

Review

Topical Management of Acute Radiation Dermatitis in Breast Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract. *Aim: To evaluate the efficacy of topical corticosteroids in managing acute radiation dermatitis (RD) in female breast cancer patients. Materials and Methods: MEDLINE, EMBASE, CINAHL, CENTRAL, ScienceDirect, Google Scholar and Clinicaltrials.gov. were searched up to and including March 2017 to identify Randomised Controlled Trials (RCTs) assessing topical corticosteroids for the management and prevention of acute RD. Results: Ten RCTs (919 participants) were identified. Meta-analysis, including results for 845 participants, demonstrated significant benefits of topical corticosteroids in preventing the incidence of wet desquamation (OR: 0.29; 95%CI: 0.19-0.45; $p < 0.0001$) and reducing the mean RD score (SMD: -0.47 , 95%CI: -0.61 - -0.33 , $p < 0.00001$). Conclusion: Topical corticosteroids impacted on the incidence of wet desquamation and the average RD score observed in female breast cancer patients. The use of topical corticosteroids can reduce pruritus in participants and improve quality of life.*

Radiation induces damage to the skin, activating inflammatory pathways and causing cytokines overproduction (1, 2). Radiation dermatitis is a common acute side-effect that occurs within hours to weeks after the start of radiotherapy (3, 4) and affects more than 87% of patients (2, 5). Radiation dermatitis can limit the therapeutic dose delivered to patients and can, sometimes, lead to a break in treatment, thus potentially compromising local control and survival outcome (1, 6). It can also have a considerable impact on patients' quality of life (7,

8). Despite significant development in radiotherapy techniques, efficacious interventions in the prevention of acute skin reactions is still lacking and current evidence is unable to provide adequate guidelines for the management of this side-effect (9, 10). Studies have examined numerous topical agents such as Aloe Vera, aqueous cream, Calendula, petrolatum and sulcrilate cream as a means to reducing the dehydrating effects of radiation dermatitis (6, 11, 12). However, the results in terms of managing radiation dermatitis and treatment related pain have not been clinically significant (13, 14). Corticosteroids have anti-inflammatory properties and are known to down-regulate cytokine gene expression, making them ideal for managing radiation dermatitis (15-17). A systematic review by Bolderston *et al.* concluded that there is limited evidence to support or oppose the use of topical agents for the management of acute radiation dermatitis (18).

Skin care advice given to breast cancer patients varies among institutions (19). No gold-standard for the appropriate management of this side-effect exists and in most cases the decision of care is left at the discretion of the health care professional rather than clinical evidence (20, 21). Clinical advice is often given based on anecdotal evidence (22). The present systematic review and meta-analysis was conducted to assess the potential efficacy of corticosteroids in the management of RD and its impact on pain and quality of life in female breast cancer patients. However, the anticipated adverse effect associated with steroids is not evaluated and is beyond the scope of this review. We restricted our review to one site only due to radiotherapy dose variations used in different sites.

Materials and Methods

Search strategy for identification of studies. The electronic literature search was conducted up to and including March 2017. The search terms used were corticosteroid, radiation dermatitis, breast cancer, management, and prevention. The reference lists of potentially eligible studies were subsequently hand searched to identify

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Key Words: Radiation dermatitis, breast cancer, corticosteroids, wet desquamation, review.

Table I. Search strategy for identification of studies.

EMBASE

Emtree: breast cancer: 373,140 records, radiation dermatitis: 3,131 records, steroid: 1,363,423 records

Query Builder: "breast cancer"/exp and "radiation dermatitis"/exp and "steroid"/exp: 107 items including 7 of the trials

MEDLINE

Search Builder: ("Radiodermatitis"[Mesh] and "Breast Neoplasms"[Mesh]) and "Steroids"[Mesh]: 18 items including 8 of the trials

ScienceDirect

Advanced search:

Search for: radiation dermatitis (TITLE-ABSTR-KEY) and breast cancer (TITLE-ABSTR-KEY)

Refine your search: Journals; Years: 2000-present: 78 items including 4 of the trials

Google Scholar

Radiation dermatitis (with all words) breast cancer (with the exact phrase) in the title of the article, Return articles dated between 2000-2017:

78 items including 2 of the trials

CINAHL

Search 1: (MH "Breast Neoplasms+") 59,993 records, Search 2: "radiation dermatitis" 108 records, Search 3: (MH "Steroids+") 52,686 records

Boolean Operator S1 and S2 and S3: 5 items including 2 of the trials

CENTRAL

MeSH descriptor: [Radiodermatitis] explode all trees 129 records, MeSH descriptor: [Breast Neoplasms] explode all trees 10104 records,

MeSH descriptor: [Steroids] explode all trees 44,093 records

"radiodermatitis" and "breast neoplasms" and "steroids": 4 records including 2 of the trials

Clinicaltrials.gov

"Breast cancer" and "radiation dermatitis": 38 records: 4 completed trials with results including 1 of the trials

Records identified through database searching: 107+18+78+78+5+4+4=294

Table II. Methodological quality summary: Jadad *et al.* scale for reporting randomised controlled trials.

Jadad's Methodological quality item	Bostrom <i>et al.</i> (2001)	Schmuth <i>et al.</i> (2002)	Farhan <i>et al.</i> (2003)	Shukla <i>et al.</i> (2006)	Omidvari <i>et al.</i> (2007)	Miller <i>et al.</i> (2011)	Ulff <i>et al.</i> (2013)	Hindley <i>et al.</i> (2014)	Meghrajani <i>et al.</i> (2016)	Ulff <i>et al.</i> (2017)
Randomised	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Method of randomisation is appropriate	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Blinding	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes
Method of blinding is appropriate	Yes	Yes	Yes	N/A	Yes	Yes	Yes	No	Yes	Yes
An account of all patient	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total Jadad score	5/5	5/5	4/5	2/3	5/5	5/5	4/5	4/5	5/5	5/5

additional studies. A search strategy was developed (Table I) and a PRISMA Flow chart was used in the study selection process (Figure 1) (23). RCTs assessing management and/or prevention of radiation dermatitis were included.

Types of participants and interventions. Eligible trials included female breast cancer patients of any stage receiving minimum adjuvant EBRT dose of 40 Gy to the breast or chest wall. RCTs

were also included if participants in addition to breast/ chest wall irradiation had treatment to regional lymph nodes. Studies were included if the intervention was aimed at preventing or managing RD in participants. Topical corticosteroid must have been used solely for or as part of the intervention with the intent of preventing or managing RD. The comparison could be placebo, no treatment, or a topical non-steroidal agent. Studies comparing only topical steroids or where steroids were not used as intervention were

excluded. Trials must have reported the method of measuring RD and must statistically assess it as a primary outcome.

Types of outcomes. Eligible RCTs reported severity of acute RD in both arms of studies. Incidence of wet desquamation was assessed as a primary outcome. Other outcomes evaluated were mean RD score, pain, pruritus, burning sensation and QoL.

Methodological quality. The internal quality of the included studies was assessed using the Jadad *et al.* scale for reporting randomised controlled trials (Table II) (24), and were assigned a quality score between 0 (low) and 5 (high). The Cochrane Collaboration's tool for assessing risk of bias was also employed (25) (Figure 2). Funnel plots were constructed to assess for the possibilities of publication bias and heterogeneity in the studies.

Statistical analysis. Two independent collectors extracted the data. Data on participants, intervention and outcome were extracted and these included beam energy, surgery type, overall RT dose, steroid application (Table III).

Statistical Power was calculated in RCTs using a two-sided test of significance (8, 26, 27), test was not reported for in three RCTs (28, 29) and no statistical power calculation was present for four (7, 30-32). Descriptive statistics were reported in all studies for age (quantitative numerical data) including mean, median, and range (7, 8, 26-33). Other trials reported mean and range field size (29, 33), field area (33), range of total radiation dose (7, 26), median number of nodes and range (8).

In one study homogeneity of study arms was controlled using non-parametrical tests, Kruskal-Wallis test and Friedman test (33). The factors used were age, radiotherapy field size and field arrangement and type and number of chemotherapy courses prescribed before radiotherapy. The method of ensuring homogeneity was unclear in other RCTs however the authors stated that the features of the two groups were comparable and balanced (7, 8, 26-32).

Kruskal-Wallis test (7, 32), Chi-square tests (31, 33) and unpaired *t*-tests (7) were employed to assess the differences in RD scores between study arms. The mean maximum score was assessed using a single two-sample *t*-test (26). The differences in mean responses of patients reported symptoms and QoL were analysed using the Kruskal-Wallis test. The intention-to-treat principle and two tailed tests were used in two studies (8, 29). In one of the two studies the Mann-Whitney *U*-test was used for the statistical analyses of RD and patients reported symptoms (8). In scoring RD observed in participants, a modified RTOG (27), a standard RTOG score (28, 31-33) and CTCAE version 3.0 was used (26, 29). Clinical scales were used in 3 RCTs (7, 8, 30).

The Visual Analogue Scale (VAS) and the Skindex-16 questionnaire were used to measure subjective symptoms in six RCTs (7, 8, 26, 28, 29, 32). The Dermatology Life Questionnaire Index (DLQI) was used to measure QoL in three (27-29). Pain was reported using the terms mild, moderate and severe (31). Due to the heterogeneity in the reporting of symptoms and QoL in the studies eliminating the possibilities of pooling, the data was summarised.

Forest Plots were generated wherever possible for the incidence of wet desquamation and RD scores. As mentioned previously data for symptoms and QoL were too heterogeneous to include in a forest plot and no threshold were required. The threshold for acute RD was the onset of wet desquamation or grade 3 CTCAE/RTOG scale.

PRISMA Flow Diagram

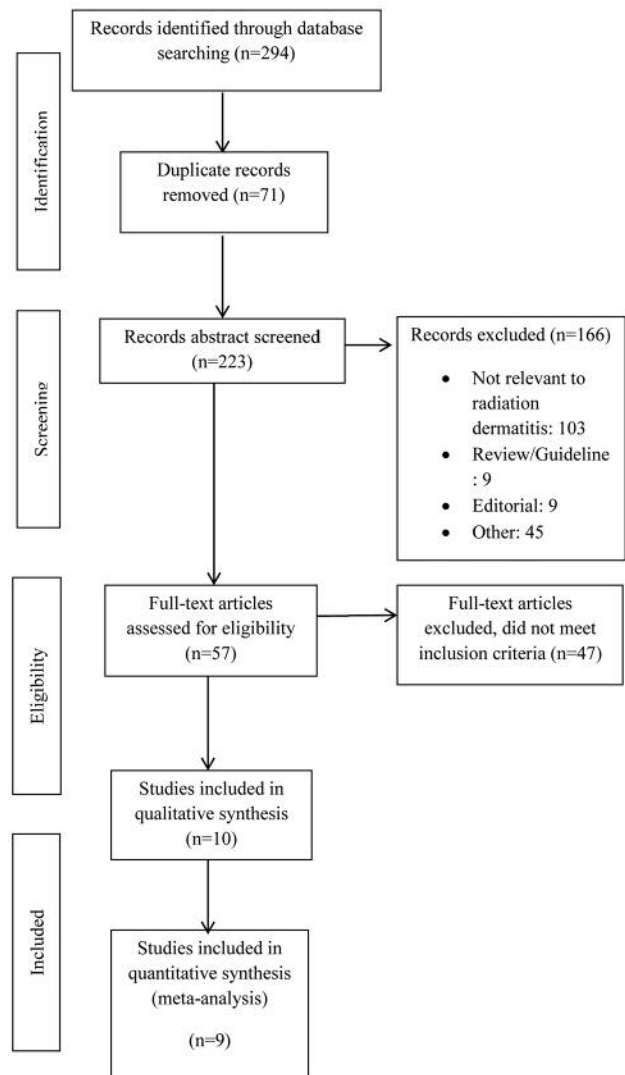


Figure 1. PRISMA flow diagram for identification of included studies.

This was the endpoint of this review. All forest and funnel plots were constructed using The Cochrane Collaboration's Review Manager, version 5.3.

Results

Description of studies. Ten studies meeting the inclusion criteria for this review were published between 2001 and 2017 (7, 8, 26-33). The main characteristics of the included studies are presented in Table III. In the ten included studies, 919 participants were randomly assigned to steroid *versus* non-steroidal agent except for one study where the control arm had no treatment (30). The steroids assessed were mometasone

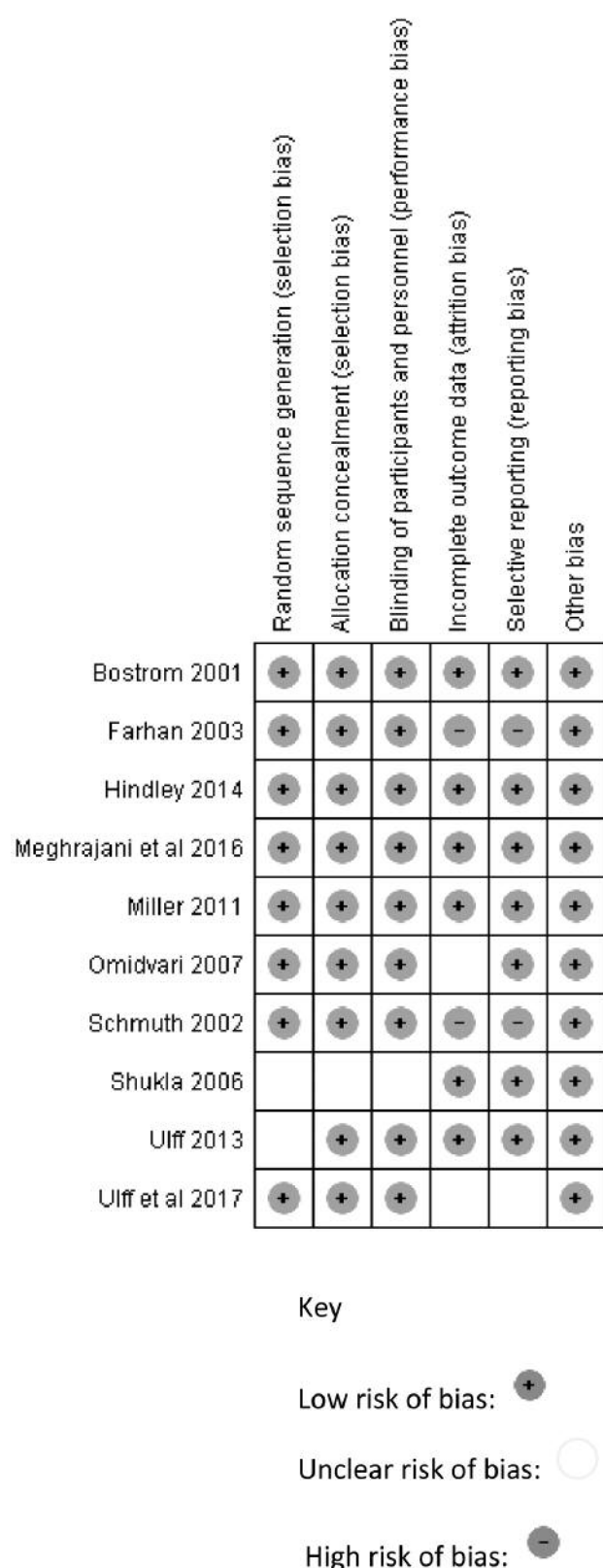


Figure 2. Risk of bias summary: review author's judgements about each risk of bias item for each included study.

furoate (8, 26, 27), beclomethasone(30), methyl prednisolone (7), betamethasone (28, 31-33) and hydrocortisone (29). All the participants had breast cancer and underwent either mastectomy or breast conservative therapy. The type of surgery was comparable within the trials (Table III). Participants were females with age ranging from 27-97 years. Radiotherapy dose ranged from 40 Gy - >56 Gy. Treatment were applied once/twice daily to the breast or chest wall from the first fraction of radiotherapy to the last fraction and in some studies up to 3 weeks after radiotherapy. The frequency of treatment application differs between the trials (Table III). Participants were not allowed to apply any other medication to the breast or chest wall during the study duration.

Risk of bias in included studies. The results of the Jadad *et al.* Scale assessed by two independent observers for the individual studies have been included (Table II). From the Jadad *et al.* scale (5 questions), all of the trials scored at least 4 out of 5 except one study (30). In this study blinding could not be done. It was scored 2 out of a maximum of 3 points. According to the Jadad *et al.* scale all studies would be deemed to be moderate to high quality. In accordance with the Cochrane risk of bias tool (25) (Figure 2), four of the studies had low risk of bias (8, 26, 27, 29), two had high risk features (7, 31) and four had unclear risk in one or more domains (28, 30, 32, 33). The intention-to-treat approached was employed by Bostrom *et al.* and Meghrajani *et al.* thereby rated low risk for incomplete outcome data and selective reporting (8, 29). Drop out was highest in Schmuth *et al.* with 8.7 % (7) (Table III). Two participants dropped out of this study compared to ten in Miller *et al.* however due to its small sample size, it had the highest percentage of drop outs relative to its sample size. Overall the methodological qualities of all trials were reasonable.

Incidence of wet desquamation. Nine of the ten RCTs stated the incidence of wet desquamation in their results, accounting for 845 patients out of 919 (8, 26-33). Eight out of the nine studies showed a lower incidence of wet desquamation in the steroid arm *versus* the control (8, 27-33). Pooling the results for nine RCTs, identified that topical corticosteroid significantly reduce the incidence of wet desquamation, (OR: 0.29; 95%CI=0.19-0.45; $p<0.0001$). One RCT was excluded from this analysis because incidence of wet desquamation was not presented (7). There was no evidence of heterogeneity in the pooled data following both quantitative ($\chi^2=3.85$; $df=8$; $p=0.87$; $I^2=0\%$) (Figure 3A) and qualitative analyses (Figure 3B). Test of overall effect showed that, the risk of developing wet desquamation is approximately 5 times less likely with the use of topical corticosteroids (Figure 3A).

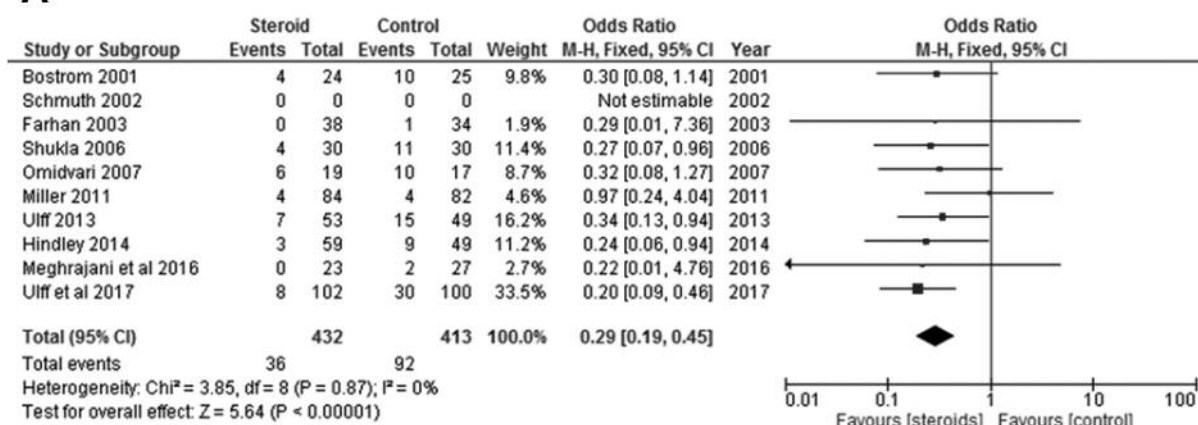
Mean radiation dermatitis score. Mean RD scores were reported in nine studies. Mean RD scores and standard

Table III. Characteristics of included studies.

	Bostrom <i>et al.</i> (2001)	Schmuth <i>et al.</i> (2002)	Farhan <i>et al.</i> (2003)	Shukla <i>et al.</i> (2006)	Omidvari <i>et al.</i> (2007)	Miller <i>et al.</i> (2011)	Ulf <i>et al.</i> (2013)	Hindley <i>et al.</i> (2014)	Meghrajani <i>et al.</i> (2016)	Ulf <i>et al.</i> (2017)
Participants										
Sample size (n)	50 (25 MF/25 placebo)	23 (12 methyl/11 dex)	76 (38 beta/38 placebo)	60 (30 beclo/30 no trt)	58	176 (90 MF/86 placebo)	104 (53 beta/24 essex/27 cano)	120 (62 MF/58 D)	50 (23 hydro/27 placebo)	202 (102 beta/100 essex)
Age range/ mean +/- SD	47-76	35-75	27-70	28-60	34-66	27-89	28-90	59 +/- 11 MF/60 +/- 10 D	31-70	27-97
surgery	BCS	BCS & MRM	BCS & MRM	BCS & MRM	MRM	BCS & MRM	BCS & MRM	BCS & MRM (+bolus)	MRM	BCS & MRM
RT machine	Linac	Linac +/- electron boost	Cobalt-60	Cobalt-60	Superficial X-rays	-	Linac	Linac +/- electron boost	Cobalt-60	Linac
Beam energy	5 MV photons	8 MV photons +/-14 MeV electrons	-	-	-	-	-	6-10 MV	-	-
RT total dose (Gy)	54-56 Gy (2Gy/#)	56 +/- 4 Gy (2Gy/#)	50 Gy [MRM]-60 Gy [BCS] (2 Gy/#)	50 +/- 16 Gy [boost] 2Gy/#	50 Gy (2 Gy/#)	>50 (1.75-2.12 Gy/#)	50 (2 Gy/#)	40 (2.67 Gy/#) +/- 10 (2 Gy/#)	50 +/- 10 Gy [boost] 2 Gy/#	42.56/50 Gy (2.66/2Gy/#)
No. of RT #	27-28	28+/-2	25-30	25 +/-8	25	>25	25	15 +/- 5	25 +/-5	16/25
Intervention										
Topical steroid	Mometasone furoate 0.1% cream	Methylpredni solone 0.1% cream	Beta-methasone 0.1% ointment	Beclo-methasone spray 100 µg/puff	Beta-methasone 0.1% ointment	Mometasone furoate 0.1% cream	Beta-methasone cream	Mometasone furoate 0.1% cream	Hydro-cortisone 1% cream	Beta-methasone cream
Comparison	Placebo cream	Dexpanthenol cream	Placebo ointment	No treatment	Petrolatum/No treatment	Placebo cream	Essex cream/canoderm cream	Diprobace cream	Placebo cream	Essex cream
Frequency of application	Twice weekly x first 2 weeks of RT, then once daily	Twice daily	Twice daily	Twice daily	Twice daily	Once daily	Once daily	Once daily	Twice daily	Once daily
Duration of RT treatment	6 weeks	6 weeks	5-6 weeks	5-6 weeks	5 weeks	>5 weeks	5 weeks	3-4 weeks	5-6 weeks	3/5 weeks
Outcome										
RD scale	Clinical scale	Clinical scale	RTOG	Clinical scale	RTOG	CTCAE	RTOG	Modified RTOG	CTCAE	RTOG
Pain/Qol scale	VAS	Skindex-16 & SF-36	Visual	-	-	CTCAE SE diary, Skindex-16,	VAS & DLQI	DLQI	VAS & DLQI	VAS
Baseline assessment of RD	Yes	Yes	-	-	-	Yes	Yes	Yes	Yes	Yes
Baseline assessment of pain/Qol	UNCLEAR	Yes	-	-	-	Yes	-	yes	UNCLEAR	Yes
Intervention duration	9 weeks	8 weeks	6-7 weeks	5-6 weeks	7 weeks	>5 weeks	7 weeks	5 weeks	6-7 weeks	5/7 weeks
Study duration	9 weeks	8 weeks	9-10 weeks	9 weeks	7 weeks	>7 weeks	7 weeks	6 weeks	6-7 weeks	4/6 weeks
Dropout	1 (MF) 2%	2 (methyl) 8.7%	4 (placebo) 5.3%	0%	7 12%	10 (6 MF/4 placebo) 1.78%	2 (cano) 1.9%	6 (3MF/3D) 5%	0	0
Eligible for evaluation	49 (24 MF/25 placebo)	21 (10 methyl/11 dex)	72 (38 beta/34 placebo)	60 (30 beclo/30 no trt)	51 (19 beta/15 no trt)	166 (84 MF/82 placebo)	102 (53 Beta/49 essex-cano)	114	50	202

BCS: Breast conservative surgery; MF: mometasone furoate; methyl: methylprednisolone; beclo: beclomethasone; cano: canoderm cream; beta: betamethasone; dex: dexpanthenol; no trt: no treatment; petro: petrolatum; D: diprobace; hydro: hydrocortisone; VAS: visual analogue scale; CTCAE: common terminology criteria for adverse events; RTOG: radiation therapy oncology group; Qol: quality of life; RT #: number of radiation therapy fraction; RT: radiation therapy; Gy: gray; RD: radiation dermatitis; MRM: modified radical mastectomy; SD: standard deviation; Linac: linear accelerator; MV: mega voltage; MeV: mega electron voltage; DLQI: dermatology life questionnaire index; SF-36: short form health survey.

A



B

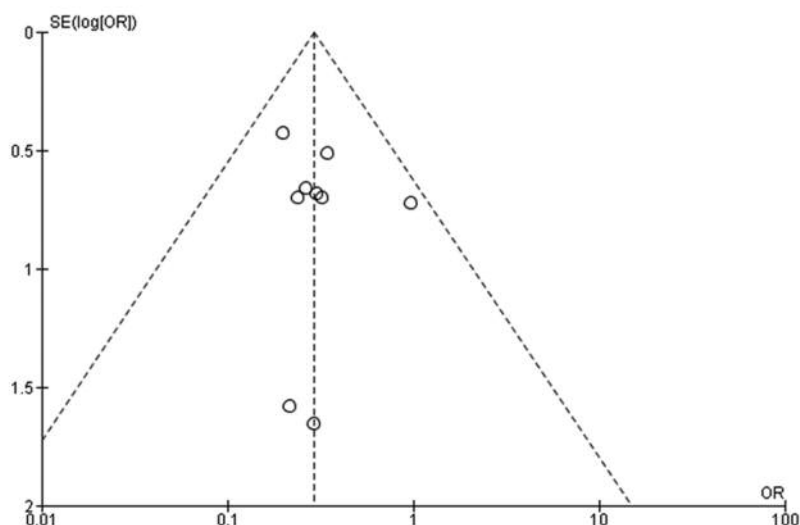


Figure 3. A) Outcome: Incidence of wet desquamation. A: Forest plot of comparison: steroid vs. control. df: degree of freedom, Fixed: Fixed Effect, M-H: Mantel Haenszel. B) Outcome: Incidence of wet desquamation. B: Funnel plot of comparison: steroid vs. control. OR: Odd ratio; SE: standard error.

deviation were read from the graphs presented (7, 33). However, they were calculated from the tables presented in four studies (8, 27, 31, 32) and were given in two (26, 29). One study was excluded in this analysis because there was no data on the mean RD score (30). Raw data was requested for one study as the mean and standard deviation could not be extracted or calculated from the data provided (28). All studies showed a lower mean score in the steroid group *versus* the control group (Table IV). Pooling results for nine RCTs; the data consisted of 806 participants. Due to the variations in the scaled used in the studies; standardised mean difference was employed for a quantitative analysis of these results. Meta analysis's results demonstrated a

reduction in mean RD scores across the trials (SMD: -0.47 , 95% CI: -0.61 -0.33 , $p < 0.00001$), with evidence of heterogeneity ($\chi^2 = 15.79$; $df = 8$; $p = 0.05$; $I^2 = 49\%$) (Figure 4A). An associated funnel plot (Figure 4B).

Patients' subjective report of pain. Patients' subjective report of pruritus and burning was explained and measured in six trials (8, 26, 28, 29, 31, 32). All six studies reported less pruritus and burning in the steroid group compared to the control. Four studies showed significant results (26, 28, 29, 31) (Table IV). Pain was reported in four trials however there was no significant difference between the two arms of study in the trials (8, 26, 29, 31) (Table IV).

Table IV. Primary and secondary outcome

Outcome	Bostrom et al. (2001) MF vs. placebo	Schmuth et al. (2002) methyl vs. dex	Farhan et al. (2003) beta vs. placebo	Shukla et al. (2006) beclo vs. no trt	Omidvari et al. (2007) beta vs. p etro vs. no trt	Miller et al. (2011) MF vs. placebo	Ulf et al. (2013) beta vs. essex vs. cano	Hindley et al. (2014) MF vs. D	Meghrajani et al. (2016) hydro vs. placebo	Ulf et al. (2017) beta vs. essex
Primary outcomes										
Incidence of wet desquamation (grade 3)	MF: 16.67% Placebo: 40%	-	Beta: 0% Placebo: 2.9%	Beclo: 13.33% No trt: 36.66%	Beta: 35% Petro: 60% No trt: 45%	MF: 4.76% Placebo: 4.87%	Beta: 15% Essex-cano: 30.6%	MF: 4.8% D: 15.5%	Hydro: 0% Placebo: 7.41%	Beta: 7.84% Essex: 30%
Secondary outcomes										
Mean RD score +SD	3.25±1.39 vs.	1.6±0.25 vs.	1.026±0.367 vs.	-	1.3±0.3 vs.	1.167±0.848 vs.	1.623±0.79 vs.	1.427±0.564 vs.	0.713±0.204 vs.	1.768±1.008 vs.
Pain and subjective report	4.32±1.49 No difference in pain (p=0.42). Less itching (p=0.069) and burning (p=0.087) in MF	2.2±0.4 -	1.429±0.558 No difference in pain. Less burning and pruritus in beta vs. placebo, p<0.05	-	-	MF: 2.5 vs. Placebo: 2.9 (p=0.15) Less itching and burning (p=0.002, 0.02)	Less in beta, p=0.048- (burning, itching, irritation)	-	No difference in pain. Less pruritus in hydro vs. placebo (p=0.032)	Less itching, burning and irritation in beta vs. essex
Qol report	-	Methyl: 4 out of 7 aspects worsened vs. dex: 7 out of 7	-	-	-	No difference	No difference in DLQI	Less DLQI in MF	Lower DLQI score in hydro (2.22 vs. 2.48). p=0.069	-

RD: Radiation dermatitis; SD: standard deviation; vs: versus; methyl: methyl prednisolone; dex: dexamethasone; MF: mometasone furoate; beta: betamethasone; DLQI: dermatology life questionnaire index; beclo: beclometasone; No trt: no treatment; petro: petrolatum; cano: canoderm cream; D: diprbase; hydro: hydrocortisone.

Quality of life. Five trials assessed Qol in their participants (7, 26-29). Skindex-16 (7, 28) and DLQI (27-29) were the tools employed to examine skin related Qol. Schmuth *et al.* observed that there was worsening in all aspects of Qol in the dexamethasone arm compared to four out of seven aspects in the methylprednisolone arm (7) (Table IV). There was no difference in Qol between the groups in two studies Ulf *et al.*, and Miller *et al.* however Hindley *et al.* and Meghrajani *et al.* found less DLQI scores in their steroid group compared to the control group (26-29) (Table IV). None of the studies reported a significant difference between the arms of study with regards to Qol except in Hindley *et al.*, however the *p*-value was not stated (27).

Discussion

Radiation dermatitis is one of the most common side-effects of radiotherapy and varies in grade from mild erythema to more severe reactions of wet desquamation; ulceration and sometimes necrosis (6). Wet desquamation mainly occurs in dose of excess of 20 Gy (4, 34). Many factors have been

reported to influence the severity of RD in patients (35), patients' related factors (*e.g.* smoking, bra size) and treatment factors (*e.g.* beam energy, dose, treatment techniques, chemotherapy, tamoxifen) (8, 21, 36). IMRT significantly reduced the severity of RD in breast cancer patients compared to conventional techniques *p*<0.001, but it is not the standard of care in breast cancer radiotherapy (37). Smaller bra size was found to be associated with decreased risk of wet desquamation in a multivariate analysis (38, 39).

Despite the vast improvement in radiation technology, RD remains a concern (6, 39, 40). Reduced skin sparing effect because of the commonly used lower beam energy in breast cancer radiotherapy coupled with tangential beam arrangement mean that a lot of patients will experience some form of RD (40, 41). Consensus regarding care for RD is still lacking and there is an urgent need for its appropriate management to improve outcome for this patient cohort (6).

Efforts have been made to quantify the degree of skin reaction and this is seen in the development of the RTOG and CTCAE scales for skin reaction; however more

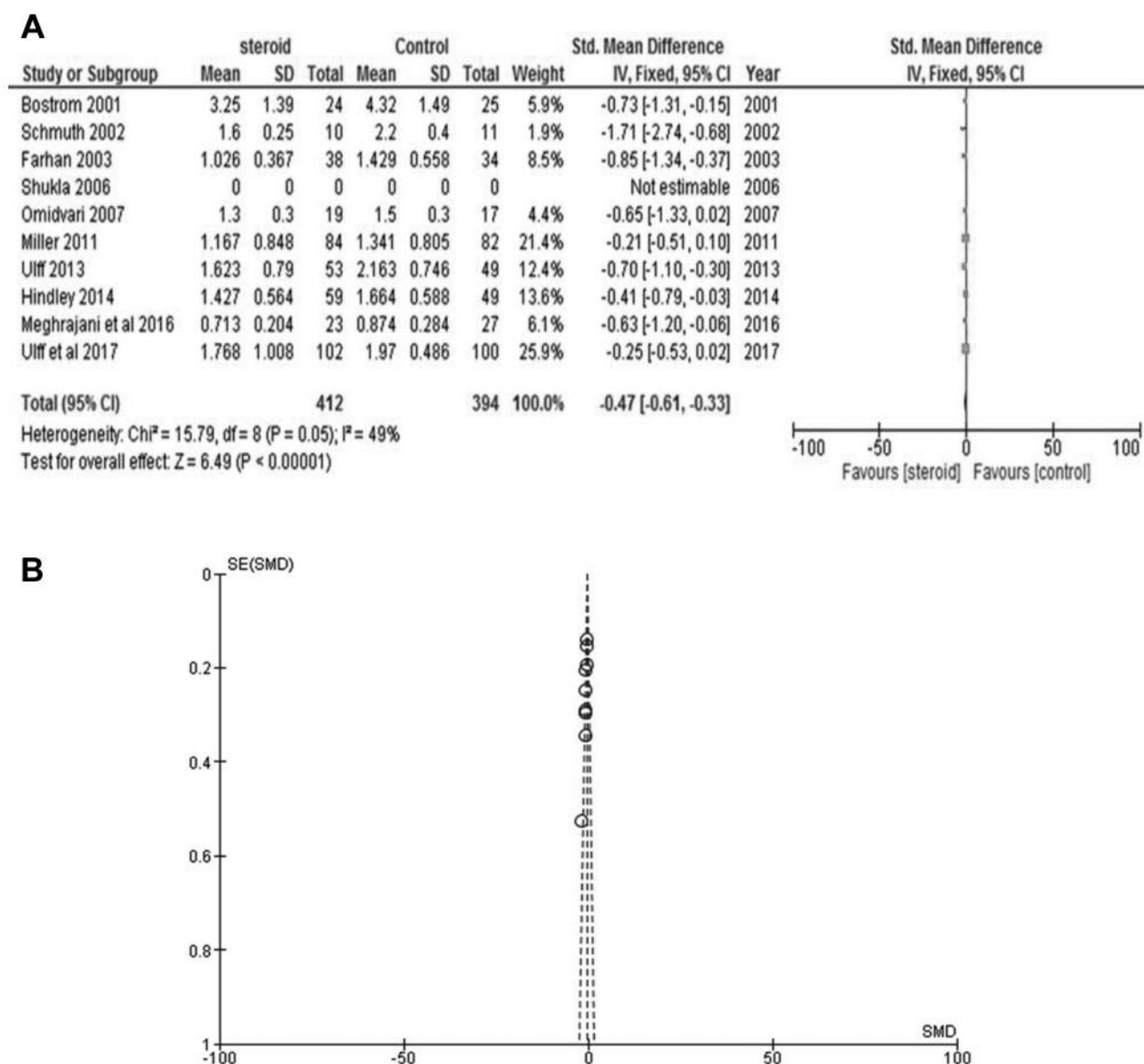


Figure 4. A) Outcome: Mean acute radiation dermatitis. A: Forest plot of comparison: steroid vs. control. df : Degree of freedom, Fixed: fixed effect, IV: inverse variance, std: standard. B) Outcome: Mean acute radiation dermatitis. B: Funnel plot of comparison: steroid vs. control. SMD: Standard mean difference, SE: standard error.

research is needed to validate these tools for accurate and precise assessment (42). Also grade 3 RTOG and CTCAE RD has been chosen as the endpoint of this review as it is the least ambiguous description of wet desquamation according to these scales. Particularly of interest are the clinical scales developed by authors used in some of the trials included in this review (7, 8, 30). These scales were not validated nor previously published and thus could be a potential source of bias.

Non-steroidal agents have been tested in trials to determine their impact on RD but studies have failed to show a positive effect (42). Steroids are already in practice and are now emerging as a suitable alternative (6, 15, 22). Clinical evidence to date is insufficient to demonstrate their clinical benefit. Therefore, it was necessary to pool the results of these trials together in a systematic review to establish a grounded and more concrete conclusion that could in turn inform practice. The topical corticosteroids in this review

vary from mild to potent and the vehicles used were mainly cream and ointment except in one study where aerosol was employed. The reason for this was to avoid the bolus effect however the increase in surface dose is not significant when a thin layer (<2 mm) of product is applied (43). The maximum application of treatment in the studies included in this review did not exceed twice daily (Table III).

A previous review by Meghrajani *et al.* identified that the incidence of wet desquamation was 2.5-times less likely with the use of topical steroids (44). The meta-analysis included 383 patients. Our results had 845 patients and demonstrated that the risk is at least 5 times less likely. This is a marked improvement however it must be stated that the qualities of the trials included could have influenced the outcome observed. In order to reduce bias towards steroids it was necessary to examine the trials individually and try to make meaning of their results. It is expected that in trials where superficial X-rays and Cobalt-60 were employed for treatment, an increased incidence of wet desquamation would be reported (30, 31, 33). This is due to a reduced skin sparing effect compared to the other trials where at least 5 MV were used (40). Also, the trials with the higher beam energies had much larger sample sizes compared to the former trials (7, 8, 26-28). Surprisingly Farhan *et al.* had no event in the steroid arm and only one incidence of wet desquamation in the control arm despite having employed Cobalt-60 as the method of radiation therapy treatment delivery (31). The 95% CI (0.01-7.38) for this trial was quite wide, implying a degree of uncertainty in the effect size and necessitating caution when interpreting the results. Upon assessing the internal validity of this trial incomplete outcome data and selective reporting were identified. Nonetheless our result agrees with the systematic review previously done by Salvo *et al.* reporting that topical corticosteroid agents significantly reduce the severity of RD (6).

The mean RD score was lower in the steroid group than in the control arm. This showed that steroid is effective in reducing the grade of RD observed in patients and that majority of patients would not be experiencing the more severe effects. Our result is on par with that of Meghrajani *et al.* (SMD: -0.47, 95%CI: -0.61 -0.33, $p < 0.00001$) even though more participants were included in our pooled analysis (345 vs. 806) (44). Heterogeneity was present ($I^2=49\%$) but less than in Meghrajani *et al.* It was sometimes difficult to extract data from the graphs provided by some of the authors and in some the raw data was absent. This could have resulted in an overestimation of effect and the heterogeneity observed in our review.

The signs and symptoms of RD are often expressed by patients as pain, burning, itching (45). Six trials examined itching and burning (8, 26, 28, 29, 31, 32). Tools employed included the Visual Analogue Scale. There was less symptom of burning and itching in the steroid group compared to the

control group. This was somewhat expected as standard management of pruritus associated with inflammatory diseases include topical corticosteroids such as mometasone and betamethasone (46, 47). Five of the trials had either mometasone or betamethasone as intervention. Therefore it was not unusual that fewer symptoms were observed in the steroid arm. In the systematic review by Koukourakis *et al.*, it was suggested that a low dose corticosteroid may be beneficial in reducing itching and irritation (48). This was also recommended in the guideline by Wong *et al.* (49). For pruritus and burning, the results of three trials out of six were significant at week 5, $p < 0.05$, 0.002, 0.032 (26, 29, 31) (Table IV). This however contrasted with the result of the review by Bolderston *et al.* where no significant difference was detected between the steroid arm and the control (18). Although the study by Ulf *et al.* observed significant difference ($p=0.048$) between the groups at week 6, the time endpoint for this review was week 5 (28).

Pain was assessed in four trials (8, 26, 29, 31). Baseline measurement of pain was performed (26); it was unclear (8, 29) and was not performed (31). There was no significant difference between the steroid arm and the control arm, leaving us to conclude that topical corticosteroid does not have any impact on pain associated with RD in line with the results of Bolderston *et al.* (18).

The distress and unfavourable impact of RD on quality of life is also an important area of assessment (21, 40, 50, 51). Radiation dermatitis can have a significant effect on patients' QoL and can determine the prescribed therapeutic radiation dose (6, 40, 49). Only five of the ten included trials examined the impact of RD on participants' QoL, highlighting the need for more emphasis to be placed on research in this area (7, 26-29) (Table IV). All five trials used either Skindex-16 or DLQI in assessing QoL. These tools have been validated in dermatology as standard assessment tools which in turn made their results plausible (52). Baseline assessment of QoL was conducted in three trials (7, 26, 27) however it was unclear in two (28, 29). Although heterogeneity in the method of reporting made quantitative analysis unfeasible, the use of topical steroid improved QoL in patients however the significance of this result could not be established. Hindley *et al.* stated that mometasone furoate significantly improved QoL but the p -value wasn't given and thus we were unable to make a definitive recommendation.

Limitations. Even though all of the RCTs were deemed to be of reasonable quality, a few high-risk features including incomplete outcome data reporting and unclear domains could have impacted on the outcome. The included studies used different tools in measuring RD leading to differences in outcome reporting. In some studies raw data was not available and was sometimes difficult to extract from studies therefore we were unable to include all studies in meta-analysis.

Although the impact of this was somewhat minimised by contacting authors for raw data and clarification in their results. We were unable to quantitatively analyze the impact of corticosteroids on subjective symptoms and QoL to establish its significance due to heterogeneity in reporting methods.

Conclusion

This review identified that topical corticosteroids can be effective in reducing the incidence of wet desquamation and lessen the mean RD scores. Administration of these agents can also improve QoL and lower subjective symptoms. Future studies are required to validate tools needed to evaluate RD, assess the comparative effectiveness of topical steroids, and address the potential adverse effects not examined in this review.

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