Topical treatment for prevention and management of acute radiation dermatitis in breast cancer patients: an integrative review

Terapia tópica para prevenção e tratamento da radiodermatite aguda das mamas: revisão integrativa da literatura

Introduction: Radiotherapy plays an important adjuvant role in the surgical treatment of breast cancer by reducing locoregional recurrence and improving overall survival. However, up to 95% of patients experience some degree of radiodermatitis. This study aims to review the literature regarding topical agent therapies in preventing and treating acute radiation dermatitis in breast cancer patients. Methods: Integrative review of LILACS, Medline and Cochrane Library databases. We searched for original articles published between 2010 and 2020, including the descriptors breast neoplasms, radiodermatitis, skincare, and skin cream. Results: The initial search returned 158 articles. After screening for eligibility, 48 articles were included. Forty different topical agent therapies were identified and grouped into seven categories to facilitate data analysis: herbal medicines, hormones/vitamins/growth factors, topical corticosteroids, barrier products (film or cream), hyaluronic acid, silver-based dressings and others. Conclusions: This review identifies that topical corticosteroids of high (betamethasone-17-valerate) and medium potency (mometasone furoate 0.1%), as well as barrier films such as Mepitel®, Mepilex Lite®, and Hydrofilm®, are effective in managing acute breast radiodermatitis. The other topical agent therapies did not show benefits in preventing and/or treating acute radiodermatitis or have limited evidence.

Keywords: Breast neoplasms; Radiodermatitis; Skin care; Skin cream; Review.
INTRODUCTION

According to data from the American Cancer Society, breast cancer accounts for 30% of all cancer cases in women, and an estimated 281,550 new cases were estimated in 2021. The incidence of this neoplasm increased by 0.5% between 2008 and 2017, probably due to decreased fertility, increased overweight and obesity in the female population.

Breast cancer treatment is multimodal and depends on factors such as staging at diagnosis, tumor biological characteristics, and patient-related factors. The available treatment modalities are radical or conservative surgery, radiotherapy, chemotherapy, hormone therapy and biological therapy, which are often associated individually for each case.

Radiotherapy plays an important role as an adjuvant to the surgical treatment of breast cancer, decreasing local recurrence rates and increasing overall survival. It is estimated that up to 95% of irradiated patients will develop some degree of radiodermatitis (RDTE). In addition to interfering with the quality of life, skin toxicity induced by radiotherapy, depending on the severity, can delay or interrupt adjuvant treatment.

RDTE is an acute or chronic inflammatory condition caused by skin exposure to ionizing radiation resulting in changes in the epidermis, dermis and local vascularization. It is a dose and time-dependent condition with a progressive spectrum of skin changes such as erythema, hyperpigmentation, dry desquamation, wet desquamation, necrosis and local ulceration. Such changes are part of the most commonly used RDTE assessment and classification scales: Radiation Therapy Oncology Group (RTOG) and National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE).

The main risk factors for the development of RDTE are related to the characteristics of the patient and the radiotherapy technique used, such as radiotherapy dose greater than 50Gy; conventional-dose splitting regimen; use of bolus or boost techniques; among others. It is known that a body mass index greater than 25kg/m², smoking and the presence of large breasts are factors that predispose to moderate and severe forms of RDTE. On the other hand, the main protective factors concern the radiotherapy technique used, and intensity-modulated radiotherapy (IMRT) and prone position have been proven to reduce radio-induced skin toxicity.

Unlike radiotherapy techniques, which have already standardized protocols to reduce the risk of skin toxicity to the patient, the management of RDTE remains heterogeneous. Numerous topical and curative drugs for the prophylaxis and treatment of RDTE have been investigated in the medical literature, but a large number of proposed interventions, the heterogeneity of reported results and the quality of studies make clinical decisions challenging. Thus, it is necessary to carry out extensive research in the medical literature in search of available evidence on this topic.

OBJECTIVE

To carry out an integrative review of the literature on the use of topical therapy for the prevention and treatment of RDTE in female patients with breast cancer undergoing adjuvant radiotherapy.

METHODS

This is a descriptive, exploratory study that rigorously followed the six steps recommended for the development of an integrative literature review.

A search was carried out for articles published between 2010 and 2020 in the Latin American and Caribbean Literature in Health Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (Medline) and Cochrane Library databases.

Four controlled descriptors were used: breast neoplasms, radiodermatitis, skin hygiene and skin cream. Original articles from primary or secondary studies were included, with female patients undergoing breast radiotherapy, published in full in Portuguese, English or Spanish, and which could be accessed online. Secondary articles, such as literature reviews and meta-analyses, were not included. However, the primary articles that made up such studies did. Articles that evaluated different anatomical sites of the breasts, publications of study protocols, studies with unavailable full text, studies that evaluated non-topical therapies, such as oral medications or non-invasive technologies, and duplicates were excluded.
After analyzing the articles’ abstracts, those that met the inclusion criteria were read in full by a single reviewer and organized using a synthesis tool developed by the main author. The data obtained were organized in an Excel spreadsheet, and the respective references were stored in the bibliography manager software EndNote (Clarivate Analytics).

RESULTS

The bibliographic research structured according to the previously established methodology resulted in selecting this integrative review’s 48 original primary articles (Figure 1). As for the type of study, 35 (73%) randomized clinical trials (RCTs) were found; three non-randomized clinical trials (6%), five pilot studies (11%), two case series (4%), one case-control study (2%), one retrospective study (2%) and one prospective cohort (2%).

In the 48 studies in this review, 40 different interventions for the prevention or treatment of breast RDTE were identified, which were grouped into seven categories to facilitate their analysis and interpretation (Table 1).

Herbal medicines

No benefits were found from the use of Aloe vera extract10, curcumin gel11; Calendula officinalis cream12-14, Centella Asiatica extracts 7%, Cucumis sativus 20%, Thunbergia laurifolia 5%15, Boswellia serrata cream 2%16, ointment of beta-sitosterol 0.25% (Mebo®)17, fatty acid emulsion18,19, blend of essential oils20, omega 3,6,9 (Quinovit®)21 and Jaungo ointment (shikonin 0.07mg/g + decursin 3.6mg/g)22 in the management of RDTE of the breasts.

A double-blind, randomized clinical trial with 47 patients showed that 3% sodium pentaborate pentahydrate gel decreased the rate of RDTE grade RTOG > 2 in the subgroup of patients undergoing radical or conservative surgery who did not receive radiotherapy boost (34% vs. 67% p=0.03)23.

Studies that evaluated silymarin 0.25%24, emulsion of olive oil and calcium hydroxide25 and natural extracts (SkinSave®)26 showed a reduction in the proportion of patients with RDTE24,25, less pain24 and erythema26. Table 2 summarizes the data for this group.

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Figure 1. Flowchart of the steps for identification and selection of articles in this review.
Table 1. Topical therapies from this integrative review and their respective references.

| Herbal Medicines                                                      | References |
|----------------------------------------------------------------------|------------|
| Aloe barbadensis extract 30mg/100ml                                  | 10         |
| Curcumin Gel (PsoriaGold®)                                           | 11         |
| *Calendula officinalis* cream                                       | 12-14      |
| Asian centella 7%, *Cucumis sativus* 20%, *Thunbergia laurifolia* 5% | 15         |
| *Boswellia serrata* cream 2%                                         | 16         |
| Beta-sitosterol Ointment 0.25% (Mebo®)                              | 17         |
| Fatty Acids and Linoleic Acid (WO1932)/ Ultra Emu Oil®              | 18, 19     |
| Blend of essential oils                                             | 20         |
| Omegas 3, 6, 9 (Quinovit®)                                          | 21         |
| Jaungo Ointment (shikonin 0.07mg/g + decursin 3.6mg/g)               | 22         |
| Sodium pentaborate pentahydrate 3% gel                              | 23         |
| Silymarin 0.25% (Leviaderm®)                                        | 24         |
| Olive oil and calcium hydroxide emulsion                            | 25         |
| Emulsion of natural extracts (SkinSave®)                            | 26         |
| **Hormones, vitamins and growth factors**                           |            |
| Melatonin cream (Praevoskin®)                                       | 27         |
| Recombinant epidermal growth factor (EGF) cream                     | 28         |
| Vitamin D (Daivonex®)                                               | 29         |
| Vitamin E                                                           | 30         |
| **Topical corticosteroids**                                         | 14.30-32   |
| Mometasone Furoate 0.1%                                             | 31         |
| 1% hydrocortisone                                                   | 32         |
| 17-Betamethasone Valerate (Betnovat®)                               | 33         |
| **Barrier**                                                         | 34.35      |
| Silicone film (Mepitel®/Mepilex Lite®)                              | 36-40      |
| Hydrofilm®                                                          | 41         |
| Cavilon® (barrier cream)                                            | 42.43      |
| Silicone gel (XtrataXRT®)                                           | 44         |
| **Hyaluronic acid**                                                 | 14, 21, 45-46, 47 |
| Hyaluronic acid gel, serum or cream                                 |            |
| **Silver**                                                          | 48         |
| 48 silver impregnated film                                          |            |
| 1% silver sulfadiazine                                              |            |
| **Others**                                                          | 49         |
| HPR Plus® (free fatty acids, ceramides and hyaluronic acid)         | 11         |
| Commercial formulations (Neoviderm®/Jxoderm®)                       | 21         |
| Aquafor® (panthenol and glycerin ointment)                         | 50         |
| Trolamine (Biafine RE®)                                             | 50         |
| RadiCare®                                                           | 50         |
| Hydrophilic gel with polyurethane polymers (Hydrosorb®)             | 51         |
| Mucopolysaccharide Polysulfate 5mg/g (Hirudoid®)                    | 52         |
| Sucralfate                                                          | 53.54      |
| Flamigel® (hydroactive colloid gel)                                 | 55.56      |
| 3% urea lotion                                                      | 57         |
**Hormones, vitamins and growth factors**

Melatonin-based cream (Praevoskin®) reduced the incidence of grade 1 and 2 RDTE in the intervention group (59% vs. 90%, \(p=0.03\)), with the benefit being greater in the subgroups of patients >50 years (\(p=0.021\)) and smokers (\(p=0.007\))27.

Recombinant epidermal growth factor (EGF) cream and vitamin D ointment could not prevent the onset or progression of RDTE28,29. In the study that evaluated vitamin E, a 55% prevalence of grades 1-2 RDTE was observed in the group of 20 patients who used this therapy (11/20)2.

**Corticosteroids**

Topical corticosteroids were studied in seven RCTs, six of which were double-blind, and one was a pilot study, totaling 794 patients. Four of the seven studies evaluated 0.1% mometasone furoate; two, 17-betamethasone valerate; and one, 1% hydrocortisone cream.

Mometasone furoate 0.1% reduced the severity of RDTE30, the incidence of wet scaling and skin toxicity31. These benefits were not observed in the pilot study14 and one of the double-blind RCTs32. In the latter, an improvement in the symptoms reported by the patient (secondary outcomes) was observed, such as less local irritation, less persistence and recurrence of symptoms and less discomfort with skin changes32.

1% hydrocortisone cream was not able to prevent the occurrence of wet desquamation33. The use of 17-betamethasone valerate (Betnovat®) twice a day, from the first day of radiotherapy until 14 days after its completion, demonstrated a protective effect against the onset and progression of RDTE, with the benefit being even greater in the subgroup of mastectomy patients34,35.

**Barrier (film or cream)**

This intervention has the second largest RCT series, totaling 774 patients in studies evaluating silicone film (Mepitel®/Mepilex®), Cavilon® cream, silicone gel (XtrataXRT®) and polyurethane film (Hydrofilm®).

Studies with silicone films showed beneficial results. Its application on the breast surface to be irradiated resulted in a lower incidence of erythema36 and cutaneous toxicity37,38, a reduction in the rate of wet desquamation39, and better control of symptoms such as pain, tenderness, itching and local burning40. Patients who used Hydrofilm® (polyurethane film) had a lower RDTE score, indicating protection against progression to more severe forms of RDTE, less erythema, itching and pain in irradiated breasts after conservative surgical treatment41.

Cavilon® barrier cream prevented the appearance of wet desquamation at the end of radiotherapy exclusively in the subgroup of mastectomized patients, and this benefit was not observed in the 8 to 10 weeks post-radiotherapy follow-up42. In addition, its use does not reduce pain and pruritus or delay progression to RDTE grade 242. Silicone gel (XtrataXRT®) was evaluated in a pilot study with 49 patients, and no benefits were observed in the prevention of RDTE43.

**Table 2. Herbal medicines.**

| Herbal                                          | Reference | Result |
|-------------------------------------------------|-----------|--------|
| Aloe barbadensis extract (30mg/100ml)            | 10        | Negative |
| Curcumin Gel (PsoriaGold®)                       | 11        | Negative |
| Calendula officinalis cream                      | 12-14     | Negative |
| Asian centella 7%, Cucumis sativus 20%, Thunbergia laurifolia 5% | 15        | Negative |
| Boswellia serrata cream 2%                       | 16        | Negative |
| Beta-sitosterol Ointment 0.25% (Mebo®)           | 17        | Negative |
| Fatty Acids and Linoleic Acid (WO1932)/ Ultra Emu Oil® | 18,19     | Negative |
| Blend of essential oils                          | 20        | Negative |
| Omegas 3,6,9 (Quinovit®)                         | 21        | Negative |
| Jaungo Ointment (shikonin 0.07mg/g + decursin 3.6mg/g) | 22        | Negative |
| Sodium pentaborate pentahydrate 3% gel          | 23        | Positive |
| Silymarin 0.25% (Leviaderm®)                     | 24        | Positive |
| Olive oil and calcium hydroxide emulsion         | 25        | Positive |
| Emulsion of natural extracts (SkinSave®)         | 26        | Positive |
Hyaluronic acid

Hyaluronic acid in different presentations as gel, serum or cream was evaluated in five studies, totaling 422 patients. In none of the studies, there was any benefit from the application of this intervention. Topical hyaluronic acid did not prevent the onset or progression of RDTE, in addition to potentially worsening skin toxicity in patients who used it.

Silver-impregnated film

Silver-impregnated film was evaluated in RCT with 196 patients undergoing breast-conserving surgery and adjuvant radiotherapy. The results obtained were negative for both preventions of wet desquamation in the inframammary fold and relief of pain and burning. On the other hand, the application of 1% silver sulfadiazine three times a day during the radiotherapy period and up to 7 days after its completion resulted in lower scores on the RTOG score, indicating a protective effect against the onset of moderate and severe forms of RDTE in mastectomized patients.

Others

This group comprises 11 studies: five RCTs, two non-randomized clinical trials, one case series, two cohort studies and one case-control study. Double-blind RCTs that evaluated Aquaforte® (panthenol and glycine), Biafine RE® (trolamine), RadiaCare® and HPR Plus® (free fatty acids + ceramides + hyaluronic acid) did not observe benefits from the topical use of these substances. The unblinded RCT with 278 patients with RDTE grades 1-2 randomized to topical treatment with Hydrosorb® (hydrogel) was also negative.

The application of Hirudoid® from 14 days after the beginning of radiotherapy until 3 months after its completion promoted less desquamation and greater skin hydration in the period of 2 and 4 weeks after the beginning of adjuvant therapy, with no difference at 3 months, as evidenced by the analysis of the corneometry of the breasts of patients submitted to breast-conserving surgery, in an unblinded and non-placebo-controlled RCT.

Studies with less evidence indicate some benefits in sucralfate gel 25% (Skincol®), hydroaactive colloid gel (Flamigel®), urea lotion 3% and various commercial formulations.

DISCUSSION

In this integrative review, 48 primary studies were identified evaluating topical therapies for the prevention or treatment of RDTE, which were grouped into seven categories.

76% (13/17) of the articles that evaluated herbal medicines found no benefits from this intervention, ten RCTs. Furthermore, studies with positive results have important methodological limitations, as they are not blinded, controlled or randomized, which determines a high risk of bias. Similarly, the evidence favoring 3% sodium pentaborate pentahydrate gel is still limited.

It is concluded that there is sufficient scientific evidence to contraindicate the use of most topical herbal formulations in the management of RDTE of the breasts. Such findings agree with those reported in a study published in 2012 that critically evaluated published systematic reviews on the management of RDTE and concluded that topical agents based on Aloe vera and Calendula, among others, are ineffective.

Positive results with the use of melatonin-based cream (Praevoskin®) and 1% silver sulfadiazine need confirmation in studies with larger series, as scored by the authors; or in studies with better methodological design regarding the use of placebo in the control group and efficiency of blinding.

Topical corticosteroids have been extensively investigated in RCTs over the last 10 years, building solid evidence from double-blind, placebo-controlled studies favoring 0.1% mometasone furoate and 17-beta-methasone valerate. These findings corroborate the results of a systematic review comprising six RCTs published in 2013: a meta-analysis of five RCTs showed that the risk of wet desquamation is 2.5 times lower with topical corticosteroids. A lower mean RDTE score was also evidenced; however, the heterogeneity between the studies did not allow a meta-analysis to be carried out for this outcome.

In the review mentioned above, the authors emphasized that future studies should investigate which topical corticosteroid would be most effective in managing RDTE. In the present review, we observed that high (17-beta-methasone valerate) and medium (0.1% mometasone furoate) steroids were beneficial, whereas no benefits were observed from topical hydrocortisone 1%, a low potency corticosteroid.

The benefit of using silicone barrier films (Mepitel®/MepilexLite®) or polyurethane (Hydrofilm®) is based on the results of RCTs with a restricted series (n<100). Furthermore, the risk of observational bias cannot be ruled out due to the absence of blinding in most studies. On the other hand, Cavilon® barrier cream showed a limited and transient benefit in preventing wet peeling. In contrast, silicone gel reduced the incidence of erythema and hyperchromia (secondary outcomes) without changing the severity.
of RDTE, which was the primary outcome of the study by Ahn et al.44.

Formulations based on hyaluronic acid14,21,45-47, silver-impregnated films48, Aquafor®50, Biafine RE®50, RadiaCare®50, HPR Plus®51 and Hydrosorb®51 were evaluated in RCT and proved to be ineffective in the management of RDTE.

Hirudoid® promoted greater skin hydration, assessed by corneometry, up to 4 weeks after the end of adjuvant RT in patients undergoing conservative surgery. It also improved xerosis and skin scaling without changing the degree of erythema and local pruritus52. Thus, the evidence for the indication of Hirudoid® in managing RDTE is still limited.

The positive results reported with the use of 1% silver sulfadiazine49, 25% sucralfate gel53,54, hydroactive colloid gel (Flamigel®)55,56, 3% urea lotion57 and commercial formulations such as Neoviderm® and Ixoderm®51, do not come from placebo-controlled RCTs. Thus, such benefits should be carefully evaluated, as the limitations inherent to the methodology of these studies do not allow inferences about the effectiveness of these substances in the management of RDTE.

This integrative review has limitations resulting from the evaluation period restricted to the last 10 years and from exclusively contemplating articles published in journals indexed in the three predetermined languages. However, previously published reviews that considered the literature prior to 2010 concluded that the available evidence regarding topical therapies for RDTE was insufficient, heterogeneous and, therefore, a greater number of better quality studies were needed58,60,61.

The present study updated the literature related to the topic, clarified questions raised by previous reviews, and critically evaluated the scientific evidence supporting the indication or contraindication of topical therapies available for the management of RDTE of the breasts.

**CONCLUSION**

For the prevention of breast RDTE, there is sufficient scientific evidence from good quality randomized clinical trials to support the indication of topical corticosteroids, mometasone furoate 0.1% and 17-betamethasone valerate. Barrier films such as Mepitel®, Mepitex Lite® and Hydrofilm® have also been shown to be beneficial.

On the other hand, topical hyaluronic acid formulations, Aloe barbadensis extract, Centella Asiatica 7%, Cucumis sativus 20%, Thunbergia laurifolia, Boswellica serrata 2%, Calendula officinalis cream 5 or 10%, silver-based films, curcumin (PsoriaGold®), HPR plus® cream, 0.25% beta-sitosterol ointment (Mebo®) and Biafine RE® (trolamine) were shown to be ineffective in the management of RDTE of the breasts. Thus, the available evidence contraindicates such substances’ use in managing RDTE.

Sodium pentaborate pentahydrate gel 3%, Praevoskin® (melatonin cream), Leviaderm® (silymarin 0.25%), Cavilon®, silver sulfadiazine 1% and Hirudoid® (mucopolysaccharide polysulfate 5mg/g) showed positive results in the management of breast RDTE in clinical trials with limited series and/or of lower methodological quality. Although promising, such substances need additional studies proving their effectiveness.

**COLLABORATIONS**

MARM Analysis and/or interpretation of data, Final approval of the manuscript, Data collection, Conception and design of the study, Methodology, Writing - Preparation of the original.

MGC Final approval of the manuscript, Conception and design of the study, Writing - Review and Editing, Supervision.

AH Final approval of the manuscript, Conception and design of the study, Writing - Review and Editing.

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