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Use of trolamine to prevent and treat acute radiation dermatitis: a systematic review and meta-analysis

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Trabalho de Conclusão de Curso (TCC) apresentado como requisito para aprovação na disciplina TCC 2 do Curso de Graduação em Enfermagem da Universidade de Brasília.

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Use of trolamine to prevent and treat acute radiation dermatitis: a systematic review and meta-analysis

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Abstract

Objective: to evaluate the effects of trolamine in the prevention or treatment of radiation dermatitis. **Method:** systematic review and meta-analysis. Detailed individual search strategies for Cinahl, Cochrane Library Central, LILACS, PubMed, and Web of Science were developed, in January 2016. Hand searching was also performed to find additional references. A grey literature search was taken by using Google Scholar. Two researchers independently read the titles and abstracts from every cross-reference. The risk of bias of the included studies was analysed by the Cochrane Collaboration Risk of Bias Tool. The quality of evidence and grading of strength of recommendations was assessed using Grades of Recommendation, Assessment, Development and Evaluation (GRADE). **Results:** seven controlled clinical trials were identified in this study. The controls used were calendula, placebo, institutional preference / usual care, Aquaphor®, RadiaCare™, and Lipiderm™. The studies were pooled using frequency of events and risk ratio (RR) with 95% confidence intervals, in subgroups according to radiation dermatitis graduation. **Conclusion:** Based on the studies included in this review, trolamine cannot be considered as a standardized product to prevent or treat radiation dermatitis in patients with breast and head and neck cancer.

Descritores: Revisão; Radiodermatite; Higiene da Pele; Radioterapia, Enfermagem.

Descriptors: Review; Radiodermatitis; Skin Care; Radiotherapy; Nursing.

Descriptors: Revisión; Radiodermatitis; Cuidados de la Piel; Radioterapia, Enfermería.

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Introduction

The most common effect of the radiotherapy is radiation dermatitis, which has greater impact in patients with head and neck and breast cancer[1]. About 80 to 90% of these patients treated by radiotherapy experience radiation dermatitis during treatment[2,3].

The skin is an organ with high radiosensitivity and susceptible to damage by radiotherapy due to rapid cell proliferation and maturation. The epidermis loses a percentage of their basal cell exposure beginning at the first fractionated dose of radiotherapy, and the repeated exposure of the subsequent fractions leads to continuous cell destruction, which avoid tissue repair[4].

Although the skin damage starts after the first exposure to radiation, the clinical signs are often present from the second week of radiotherapy. They are characterized by mild erythema, which can develop to dry or moist desquamation, and ulcerations in some cases[5,6].

Acute skin reactions generate local discomfort, itching, and varied degrees of pain that impact the quality of life of patients, affect the therapeutic efficacy, and the planning of radiotherapy, considering that severe intensity lesions can cause interruption of treatment[1,7].

Trolamine has been indicated to prevent and treat radiation dermatitis but to the best of our knowledge, there is no systematic review that evaluated the trolamine as a potential topical product to manage skin reactions due to radiotherapy.

Background

Skin reactions may be intensified according to the treatment plan received as full high dose, fractional high dose, and the extension of the irradiated area. Chemotherapy and patient related factors as age, skin color, smoking habits, and obesity also aggravate the skin reactions[6,8].

Topical products are commonly used as alternative to manage skin reactions due to radiotherapy, although there is insufficient evidence regarding to skin care products for the prevention or treatment of radiation dermatitis[6].

Topical application of emulsions containing trolamine is used in clinical practice for more than three decades ago in Europe and in the United States for the management of radiation dermatitis. The trolamine has the capacity for healing through the recruitment of macrophages to the wound, promoting the growth of granulation tissue[9]. Trolamine emulsion is a compound with properties similar to nonsteroidal anti-inflammatory and has been considered as a safety and tolerable topical intervention, with low potential to develop contact dermatitis. Trolamine promotes skin hydration, reduces discomfort and pain that contribute to the non-interruption of treatment[9].

The evidence and clinical observations demonstrate the advantages and disadvantages between trolamine and other topical products, including steroidal creams, non-steroidal anti-inflammatory compounds, and antihistamines[1,10].

The aim of this study is to systematically review the literature about the evidence of the trolamine compared to other topical products in the prevention and treatment of acute radiation dermatitis in cancer patients.

Method

Protocol and registration

The reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA Checklist[11]. The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42016032805[12].

Eligibility criteria

Only original prospective studies in which the objective was to investigate the effects of the use of trolamine as the only active ingredient (without associations) to prevent and treat acute radiation dermatitis compared to other topical products in cancer patients undergoing radiotherapy were eligible. Studies published in Portuguese, English, Spanish, and French were included. There were no restrictions to the year of publication. Age of the participants, sex, previous or concurrent therapies, health status or dosage of treatment was also not restricted.

Studies were excluded for the following reasons: 1. cobalt therapy; 2. studies that compared interventions only to chronic radiation dermatitis; 3. trolamine associated with others compounds; 4. trolamine compared with no topical products; 5. 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, and Web of Science. 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 grey literature search was performed using Google Scholar.

We used the following search terms to search PubMed and adapted the strategy for the other databases: ("biafine" OR "triethanolamine" OR "trolamine" OR "trolamine emulsion" OR "emulsion containing trolamine") AND ("radiodermatitis" OR "dermatitis" OR "radiation dermatitis" OR "radio-dermatitis" OR "skin damage" OR "skin toxicity" OR "skin reaction" OR

"skin injuries" OR "radiation reaction" OR "radio-epithelitis" OR "acute skin toxicity" OR "acute skin reaction" OR "acute dermatitis" OR "acute radiodermatitis" OR "acute cutaneous toxicity" OR "acute radiation dermatitis" OR "acute radiation reactions" OR "acute radiation-induced skin reactions" OR "radiation-induced acute skin" OR "radiation induced skin injuries" OR "radiation-induced skin reaction" OR "radiation induced dermatitis" OR "radio-induced damage" OR "radiotherapy-induced skin reactions" OR "radiation skin reactions" OR "radiation-induced skin injuries").

After obtaining all references, duplicates were excluded by using appropriate software (EndNoteBasic®, Thomson Reuters, USA). All the electronic database searches were conducted on January 18th, 2016.

Study selection

For phase of screening, and data extraction was used the ©Covidence (Web-based systematic review tool designed to facilitate the process).

Study selection was conducted in two phases. In phase 1, two investigators (A.G.M. and E.B.F.) 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 (P.E.D.R.) was involved to make a final decision. Studies that were excluded after full-text assessment and the reasons for their exclusion are listed in Figure 1.

Data collection process and items

Two investigators (A.G.M. and E.B.F.) independently collected the data from the selected articles: study characteristics (author(s), year of publication, setting, objectives, methods), population characteristics (sample size, age, irradiated area), intervention characteristics (groups, follow-up period, primary outcomes, radiation dermatitis criteria, and statistical analysis), and outcome characteristics (main results). The third author (P.E.D.R.) crosschecked 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[13], 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 (A.G.M. and E.B.F.). Disagreements between the 2 reviewers were resolved by a third investigator (P.E.D.R.).

Summary measures

The primary outcome was the development of different degree of radiation dermatitis or the reduction of the intensity/degree of reaction. Further measurements considered in this review were risk ratio (RR) 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 controls and results), methodological (design and risk of bias) and statistical (effect of studies) characteristics or by using I^2 statistical test. A value from 0 to 40% was considered of not important consistency, between 30 to 60% moderate heterogeneity, whereas 50 to 90% was considered to represent substantial heterogeneity [13].

The Cochrane Collaboration´s Review Manager® 5 (RevMan 5) was used to summarize the results by Mantel-Haenszel model. The results were presented with 95% confidence intervals (95% CI).

Risk of bias across studies

The quality of evidence and grading of strength of recommendations was assessed using Grades of Recommendation, Assessment, Development and Evaluation (GRADE)[14,15]. The criteria for this assessment were study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The quality of evidence must be characterized as high, moderate, low, or very low[15].

No Funnel plot was constructed to assess the possibility of publication bias because there were few trials per subgroups of meta-analysis.

Results

Study Selection

In phase 1 of study selection, 195 citations were identified across five electronic databases. After the duplicated articles were removed, 138 citations remained. No references from grey literature was added. A thorough screening of the titles and abstracts was completed and 126 references were excluded. Hand search from the reference lists of the identified studies yielded no additional studies. Thus, 12 articles remained for a full-text screening (phase 2). This process led to the exclusion of 5 studies (Figure 1). In total, 7 articles[16-22] were selected for data extraction and qualitative synthesis (Table 1). Figure 1 (flow chart) details the process of identification, inclusion, and exclusion of studies with reasons.

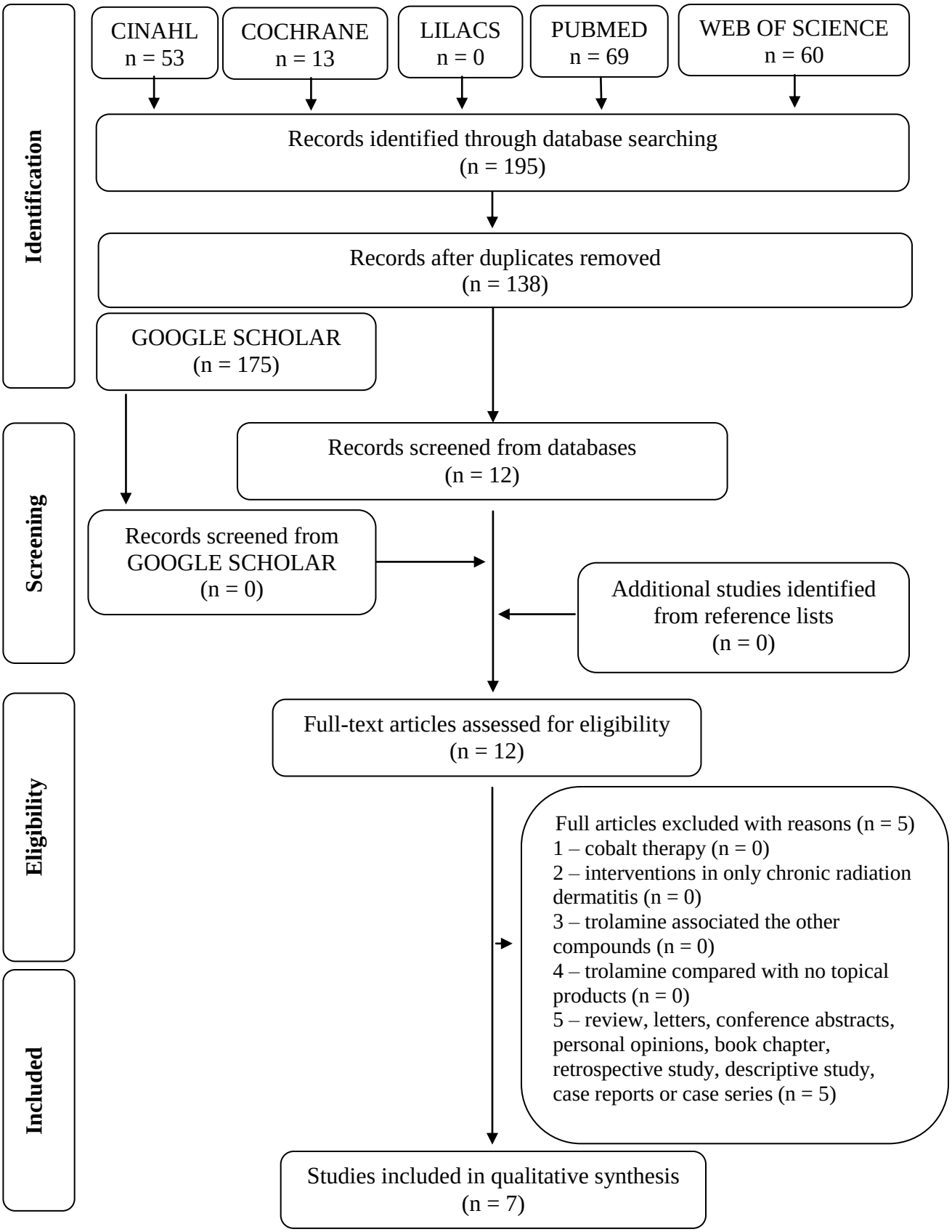

Figure 1 Flow diagram of literature search and selection process. Brasília, DF, Brazil, 2016.

Study characteristics

The studies were published in English[16-19,21,22] and French[20], from 2000 to 2012.

Two studies included patients who also underwent concurrent chemotherapy[19,22]. Radical radiotherapy has been reported in five studies[16-18,20,21]. The use of tamoxifen has been described in only one study, among those included patients with breast cancer[17].

Two studies[19,22] included only head and neck cancer patients, and four studies[16-18,21] included only breast cancer patients in the sample. Only one[20] of the selected studies included heterogeneous sample of patients with different cancer types and irradiated areas: breast and head and neck cancer.

All studies evaluated trolamine as intervention to prevent radiation dermatitis and only one evaluated trolamine as treatment[19]. The topical controls were usual care/institution routine[16,19,22], calendula[18], water thermal gel[20], placebo, Aquaphor®, RadiaCare™[21], Lipiderm and no intervention[17].

Table 1 summarizes the descriptive characteristics of the studies.

Table 1 – Summary of descriptive characteristics of included articles (n=7). Brasília, DF, Brazil, 2016.

STUDY CHARACTERISTICS		**POPULATION CHARACTERISTICS**		**INTERVENTION CHARACTERISTICS**					**OUTCOME CHARACTERISTICS**
Author, Year, Country	**Objective**	**Total *n* Irradiated area**	**Age Mean (years)**	**Intervention (*n*)**	**Control (*n*)**	**Follow-Up (months)**	**Primary outcomes**	**RD Criteria**	**Main Results**
Abbas, Bensadoun 2012[22] Egypt	To compare trolamine with usual care for patients with head and neck cancer undergoing RT with concurrent chemotherapy	30 Head and neck	54.5	Trolamine emulsion (15)	Usual care (15)	16	Development of mild reaction (grades 1 and 2), and higher-grade RD	RTOG Acute Radiation Toxicity Criteria	Grade 1-2 TA: 80% (12/15) CA: 46.6% (7/15) *P*< 0.01 Grade 3 TA: 20% (3) CA: 53.4% (8) *P*<0.01 Grade 4: none
Elliot et al, 2006[19] Canada	To compare trolamine emulsion, as a prophylactic agent and as an interventional agent, with	494 Head and neck	59.0	Trolamine emulsion Prevention (163) Treatment (172)	Institutional preference (159)	19	Reduction of grade 2 or higher RD.	NCI/CTC version 2.0 ONS - toxicity scoring system	PG: 18% (30/163) CG: 20% (31/159) *P* = 0.82 Grade 0 PG: 3% (5/163) CG: 1% (2/159) Grade 1 PG: 16% (26/163) CG: 14% (23/159) *P* = 0.86

	declared institutional preference in reducing the incidence of higher grade RD								
Fenig et al, 2001[17] Israel	To evaluate the effectiveness of Biafine and Lipiderm in preventing RD	75 Breast	69	Biafine (25)	Lipiderm (24) Control (25)	-	Incidence of RD	RTOG	Grade 3-4 reaction* TA: 25% (6/25) Lipiderm: 23% (5/24) Control: 25% (6/25) *P* = 0.98
Fisher et al, 2000[16] USA	To compare Biafine to best supportive care (BSC) in preventing RD	140 Breast	61	Trolamine (66)	Best supportive care (74)	4	Prevention or reduction of RD Time to development of grade 2 or high skin toxicity	RTOG	Grade 0 TA: 9% (6/66) CA: 7% (5/74) Grade 1 TA: 50% (33/66) CA: 58% (43/74) Grade 2 TA: 41% (27/66) CA: 32% (24/74) Grade 3 TA: 0% (0/66) CA: 3% (2/74)
Gosselin et al,	To evaluate three	208 Breast	Placebo 55.8	Trolamine (Biafine®	Placebo (49)	48	Prevention or	RTOG	Grade 2 to 4† TA: 90% (47.7/53)

2010[21] USA	commonly used skin care products for women receiving whole-breast RT against a placebo.		Aquaphor® 54.8 Biafine® RE 56 RadiaCare™ 55.6	RE) (53)	Aquaphor® (53) RadiaCare™ (53)		reduction of RD		Placebo: 80% (39.2/49) Aquaphor®: 80% (42.4/53) RadiaCare™ 72% (38.16/53)
Pommier et al, 2004[18] France	To assess the effectiveness of calendula for the prevention of acute RD of grade 2 or higher during postoperative RT for breast cancer, compared with trolamine.	254 Breast	Calendula 56.5 Trolamine 55.1	Trolamine (128)	Calendula (126)	20	Occurence of acute RD of grade 2 or higher	RTOG	Grade 2 to 3 TA: 63% (95% CI, 59 to 68) CA: 41% (95% CI, 37 to 46) *P* < 0.001 Grade 4: none
Ribet et al, 2008[20]	To evaluate the efficacy and	69 Head and neck	57.9	Trolamine cream (34)	Avène Termal Spring	-	Time to onset of the first signs	NCI	Grade 0 TA: 24.1% (7/29) CA: 23.3% (7/30)

France	tolerance ATSW gel versus trolamine cream in the prevention of RD	Breast			Water anti burning gel (ATSW gel) (35)		of RD		Grade 1 TA: 34.5% (10/29) CA: 46.7% (14/30) Grade 2 TA: 34.5% (10/29) CA: 26.7% (8/30) *P* = 0.347

*Nurse's impression

†Data calculated by review authors

Abbreviation: CA = control arm, RCT = randomised controlled trial, RD = radiation dermatitis, RT = radiotherapy, RTOG = Radiation Therapy Oncology Group, AUC = area under curve, NCI = National Cancer Institute, CTC = Common Toxicity Criteria, CTCAE = Common Terminology Criteria for Adverse Events, ONS = Oncology Nursing Society, TA = Trolamine arm

Risk of bias within studies

The risk of bias was performed individually in all studies included. One randomized clinical trial was graded as having a low risk of bias in the six domains assessed[21] (Figure 2). Four studies[16,19,20,22] exhibited an unclear risk of selection bias due to the poor description of the randomization strategy. One of the studies[17] have a high risk of bias due to randomization description of the inclusion of participants in the intervention groups consecutively. The domain "selective reporting" showed predominantly low risk of bias in the evaluation of the studies (100%).

Four studies were classified as *high risk of bias* because they contained one or more compromised domains[16,17,19,20]. Two studies were classified as *uncertain risk of bias*[18,22]. One of them received positive bias ratings, with low risk of bias in 91% of the evaluated domains[18]. Only one study presented *low risk of bias* in all domains evaluated[21], allowing us to ascribe the results of the study as of increased reliability.

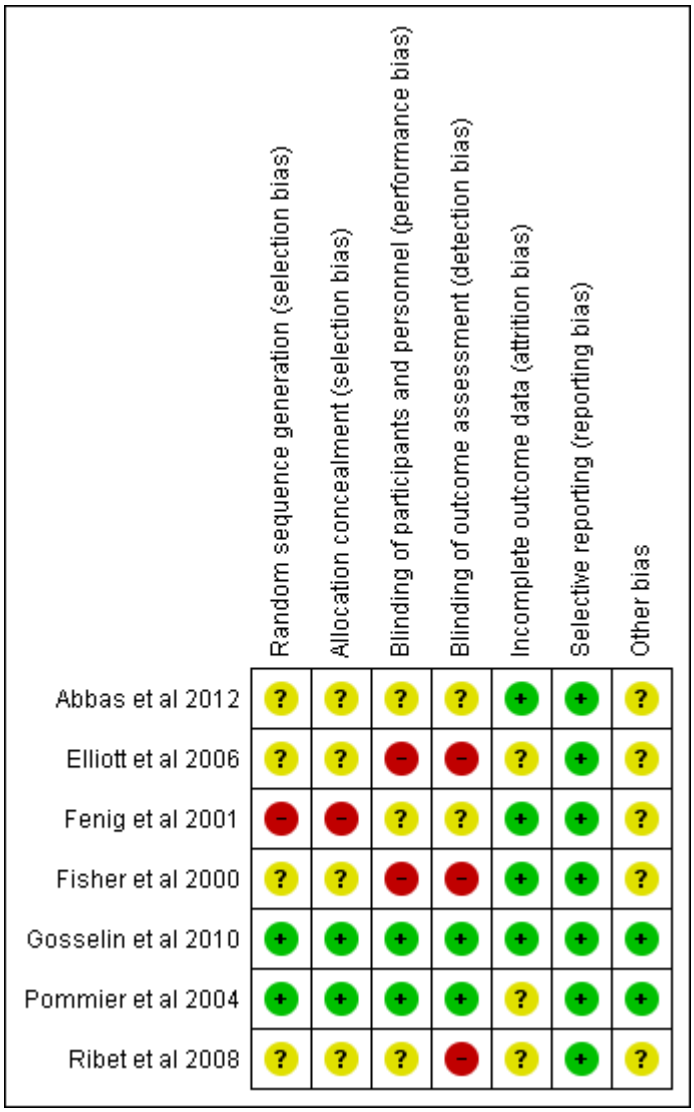

Figure 2 – Risk of Bias assessment for individual studies. Brasília, DF, Brazil, 2016.

Results of individual studies

The studies used trolamine to prevent or treat radiation dermatitis and reported different results for all 7 articles. Characteristics and results of the included studies are listed in Table 1.

Synthesis of results

Regarding the rating scales, five studies used exclusively the RTOG scale (71.4%)[16-18,21,22], one of them used only NCI-CTC (14,1%)[20], and one study used both NCI-CTC and ONS scales to assess the skin reactions of their patients[19].

The studies were grouped into subgroups according the graduation of radiation dermatitis[16,18-22]. Overall, the results of this random-effect meta-analysis demonstrate that there is no difference between the use of trolamine and evaluated controls to prevent radiation dermatitis (RR 1.02, 95% CI: 0.92 – 1.14. I^2 = 49%) (Figure 3).

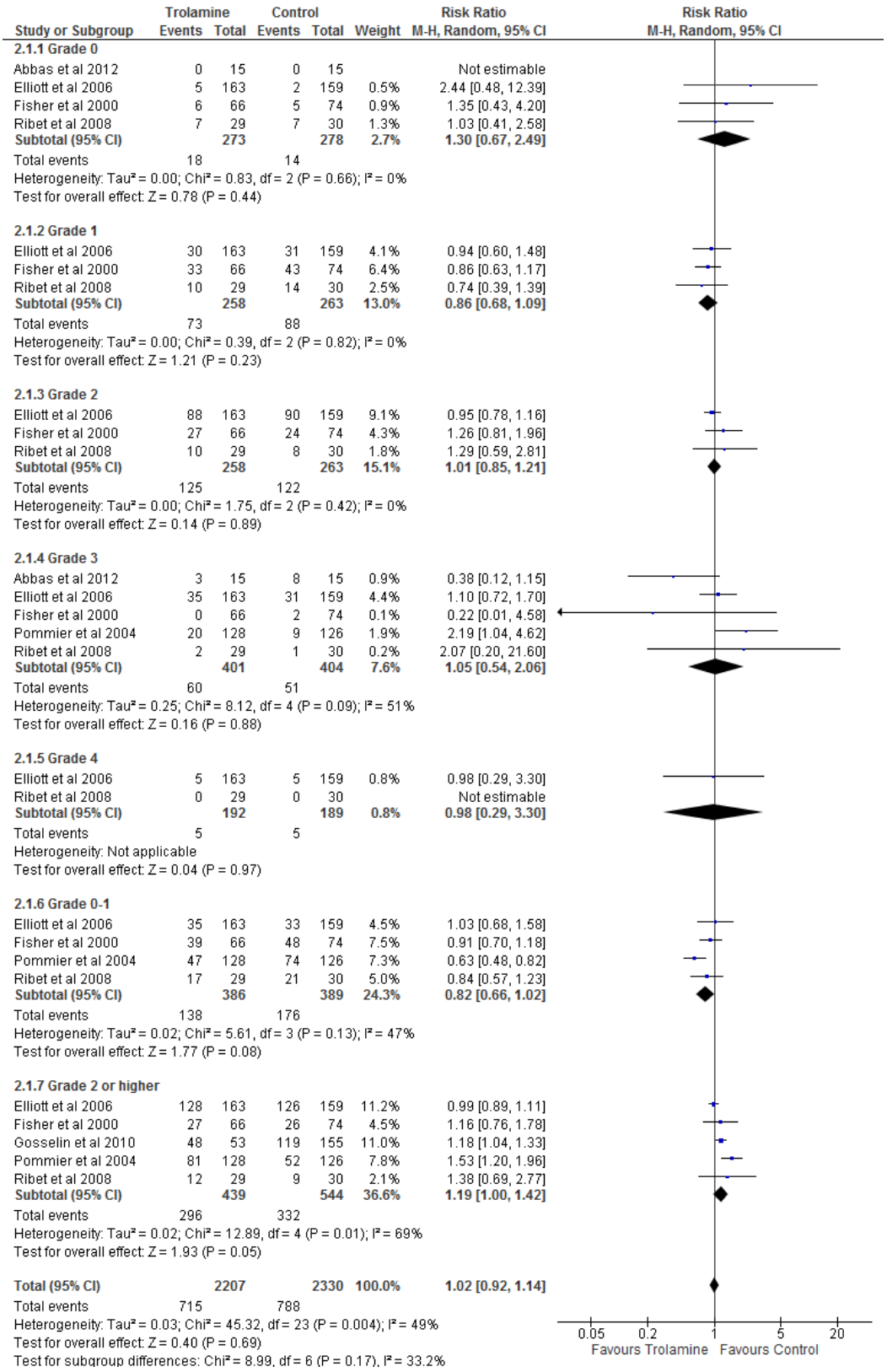

Figure 3 – Forest plot of trolamine vs. controls according to the degree of radiation dermatitis.

Risk of bias across studies

The quality of the evidence from the outcomes evaluated by the GRADE system was assessed as very low (Table 2), suggesting very low confidence in the estimated effect from the outcomes assessed. It means that the true effect is likely to be substantially different from the estimate of effect. The important limitations in the studies, and inconsistency were the main factors responsible for the low quality of the evidence from studies evaluated.

Table 2 – GRADE assessment. Brasília, DF, Brazil, 2016.

Quality assessment							Quality	Importance
# of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Incidence of moderate/severe reaction (grade 2 or higher) (assessed with: RTOG)								
5	randomized trials	serious *	serious †	not serious	not serious	none	⊕⊕◯◯ LOW	CRITICAL
Incidence of no reaction or mild reaction (grade 0 and 1) (assessed with: RTOG)								
4	randomized trials	serious *	serious ‡	not serious	not serious	none	⊕⊕◯◯ LOW	CRITICAL

* Two studies not blinded sample and indicate that the absence of blinding can entail bias. The random sequence generation of three studies are unclear.

† I^2=69%.

‡ I^2=47%.

Discussion

In this review, seven studies evaluating trolamine to prevent or treat radiation dermatitis were included. In four studies[17-19,21] no benefits for the use of trolamine to prevent radiation dermatitis was shown, and in two studies[16,20] there was no difference to prevent radiation dermatitis between trolamine and evaluated controls. Only one study[22] showed satisfactory using trolamine in the prevention of radiation dermatitis, however, their results showed benefit only to prevent grade 3 radiation dermatitis.

Trolamine has been considered because its good tolerability and its ability to moisturize skin and reduce local discomfort, however it has not been proven that trolamine is a topical skin radioprotective[9]. Some controls presented more or similar efficacy than trolamine[16-21]. According with the meta-analysis, there is no difference between trolamine and controls to prevent radiation dermatitis[16,18-22].

The skin moisture and the skin reactions from the radiotherapy could be influenced by the number of intervention applications along the day. Some studies instructed the patients to apply the intervention three times a day[16,19,22] or twice daily[17,21] or five times a day[20]. Only one study[18] allowed patients to apply the intervention twice a day or more according to the frequence of radiation dermatitis and pain. None of this studies described a relation between the frequence of intervention and controls applications and the skin moisture. One of the studies[17] asked to patients start the product application 10 days before the radiotherapy onset, but no contribution was added to prevent radiation dermatitis.

The product quantity in each application was not measured by the studies, except for one of the studies[18] in which the mean total number of tubes was 1.62 times more used in trolamine group than in calendula group.

Trolamine use was considered by patients more satisfactory than controls when compared to calendula[18] and Aquaphor^{R} and RadiaCare^{R} [21].

Some studies have shown that chemotherapy and tamoxifen increased the intensity of skin reactions in patients undergoing radiotherapy[23-26]. Two studies used chemoradiotherapy[19,22], and in one study

tamoxifen was used concomitant with radiotherapy in breast cancer patients[17], however, these studies did not report significant differences in the skin reactions between the groups using trolamine or controls.

Only one study evaluated the efficacy of trolamine to treat radiation dermatitis, and considered no efficacy for trolamine in head and neck cancer patients[19]. It is important that other studies evaluated trolamine to treat grade 1 and grade 2 of radiation dermatitis, because these grades require products with moisturize and anti-inflammatory action. One of the studies[22] considered that trolamine prevents grade 3 of radiation dermatitis in head and neck cancer patients, however this conclusion is only based on those patients that do not developed grade 3 of radiation dermatitis. Moreover, do not developed maximum grades of radiation dermatitis depends on extrinsec factors (total dose, fractionation, radiation energy, volume of treated regions, treatment duration, boost aplication, and treatment site) and intrisec factors (age, commorbid conditions, skin phototype, and genetic predisposition)[27].

Conclusion

Based on the studies included in this review, trolamine cannot be considered as a standardized product to prevent or treat radiation dermatitis in patients with breast and head and neck cancer. Further well-structured blinded studies using trolamine as a treatment are required to evaluated the moisturize and anti-inflammatory action.

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