A Systematic Review on the Role of Topical Corticosteroids for the Management of Radiation Dermatitis

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Radiation dermatitis (RD) is a widespread complication of radiation therapy; however, there is still no agreement on the best treatment. The goal of this review is to go over how corticosteroids work throughout the treatment of radiation dermatitis.

Methodology: A comprehensive evaluation of randomized controlled trials, retrospective and prospective studies involving topical corticosteroid (TC) for the treatment of radiation dermatitis. A thorough search was carried out in Medline, Embase, the Cochrane library, Clinical trials.gov, and Google scholar. The original search took place in August and was updated on September 2021. There were no restrictions on terminology or dates. Two reviewers independently examined each of the listed papers. A search of the relevant studies of all of the mentioned publications yielded additional papers.

Results: We identified 19 studies on the role of corticosteroids for the prevention of radiation therapy. All the papers were published between 2001 and 2021. The total sample size of the included studies was 1974 with a mean sample size of 103.89. Among the included studies, four studies (21.05 %) represented head and neck cancer, 14 studies (73.68 %) were regarding breast cancer and 1 (5.26 %) hospital-based cross-sectional study represented multiple malignancies such as head and neck, breast and cervix carcinoma, respectively. Among all the participants, 1696 (85.91 %) were females while 278 (14.08 %) were males.

Conclusion: Prophylactic treatment with TC was found to minimize the rate of RD and wet desquamation. Participants who used topical steroids reported improved symptoms and a higher quality of life, whereas the use of topical steroids during radiation had few side effects. ARD can be prevented using topical corticosteroids, based on these findings. As a result, further research must be done on the most effective TC to utilize during radiation.

Keywords: Radiation dermatitis; topical corticosteroid; moist desquamation.

ABBREVIATIONS

TC : Topical corticosteroids
RD : Radiation dermatitis
SD : Standard deviation
CTCAE : Common terminology criteria for adverse events
RTOG : Radiation therapy oncology group
RT : Radiation therapy
CS : Corticosteroids
QoL : Patients’ quality of life

1. INTRODUCTION

The human skin is a highly radiosensitive organ, and it undergoes a series of physical changes when the radiation dose accumulates over time. A cutaneous reaction is common when treatment is administered to the head and neck region, breast, head and neck area, post-modified radical mastectomy chest wall, groin region, perineum or axilla. Radiation-induced physiological reactions can cause a great deal of discomfort, which can be harmful to a patient’s overall health. If the disease is severe, the treatment programme might well be completely eliminated [1].

Radiation damages the skin by activating inflammatory pathways and producing an overproduction of cytokines [1,2]. RD is a frequent severe side effect that develops within hours to weeks of starting radiation [3,4] and influences around 87 % of victims [2,5]. Treatment interruptions and dose reductions can occur as a result of radiation dermatitis. [1,6]. It can also have a significant influence on the quality of life of patients [7,8]. The overall radiation dosage, dose fractionation program, and amount of tissue or organ given, as well as concomitant treatment and comorbid diseases, all have a role in RT toxicity [9]. In days to weeks after exposure, RT produces significant genetic damage, cutting into double strands in nuclear and mitochondrial DNA and limiting cells’ ability to multiply and reproduce. RD is caused by this damage, as well as additional structural tissue deterioration, the production of reactive oxygen species (ROSs), the loss of functional stem cells, the beginning of epidermal and dermal inflammatory responses, and skin cell necrosis [1].

There are presently no effective therapies for preventing acute skin reactions, and existing evidence is insufficient to provide adequate recommendations for treating this side effect [10,11]. Several topical treatments, including aqueous cream, Aloe Vera, Calendula, sucralfate
cream, and petrolatum, have been studied to reduce RD’s drying impacts. Nevertheless, in terms of treating RD and medication-related pain, the findings were not clinically significant. The goal of this review is to go over how corticosteroids work throughout the treatment of radiation dermatitis, a widespread complication of radiation therapy. Since there is still no agreement on the best treatment and corticosteroids are used quite commonly in many countries, investigating this issue will be extremely helpful and clinically significant.

2. MATERIALS AND METHODS

The study was conducted using the standard reporting requirements for systematic reviews and meta-analyses (PRISMA). Methodology for doing a literature search: PubMed, Embase, Ovid, Google Scholar, and Science Direct were used to perform a thorough review of the literature. The search took place between in August and was updated on September 2021. “Radiation dermatitis,” “topical corticosteroids,” and “topical corticosteroid for radiation dermatitis” were among the search terms used in various combinations. The findings were filtered using the titles and abstracts of the provided results. Duplicate articles were removed.

2.1 Inclusion and Exclusion Criteria

This review covered studies on TC for the treatment and prevention of RD. The publications considered were retrospective, prospective, and randomized controlled trials (RCTs). People with Cancer undergo exogenous radiation for any type of malignancy, male or female, without any limitation based on age or other independent factors. Corticosteroids can come in ointment, cream, ointment, spray or lotion form. Any dosage schedule was deemed to be acceptable. A placebo, another topical drug, or no therapy might be used as a comparator. No language barrier was considered for this review.

2.2 Data Extraction

The papers were chosen by separate investigators mentioned in previous inclusion and exclusion criteria. If the investigators’ choices for the number of articles disagreed, an agreement was reached following discussion. Following that, each investigator independently examined the entire contents of the articles and extracted the relevant data into excel sheets. Finally, the findings were reviewed by a third investigator.

3. RESULTS

We identified 19 articles using topical steroids to prevent RD (Fig. 1). This review includes all trials that compared a TC to other emollients or no therapy as RD prevention. The studies were published in between 2001 – 2021. The eighteen studies included a total of 1974 individuals. All of the individuals who had post-operative radiation exhibited histopathologic evidence of breast and head and neck cancer. Four studies (21.05%) represented head and neck cancer, 14 studies (73.68%) represented breast cancer, and 1 (5.26%) hospital-based cross-sectional research represented various malignancies such as head and neck, breast, and cervical carcinoma, respectively. There were 1696 females (85.91 %) and 278 men (14.08 %) among all participants. Participants were randomly allocated to take a TC, another emollient, a vehicle, or no therapy. Among the TCs, 7 (36.84%) studies used betamethasone valerate, 6 (31.57%) used mometasone furoate, 1 (5.26%) used hydrocortisone, 1 (5.26%) used beclomethasone dipropionate, 1 (5.26%) used methylprednisolone, and 3 (15.78%) studies did not reveal the TC they used (Table 1). Furthermore, from the first to the last day of radiation, the TC were used once or twice a day. In addition, Fig. 2, presents the Cochrane risk-of-bias assessment for the 19 articles included in this review. In terms of randomization process, 15 studies had low risk of bias while 4 had high risk of bias. Concerning the risk of missing data, all had low risk of bias except 3 with high risk of bias. Overall, most of the studies had low risk of bias, except 7 with high risk of bias.

3.1 Radiation Dermatitis Score

Almost all the studies reported RD scores. The clinical scales utilized in each research, however, vary. For example, 15 (78.94 %) of the studies used the RTOG (Radiation therapy oncology group) scale to generate RD scores, that is similar to the CTCAE (Common terminology criteria for adverse events) scale. Farhan et al., [19] utilized maximal dermatitis intensity, whereas Schmutz et al., [7] and Bostrom et al., [8] employed their own clinical measures to score RD. In the majority of the trials covered in this article, topical corticosteroids were beneficial in decreasing the incidence or delaying the development of RD. Sunku et al. [16], for
example, grouped 106 patients with head and neck cancer into two groups: group A (52) and group B (54) patients. Patients in trial group A received topical betamethasone 0.1 percent twice daily during radiotherapy/chemo-radiotherapy, while patients in study group B received no treatment. Both groups' RD scores were assessed weekly using the RTOG scale. According to the authors, patients in the control group had an earlier onset grade 1 reaction (5.7 % in group – A vs 16.7 % in group – B at the second week, P value 0.157 and 28.8 % in group – A vs 0 % in group – B), whereas group – B had a higher grade 2 reaction (66.7 % in group – B vs 55.8 % in group – A). The authors came to the conclusion that topical betamethasone might delay the start and progression of RD in head and neck cancer while not causing substantial delays in wound healing. Similar findings were made by [8,16-24,26-29], who discovered that TC can effectively prevent the advancement of RD in breast, head, neck, and cervix cancer.

In contrast, several studies found no delay or a low RD score among the cancer patients they included. For example, Kianinia et al. [21] conducted a double-blind, randomized trial in which 120 patients who had had breast-conserving surgery for breast cancer were randomly allocated to use Mometasone 0.1 percent cream, hydrocortisone 1 percent cream, or moisturizing base cream starting on the first day of RT and continuing throughout the course. Compared to utilizing daily skin care with an emollient, the authors discovered that using CS did not result in a significant difference in ARD the duration and incidence of ARD development. Yokota et al., [22] and Schmuth et al., [7] discovered similar findings. In terms of reducing or delaying RD, both authors found nonsignificant findings.

**Fig. 1. An overview of the approach for doing a literature search**
3.2 Wet Desquamation

Wet desquamation as a radiation-induced skin response was documented in just three investigations. Shukla et al. [20], for example, recruited sixty patients with breast cancer who were scheduled for post-operative loco regional RT (50 GY in 25 fraction over five weeks). Patients were randomly assigned to one of two groups: one group was instructed to apply beclomethasone dipropionate spray in irradiated axillas beginning on day one of RT. In contrast, the other group was not permitted to use any topical treatment. The authors reported that 4/30 (13.33 %) of patients in the intervention group had moist desquamation of the axillary skin at the conclusion of RT, compared to 11/30 (36.66 %) of patients in the control group. The difference in axillary skin moist desquamation between the two groups was statistically significant (P-value = 0.0369). The authors concluded that CS effectively lowered the risk of moist desquamation of the skin during RT. Meghrajani et al., [23] and Miller et al., [32] obtained a similar result using hydrocortisone 1% and mometasone furoate 0.1 % as CS. They reported that CS decreased the probability of wet desquamation in breast cancer patients as evaluated to the placebo group.
Table 1. Characteristics of the studies included

| Author          | Population | Male/Female | Dermatitis        | Corticosteroid       | Comparator       | Result Outcome                                                                                                                                 |
|-----------------|------------|-------------|-------------------|----------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Sunku et al.,   | 106        | 92/14       | Head and neck     | Betamethasone valerate 0.1 % | Control          | TC delayed the onset and progression of RD compared to control group.                                                                           |
| [16]            |            |             | cancer            |                       |                  |                                                                                                                                                |
| Uysal et al.,   | 50         | NA          | Breast cancer     | Betamethasone        | Moisturiser      | Betamethasone reduced dermal sparing and ARD of patients receiving RT for breast cancer.                                                        |
| [17]            |            |             |                   |                      |                  |                                                                                                                                                |
| Omidvari et al.,| 51         | NA          | Breast cancer     | Betamethasone 0.1 %  | Petrolatum or none | TC was successful in delaying ARD but wasn’t efficient in preventing it.                                                                      |
| [18]            |            |             |                   |                      |                  |                                                                                                                                                |
| Farhan et al.,  | 76         | NA          | Breast cancer     | Betamethasone        | Control          | TC was effective in reducing RD, burning and pruritus but no significant difference was found in terms of pain.                                   |
| [19]            |            |             |                   |                      |                  |                                                                                                                                                |
| Shukla et al.,  | 60         | NA          | Breast cancer     | Beclomethasone dipropionate (spray) | Control          | CS was effective in reducing the risk of wet desquamation of the skin. (desquamation)                                                         |
| [20]            |            |             |                   |                      |                  |                                                                                                                                                |
| Kianinia et al.,| 120        | NA          | Breast cancer     | Mometasone 0.1 % or hydrocortisone 1 % | Moisturiser      | When compared to the control, neither CS resulted in a significant difference in the frequency or prevalence of ARD.                           |
| [21]            |            |             |                   |                      |                  |                                                                                                                                                |
| Yokota et al.,  | 203        | 170/33      | Head and neck     | NA                   | Petrolatum       | CS reduced the frequency of only grade ≥3 RD while no significant difference was observed in grade ≥2 RD compared to control.            |
| [22]            |            |             | Cancer            |                      |                  |                                                                                                                                                |
| Meghrajani et al., | 50        | NA          | Breast cancer     | Hydrocortisone 1 %   | Control          | CS reduced the risk of wet desquamation, mean ARD score and incidence of grade 1 and 2 RD.                                                |
| [23]            |            |             |                   |                      |                  |                                                                                                                                                |
| Saini et al.,   | 47         | 16/31       | Multiple          | NA                   | NA               | CS are helpful in delaying progression of RD.                                                                                                  |
| [24]            |            |             |                   |                      |                  |                                                                                                                                                |
| Schmuth et al., | 36         | NA          | Breast cancer     | 0.1 % Methylprednisolone | 0.5 % dexamethasone | TC only delayed the clinical and transepidermal water loss score                                                                             |
| [7]             |            |             |                   |                      |                  |                                                                                                                                                |
| Author            | Population | Male/Female | Dermatitis            | Corticosteroid            | Comparator | Result Outcome                                                                 |
|-------------------|------------|-------------|-----------------------|----------------------------|------------|--------------------------------------------------------------------------------|
| Hindley et al.,  | 120        | NA          | Breast cancer         | Mometasone furoate         | Deprobase  | compared to dexpanthenol or control group. Mometasone significantly reduced RD during or after RT. It also showed beneficial effect on QOL by using DLQI. Mometasone was significant in reducing incidence of MD, maximum skin toxicity and longer time to develop grade 3 dermatitis as compared to Eucerin. |
| [25]              |            |             |                       |                             |            |                                                                                 |
| Alice et al.,     | 124        | NA          | Breast cancer         | 0.1 % Mometasone furoate   | Eucerin    | When compared to the control and 3M no string barrier film or control, Mometasone was significant in reducing incidence of MD, maximum skin toxicity and longer time to develop grade 3 dermatitis as compared to Eucerin. |
| [26]              |            |             |                       |                             |            |                                                                                 |
| Shaw et al.,      | 39         | NA          | Breast cancer         | Mometasone furoate         | 3M no string barrier film or control | When compared to the control and 3M no string barrier film, CS substantially delayed the onset of grade 2 dermatitis. |
| [27]              |            |             |                       |                             |            |                                                                                 |
| Ulff et al.,      | 104        | NA          | Breast cancer         | Betamethasone + Essex cream| Essex or Canoderm cream | TS was more efficient for the control of RTD compared to emollient creams. |
| [28]              |            |             |                       |                             |            |                                                                                 |
| Ulff et al.,      | 202        | NA          | Breast cancer         | Betamethasone-17-valerate  | Essex      | CS along with prophylactic treatment was effective for the prevention and control of ARD. Betamethasone was effective in reducing grade 2 and 3 RD. TS may only be beneficial for management of symptomatic RD rather prophylactic intervention. |
| [29]              |            |             |                       |                             |            |                                                                                 |
| Menon et al.,     | 150        | NA          | Head and neck cancer  | 0.1 % Betamethasone valerate| Control   | MMF along with moisturizer was more effective in reducing RD than moisturizer alone. |
| [30]              |            |             |                       |                             |            |                                                                                 |
| Yokota et al.,    | 211        | NA          | Head and neck cancer  | NA                         | Control    | MMF along with moisturizer was more effective in reducing RD than moisturizer alone. |
| [31]              |            |             |                       |                             |            |                                                                                 |
| Bostrom et al.,   | 49         | NA          | Breast cancer         | Mometasone furoate         | Moisturiser| MMF along with moisturizer was more effective in reducing RD than moisturizer alone. |
| [8]               |            |             |                       |                             |            |                                                                                 |
| Miller et al.,    | 176        | NA          | Breast cancer         | Mometasone furoate         | Control    | MMF reduced acute skin toxicity in comparison to control group. |
| [32]              |            |             |                       | 0.1 %                      |            |                                                                                 |

TC (Topical steroid), RD (Radiation dermatitis), ARD (Acute radiation dermatitis), RT (Radiation therapy), CS (Corticosteroid spray), RT (Radiation therapy), DLQI (Dermatology life quality index), MD (Moist desquamation)
3.3 Pruritus and Pain

Only eight research [8,16,19,23,26,28,29,32] showed pruritus. All eight trials found that the TS group had less irritation and burning than the control or comparison group. However, only four research [19,23,28,32] yielded statistically significant findings. In three studies, the pain was noted, but there was no statistically significant difference among the intervention and control groups. [8,19,23,32].

3.4 Quality of Life

Six research [7,20,23,25,28,32] assessed participants' quality of life (QoL). Skin-related QoL was assessed using the DLOI [23,25], SD-16 [20], Skindex [7,28], and SF-36 [7]. Schmuth et al. [7] reported a deterioration in QoL in the dexpanthenol arm vs 4 out of 7 characteristics in the methylprednisolone arm. Ulff et al., [28] and Miller et al., [32] discovered no change in QoL between the intervention and control groups, but Hindley et al., [25] discovered lower DLOI ratings in the CS group as compared to the placebo group.

4. DISCUSSION

Radiation dermatitis is among the most common adverse events of radiation therapy, with symptoms ranging from mild erythema to severe ulceration, necrosis, and wet desquamation. [6]. Wet desquamation occurs mainly at doses greater than 20 Gy [4]. Many variables have been documented to impact the severity of RD in patients [33], including patient-related factors (e.g., smoking, bra size) as well as therapeutic aspects (e.g., beam energy, dosage, treatment methods, chemotherapy, tamoxifen) [34]. IMRT significantly decreased the incidence of RD in prostate cancer patients when compared to traditional techniques (p<0.001), despite the fact that it is not the standard of care in melanoma radiation. [35]. A smaller bra size was associated to a decreased incidence of moist desquamation in a multivariate analysis. [36]. RD remains a problem, despite significant advancements in radiation technology [37]. Many patients will have RD as a result of the frequently used lower beam intensity in breast cancer radiation, as well as the tangential beam arrangement. [38]. Consensus on RD care is still lacking, and there is an urgent need for it to be managed appropriately in order to enhance outcomes for this patient population [6].

Efforts have been undertaken to measure the intensity of skin reaction, as evidenced by the creation of the RTOG and CTCAE skin reaction scales; however, further study is required to verify these tools for accurate and exact evaluation [39]. In addition, grade 3 RTOG and CTCAE RD were preferred as the review's endpoints because they provide the least confusing definition of wet desquamation. The clinical measures created by the authors and utilized in several of the trials included in this analysis are of particular interest [7,8]. These scales have never been validated or published before, and so might be a source of errors. Nonsteroidal medications have now been investigated in clinical studies to determine whether they can assist with RD, but no positive results have been discovered. [39]. Steroids are already being used and are developing as a viable option [6]. To yet, clinical evidence is insufficient to establish their therapeutic value. As a result, the findings of these research required to be compiled into a systematic review in order to arrive at a more solid and certain conclusion that could then be used to guide practice. The steroid group's mean RD score was lower in the intervention group. This showed that steroids can benefit patients with RD symptoms by reducing their intensity, and that the majority of people would not suffer the more severe symptoms. Patients frequently describe the signs and symptoms of RD as discomfort, burning, and itching [40]. Itching and burning were observed in eight investigations [8,16,19,23,26,28,29,32]. The Visual Analogue Scale was one of the tools used. Compared to placebo, the steroid group had less symptoms of burning and itching. This was partly predicted given that topical corticosteroids such as mometasone and betamethasone are commonly used to treat itch associated with inflammatory disorders. Mometasone or betamethasone was used as an intervention in five of the studies. As a result, it was not surprising that the steroid arm had less symptoms. Four studies out of six yielded substantial effects for pruritus and burning [19,23,28,32]. Because there was no notable change between CS and control groups, we concluded that topical corticosteroids had no effect on RD pain, consistent with Bolderston et al findings... [41]. RD's discomfort and negative influence on quality of life is another important topic of evaluation [38,42]. RD can substantially impact patients' quality of life and can influence the therapeutic radiation dose given [6,38]. Only Six of eighteen studies [7,20,23,25,28,32] looked at the impact of RD on patients' quality of life...
(QoL). The DLQI [23,25], SD-16 [20], Skindex [7,28], and SF-36 [7] were utilized in all six trials to assess QoL. These measures have been verified as standard evaluation techniques in dermatology, making their results credible [43]. The baseline evaluation of QoL was carried out in three studies [7,25,32]; however, it was unclear in two others [23,28]. Although the quantitative analysis was unfeasible due to the reporting heterogeneity approach, using a topical steroid improved patients’ QoL. However, the significance of this result could not be validated. According to Hindley et al., mometasone furoate significantly improved QoL, but no p-value was supplied; thus, we could not make a definitive recommendation.

This systematic review, like any other, suffers from a lack of comprehensive information, probable selection biases, publishing biases, and a lack of a controlled method to reporting. Furthermore, the quality of research, an unclear blinding technique, inadequate outcome data reporting, and variations in the use of scales for measuring RD are also factors to consider. While our technique may have missed some actual NUC instances, many more are likely to have gone unreported, a shortcoming that continues to impede attempts to correctly assess the impact of CS in the prevention of RD.

5. CONCLUSION

There were 19 studies on the use of TC for the prevention of RD. The studies discovered that preventive use of topical corticosteroids reduced the incidence of wet desquamation and reduced the average RD scores. The use of topical steroids was found to improve patient-reported symptoms and QoL, with minor side effects associated with its usage during radiation. This implies that TC are useful in avoiding RD. More investigation is necessary to identify which TC is by far the most effective for patients to use during radiotherapy in terms of effectiveness.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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