Collaboration Risk of Bias Tool [22], including judgments about the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias was assessed as low, high, or unclear. Two investigators performed this process independently (E.B.F. and P.E.D.R.). Disagreements between the two reviewers were resolved by a third investigator (C.I.V.).

Summary measures

The primary outcome was the development of grades 1 and 2 according to the RTOG criteria for radiation dermatitis. Further measurements considered in this review were odds ratios (OR) or risk differences for dichotomous outcomes.

Synthesis of results

The overall data combination of the included studies was performed by a descriptive synthesis. Statistical pooling of data using meta-analysis was planned whenever trials were considered combinable and relatively homogeneous in relation to design, interventions, and outcomes. Heterogeneity within studies was evaluated either by considering clinical (differences about participants, type of interventions, and results), methodological (design and risk of bias), and statistical characteristics (effect of studies).

Risk of bias across studies

The quality of evidence and grading of strength of recommendations were assessed using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) [23, 24]. The criteria for this assessment were study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. The quality of evidence must be characterized as high, moderate, low, or very low [24].

Results

Study selection

In phase 1 of study selection, 1257 citations were identified across six electronic databases. After the duplicated articles were removed, 972 citations remained. The results from gray literature added 44 references. A thorough screening of the abstracts was completed, and 992 references were excluded. Hand search from the reference lists of the identified studies yielded no additional studies. Thus, 24 articles remained for a full-text screening (phase 2). This process led to the exclusion of 11 studies (Appendix 2). In total, 13 articles [25–37] were selected for data extraction and qualitative synthesis (Table 1). Figure 1 (flowchart) details the process of identification, inclusion, and exclusion of studies with reasons.

Study characteristics

Table 1 summarizes the descriptive characteristics of the studies. The studies were published in Chinese [35], English [25–34, 37], and French [36], from 1980 to 2015. All selected articles were prospective clinical trials.

Table 1 Summary of descriptive characteristics of included articles

Study characteristics			Population characteristics		Intervention characteristics
Author, year, country[a]	Study design	Objective	Total *n* (H&N)	Age mean/range (years)	Intervention (*n*)
Abbas and Bensadoun 2011 [25] Egypt	RCT	To compare trolamine with usual care for patients with head and neck cancer undergoing radiation therapy with concurrent chemotherapy	30	54.5	Trolamine emulsion (15)
Chan et al. 2014 [26] Australia	RCT	To investigate the effects of a natural oil-based emulsion containing allantoin versus aqueous cream for preventing and managing RD skin reactions	65	Cream 1 60.03 Cream 2 60.74	Cream 1 NOCA (33)
Cui et al. 2015 [27] China	RCT	To evaluate the effectiveness of topical olive oil in the prevention of acute radiation dermatitis in patients with nasopharyngeal carcinoma who were undergoing concurrent chemoradiotherapy	94	Group 1 56.3 ± 4.9 Control group 55.5 ± 7.6	Olive oil (47)
Elliot et al. 2006 [28] Canada	RCT	To compare trolamine emulsion, as a prophylactic agent and as an interventional agent, with declared institutional preference in reducing the incidence of higher grade RD	331[b]	59.0	Trolamine emulsion (initial *n* = 166, final *n* = 163)
Evensen et al. 2001 [29] Norway	Self-controlled clinical trial	To evaluate the protective effect of Na-SOS gel on RD skin damage in head and neck cancer	60	60/21–81	Na-SOS gel (60)
Haddad et al. 2013 [30] Iran	Self-controlled clinical trial	To evaluate an *aloe vera* lotion for prevention of RD	13	52/21–78	Aloe vera lotion (13)
Liguori et al. 1997 [31] Switzerland	RCT	To analyze whether the prophylactic use of a cream with hyaluronic acid postpones the first signs of acute RD and/or reduces its severity	90	Ialugen 59.9/33–89 Placebo 55.7/24–82	Hyaluronic acid 0.2% cream (Ialugen®) (42)
Løkkevik et al. 1996 [32] Norway	Self-controlled clinical trial	To compare Bepanthen cream with no topical ointment at all	16	69/51–85	Dexpanthenol cream Bepanthen® Roche (16)
Ma et al. 2007 [33] China	RCT	To observe the effect of Lianbai liquid in prevention and treatment of acute RD	24	Lianbai liquid 43/24–75 Usual care 39/18–71	Lianbai liquid (14)
Olsen et al. 2001 [34] USA	RCT	To determine whether the use of mild soap and aloe vera gel versus mild soap alone would decrease the incidence of skin reactions in patients undergoing radiation therapy	30	56/18–84	Aloe vera gel + soap (13)
Ren et al. 2005 [35] China	RCT	To evaluate trolamine cream in the prevention and treatment of RD	74[b]	43	Trolamine (37)
Ribet et al. 2008 [36] France	RCT	To evaluate the efficacy and tolerance ATSW gel versus trolamine cream in the prevention of RD	8	57.9	Trolamine cream[d] (34)
Wells et al. 2004 [37] Scotland	RCT	To examine the effect of aqueous cream, sucralfate cream, and no cream, on the development of and discomfort associated with RD during radical radiotherapy	103	–	Sucralfate cream (34)

Study characteristics	Intervention characteristics				
Author, year, country[a]	Control (*n*)	Follow-up period (months)	Primary outcomes	RD criteria	Statistical analysis
Abbas and Bensadoun 2011 [25] Egypt	Usual care (15)	15	Development of mild RD (grades 1 and 2 or higher)	RTOG Acute Radiation Toxicity Criteria	Chi-squared test χ^2 Pearson
Chan et al. 2014 [26] Australia	Cream 2 Aqueous cream (32)	7	Severity of RD	CTCAE 4.0	X^2 test; *t* test; Kaplan-Meier with t he log-rank test. IC 95% univariate logistic regression/multivariate logistic regression
Cui et al. 2015 [27] China	Placebo (47)	17	Occurrence of primary signs of RD	RTOG	Chi-squared tests multivariate analyses *t* tests

Table 1 (continued)

Study characteristics	Intervention characteristics				
Author, year, country[a]	Control (*n*)	Follow-up period (months)	Primary outcomes	RD criteria	Statistical analysis
Elliot et al. 2006 [28] Canada	Institutional preference (initial *n* = 165, final *n* = 159)	19	Development of RD for grade 2 or higher	NCI/CTC version 2.0 ONS toxicity scoring system	χ^2 test AUC
Evensen et al. 2001 [29] Norway	Placebo (60)	34	Development of erythema and desquamation	Expansion of the EORTC/RTOG acute skin reaction scoring system	AUC; Wilcoxon's signed rank test
Haddad et al. 2013 [30] Iran	No medication (13)	–	Development of RD	RTOG Acute Radiation Toxicity Criteria	Not mentioned
Liguori et al. 1997 [31] Switzerland	Placebo creams (48)	20	Development of RD	0, normal skin; 1, light epidermal irritation; 2, erythema with dry desquamation; 3, exudate < 50%; 4, exudate > 50%; 5, ulcer	Student's *t* test or Pearson chi-squared test; Wilcoxon test (intra-group variation)
Løkkevik et al. 1996 [32] Norway	No topical ointment (16)	–	Development of RD between each side	Expansion of the EORTC/RTOG acute skin reaction scoring system	Wilcoxon's signed rank test; logistic regression
Ma et al. 2007 [33] China	Usual care (10)	68	Development of RD for grades 1, 2, and 3	NCI-CTC. version 2.0	Pearson's chi-squared test
Olsen et al. 2001 [34] USA	Mild soap (17)	–	Development of skin reaction	RTOG	Kaplan and Meier's; log-rank test; chi-squared and *t* test
Ren et al. 2005 [35] China	No intervention (37)	26	Development of RD	NCI CTC version 2.0	χ^2 test
Ribet et al. 2008 [36] France	Avène termal spring water anti-burning gel (ATSW gel)[d] (35)	–	Development of primary signs of RD	NCI	Student's *t* test; Mann-Whitney; chi-squared test (or Fisher); Kaplan-Meier
Wells et al. 2004 [37] Scotland	Aqueous cream (34) No cream (35)	24	Development of RD	Modified RTOG	IC 95%

3D-CRT 3D conformal radiation therapy, *NOCA* natural oil-based emulsion containing allantoin, *RCT* randomized controlled trial, *RD* radiation dermatitis, *RTOG* Radiation Therapy Oncology Group, *AUC* area under curve, *Na-SOS* Na-sucrose octasulfate, *NCI* National Cancer Institute, *CTC* Common Toxicity Criteria, *CTCAE* Common Terminology Criteria for Adverse Events, *ONS* Oncology Nursing Society, *H&N* head and neck, *PG* preventive group, *CG* control group

[a] Country of the study coordinator

[b] Sample size without therapeutic group

[c] Institutional preference was gel, cream, and Aquaphor. Corticosteroid was applied for grade 2 or greater radiation dermatitis

[d] The groups were changed in the present review. In the original article, the authors considered trolamine as control group and Avene as prevention group

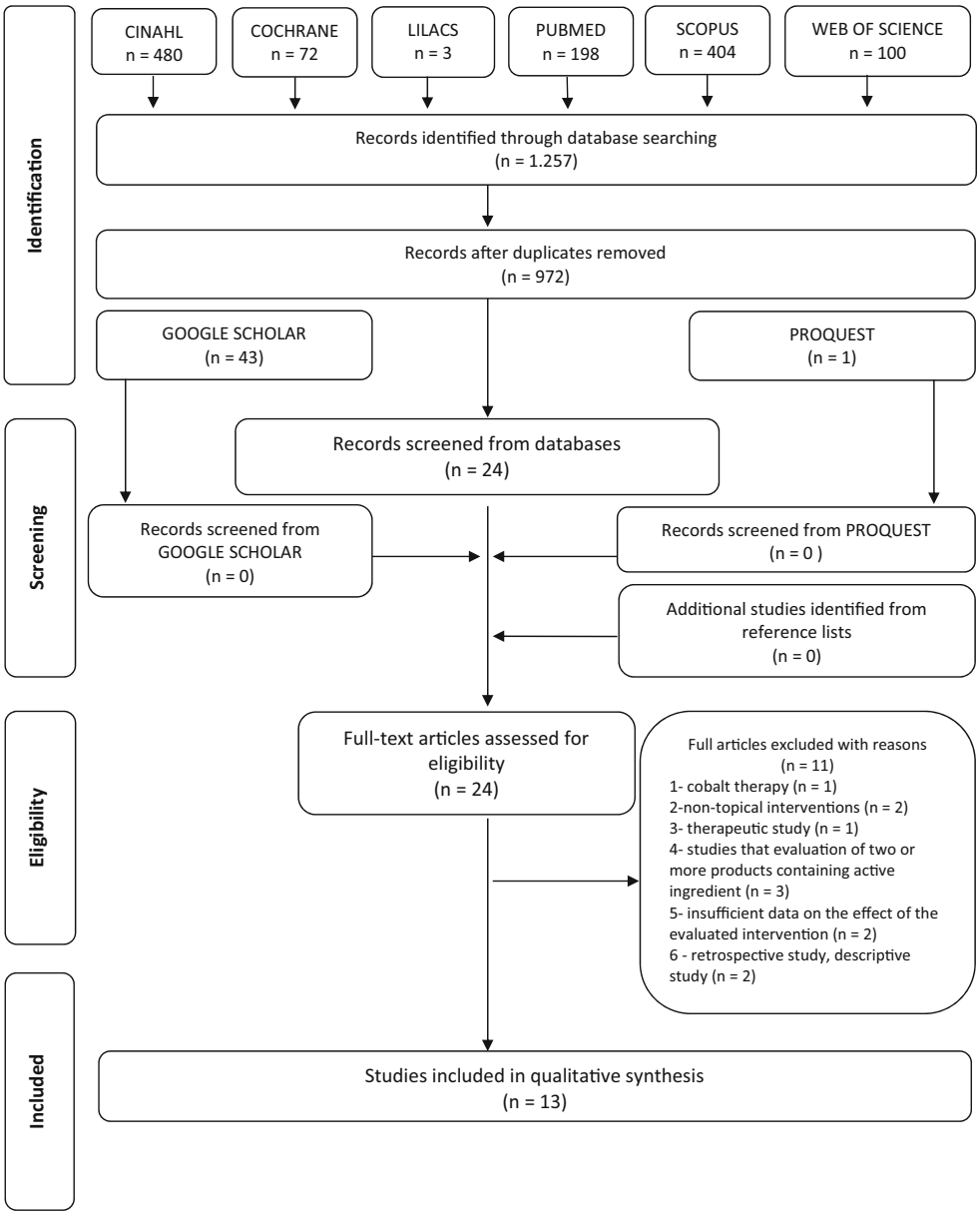

Fig. 1 Flow diagram of literature search and selection process (adapted from PRISMA)

[1]Adapted from PRISMA.

The follow-up period was mentioned in 9 out of the 13 studies (mean 25.5 months, range 7–68 months). With regard to the radiation dose received by the participants, four studies indicated minimal doses <50 Gy, and of these, two presented the dose averages, as follows: 59.7 Gy [29] and 54 Gy [30]. The ionizing radiation doses applied to patients are described in Fig. 2.

Seven studies included patients who also underwent concurrent chemotherapy [25–28, 30, 34, 37]. The chemotherapy protocol was specified in only two studies: cisplatin 40 mg/m^2 weekly [25] and cisplatin 25–30 mg/m^2 and docetaxel 25–30 mg/m^2 [27]. Exclusive RT has been reported in two studies [32, 36]. The remaining four studies did not mention the use of chemoradiotherapy [29, 31, 33, 35].

Most studies evaluated trolamine [25, 28, 35, 36] as active principle to prevent radiation dermatitis and *aloe vera* [30, 34]. Other pharmacological interventions were allantoin [26], olive oil [27], Lianbai liquid [33], sucralfate [37], Na-sucrose octasulfate (Na-SOS) [29], hialuronic acid [31], and dexpanthenol [32]. Non-pharmacological topical controls were usual care/institution routine [25, 28, 33], aqueous cream [26, 37], mild soap [34], water thermal gel [35], placebo [27, 29, 31], and no intervention [30, 32, 35].

Eight of the selected studies (61%) included heterogeneous samples of patients with different cancer types and irradiated areas: breast, lung, pelvis, and anorectal cancer.

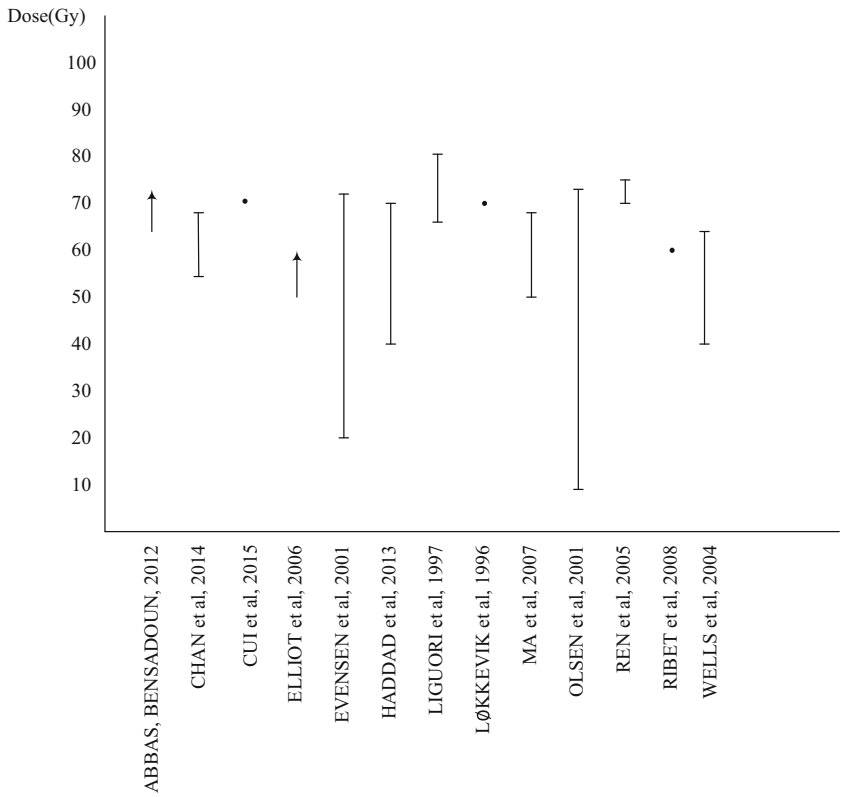

Fig. 2 Ionizing radiation doses applied to patients in the included studies

Risk of bias within studies

In this review, it was considered uncertain/unclear when those criteria were not clearly reported in the original study, with incomplete or missing information. This situation occurred in 8 (61.5%) and 10 (76.9%) of the included studies on the domains "*random sequence generation*" and "*allocation concealment*," respectively.

For the domain "*blinding of participants and personnel*," while there was an understanding that blinding of participants would not be feasible, for comparing different interventions not possible to blind and/or understanding that his absence would not alter the degree of radiation dermatitis, it was judged as *low* risk of bias. However, for the self-controlled studies in which the patients themselves chose the product application side or the information on the randomization was unclear [30, 32] and those in which the authors themselves concluded that lack of blinding could have caused bias [28], the risk was rated *high*.

The domain "*incomplete outcome data*" showed predominantly low risk of bias in the evaluation of the studies (10 studies; 76.9%). This was the best result found for one single domain.

Five studies were classified as *high risk of bias* because they contained one or more compromised domains regarding the reliability of results [28–30, 32, 36]. Five studies were classified as *uncertain risk of bias* [25, 27, 33–35]. Two of them received positive bias ratings, with low risk of bias in 91% of the evaluated domains [31, 37]. Only one study presented *low risk of bias* in all domains evaluated [26], allowing us to ascribe the results of the study as of increased reliability. Risk of bias assessment is reported in Fig. 3.

Results of individual studies

The studies used different types of interventions to prevent radiation dermatitis and reported different results for all 13 articles. Characteristics and results of the included studies are listed in Table 1.

Synthesis of results

First of all, the 13 selected studies were analyzed by a descriptive synthesis.

Corticosteroids and non-steroidal anti-inflammatory drugs were administered to manage more severe levels of radiation dermatitis in some studies [28, 34]. Thus, given the inclusion and exclusion criteria of the current review, the graduations controlled by medications such as corticosteroids and non-steroidal anti-inflammatory drugs were excluded from the analysis.

Regarding the rating scales, 30.7% used the RTOG scale [25, 30, 34], 30.7% used National Cancer Institute Common Toxicity Criteria (NCI-CTC) [28, 33, 35, 36], 23% used

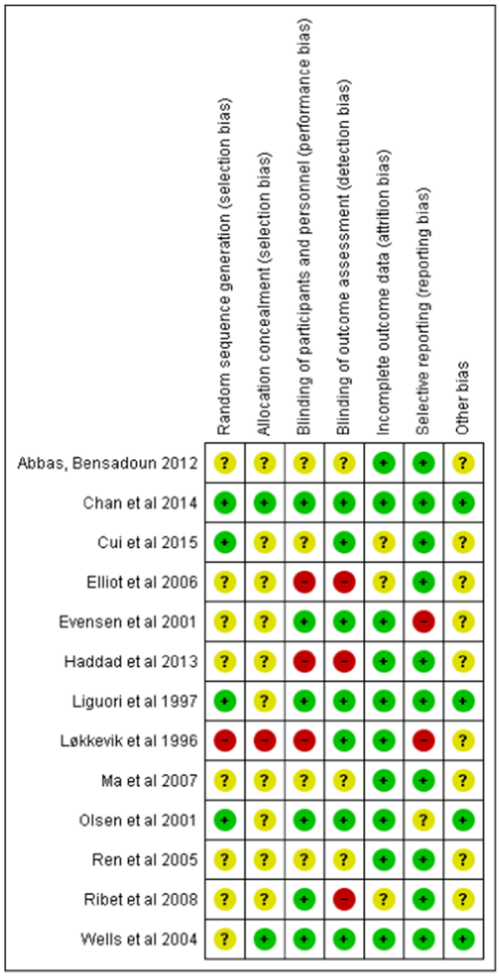

Fig. 3 Risk of bias assessment for individual studies. *Question marks* mean unclear; *plus signs* mean yes; *minus signs* mean no

expanded or modified scale RTOG [29, 32, 37], 7.7% used CTCAE version 4.0 [26], and, finally, 7.7% used a scale described in the study itself [31]. One study used both NCI-CTC and ONS scales to assess the skin reactions of their patients [28].

Taking into consideration the similarity between grades 1 and 2 of both the NCI-CTC and the RTOG grading systems, the NCI-CTC grades 1 and 2 were reclassified as RTOG grades 1 and 2 for the two studies using NCI-CTC [28, 35].

In one study [28], where institutional care included hydrocortisone treatment of patients with grade 2 and above, only patients with grade 1 were included in the analysis for this review.

At the assessment of heterogeneity, some studies represented data for patients with cancers in other areas than the head and neck region [26, 29–33, 35, 36].

The studies selected for this review were considered to be relatively homogeneous, however, showed some heterogeneous points, as the interventions, controls, assessment tools of radiation dermatitis, and outcomes assessed, which influenced the quantitative analysis of data extracted from studies. Thus, there were no data that would allow a meta-analysis.

Risk of bias across studies

Overall, the quality of the evidence from the outcomes evaluated by the GRADE system was assessed as moderate (Table 2), suggesting moderate confidence in the estimated effect from the outcomes assessed. The limitations in the studies, inconsistency, and important indirect evidence were the main factors responsible for the limited quality of the evidence from studies evaluated.

Discussion

Cancer of the head and neck is relatively common. The term "head and neck cancer" comprises a large number of neoplasms from the mucosa of the upper aerodigestive tract including the oral cavity, pharynx, larynx, and sinuses [38]. Among all subtypes, carcinoma of the mouth and pharynx together rank as the sixth most common neoplasm [39]. Surgery, radiotherapy, and concurrent chemoradiotherapy have been used to manage head and neck cancer [40, 41]. This systematic review investigated evidence to evaluate the

Table 2 GRADE assessment

Quality assessment							
Studies (*n*)	Type of study	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE quality
Outcome: acute radiation dermatitis grades 1 and 2, according score RTOG							
6	RCT/self-controlled	X[a]	X[b]	X[c]	√	√	++—— Moderate

[a] Absence of blinding of participants and examiners in the study or uncertainty regarding its implementation and/or uncertainty about the process of randomization and blinding of the random allocation of the sample due to insufficient data

[b] Heterogeneity

[c] Divergence between the data presented in the study protocol and the data presented as results of the individual outcomes (e.g., absence of a specific ranking for scale previously defined)

effects of pharmacological interventions and non-pharmacological topical controls to prevent radiation dermatitis in head and neck cancer patients.

To our knowledge, this is the first systematic review of topical interventions for the prevention of acute radiation dermatitis in patients with head and neck cancer undergoing radiotherapy. We sought to comply the criteria of AMSTAR [42] in order to increase its reliability.

The studies showed differences in baseline characteristics collected from patients and between scales used to classify radiation dermatitis. The ionizing radiation dose prescribed to patients was not described in a uniform way between studies, varying from total dose, medium dose, and dose intervals.

Delivering chemotherapy concurrently with radiation increases the severity of radiation dermatitis. However, some studies do not present this information clearly [29, 31, 33, 35], making it difficult for comparisons among subgroups who received only radiotherapy or chemoradiotherapy. Not all studies described the type of chemotherapy used, which is important as cetuximab caused more severe skin reactions than cisplatin.

This systematic review aimed to analyze studies that evaluated the effect of various topical pharmacological interventions to prevent grades 1 and 2 of radiation dermatitis according to RTOG criteria in head and neck cancer patients. There was no difference between groups of pharmacological and non-pharmacological topical controls for prevention of acute radiation dermatitis; however, vehicles or bases that do not contain the active ingredient in a formulation might have clinical relevance.

A review about topical interventions for radiation dermatitis in patients with breast cancer emphasizes the relevance of creams in reducing adverse effect and the low cost of the intervention [43]. Lotions, powders, creams, ointments, gel, and other bases are examples of vehicles for topical products. Both the vehicle and the active ingredient have action on the cutaneous response to treatment. The application time product topical is another important factor. The preferable application of the product was overnight allowing the product to remain on the skin for a longer period [21].

The usual care to prevent radiation dermatitis is also considered as a non-pharmacological care. The guidelines include hygiene orientation site, reduction of exposure and friction of the irradiated area, use of appropriate clothing, preferably cotton, avoid sun exposure and contact with extreme temperatures, as compresses, avoid itching the irradiated area, and avoid using products that have strong agents in their composition, as some types of soaps [25, 33]. In the latter case, the option is at neutral soap [34]. Usual care and skin cleaning of irradiated area are consistent with other reviews that say that skin washing is important for the prevention of acute radiation dermatitis [9]. Product selection should also take into account the cost-effectiveness and ability to understand the patient, family, and caregivers.

To evaluate the radiation dermatitis, the criteria adopted by the main scales consist of visual measurements of signals as erythema and scaling, like the RTOG scale, modified RTOG scale, and CTCAE. A limitation of these scales is the subjectivity that can occur in radiation dermatitis classification related to own evaluator [44], leading to a significant bias when it comes to the evaluation of radiation dermatitis in multicenter studies [28].

It is important that the studies follow rigorous methodological standards. The RCTs must have to be conducted properly. The Standard Protocol Items: Recommendations for Interventional Studies (SPIRIT) [45] statements can assist in the study plan.

We recommend that in future studies, the randomization be stratified on the radiotherapy dose, so that the intervention and control groups are balanced regarding the radiotherapy fraction. There is also a need to clarify what type of chemotherapy was used concomitant to radiotherapy. Time and duration of product apply are a relevant item to describe in the methodology section of the studies. It is also important to have a definition about what is the prevention endpoint, for example, it can be the occurrence of RD (yes or not) or it can be the development of erythema, dry or moist desquamation, and edema, which are signs of RD, generally described in some graduation scales. None of the studies included in this review took pictures to evaluate RD, but it can be a good strategy to evaluate the progression or regression of the signs of RD.

Conclusion

There was no strong evidence indicating differences between topical pharmacological interventions and non-pharmacological topical controls related to the prevention of acute radiation dermatitis among patients with head and neck cancer undergoing radiotherapy.

Patients with head and neck cancer are usually more susceptible to develop radiation dermatitis because they are commonly exposed to high doses of radiation and combined treatment. An effort is needed in conducting studies with appropriate methodological rigor and to evaluate topical interventions with homogeneous samples.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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