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ORIGINAL ARTICLE

Topical agent therapy for prevention and treatment of radiodermatitis: a meta-analysis

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Abstract
Background Radiodermatitis (RD) is a common side effect during radiotherapy. Various topical agents have been tried to be applied on RD. However, the efficiency of topical agents applied on radiotherapy is still uncertain.
Objective This study aims to assess the efficiency of the topical agents in the prevention and treatment of RD.
Methods The Cochrane Central Register of Controlled Trials, Pubmed, and Medline were searched for relevant reports. Quantitative analysis was carried out to evaluate the efficiency of topical agents in the prevention and treatment of RD.
Results Twenty reports involving 3,098 patients were included: 2,406 patients for prophylactic trials and 692 for treatment trials, respectively. For prophylactic trials, primary meta-analysis indicated that using topical agents could not reduce the incidence of grade 2 and higher RD (P=0.128, RR=0.90, 95 % CI=0.78–1.03) with a high heterogeneity (P=0.000, I^2=71.5 %). In subgroup analyses, heterogeneity disappeared by excluding reports with low Jadad score (≤3) (P=0.292, I^2=15.2 %), and still no significant difference was found between the topical agent group and control group (P=0.625, RR=0.98, 95 % CI=0.89–1.07). In addition, for treatment trials, topical agents failed to increase the incidence of wound healing (P=0.784, RR=1.01, 95 % CI=0.92–1.12) with a high heterogeneity (P=0.067, I^2=51.5 %).
Conclusions Topical agents could not prevent or treat RD effectively. New type of agents should be developed to improve the efficiency based on the pathophysiology of RD.

Keywords Radiodermatitis · Topical agents · Meta-analysis

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Introduction

Approximately 50 % of all cancer patients will receive radiotherapy of some form, either alone or in combination with other treatment modalities such as surgery and chemotherapy [1]. A common side effect of radiotherapy is radiodermatitis (RD). Although advances in techniques of radiotherapy like intensity-modulated radiotherapy permits sparing of normal tissues and, hence, dose escalation to tumors, skin reaction is still inevitable [2]. A severe skin reaction like moist desquamation, skin necrosis, and ulceration may significantly reduce patients' compliance and impair quality of life, probably leading to interruption of treatment protocols [3]. Thus, prevention and treatment of RD is very necessary. So far, different kinds of regimens including topical agents, dressings, and skin care guidelines have been studied to prevent or treat RD, among which topical agents are most popular. Numerous investigations have been conducted to evaluate the efficiency of topical agents applied on radiotherapy. However, the efficiency of topical agents is still controversial, and there is no general consensus [2, 4–6]. In the publications included in this meta-analysis, some have demonstrated statistically significant positive effects of topical agents [7–16], while others get the opposite conclusion [17–24]. So the challenge is that there is no evidence-based practice guideline.

This study aims to investigate by searching for evidence through meta-analysis the efficiency of topical agents in preventing and treating RD.

Methods

Search strategy

The Cochrane Central Register of Controlled Trials (1982–2010), Pubmed (1987–2010), and Medline (1987–2010) were

systematically searched using the following key words: "radiodermatitis," "radiation dermatitis," "skin reaction," "skin toxicity," "skin care," "prevention," "prophylactic," "treatment," "erythema," "dry desquamation," and "moist desquamation." To make sure no studies were missed, we also searched Web of Science. We reviewed each relevant article and included only the most recent or the complete version of the trial for analysis.

Study selection

Studies were included if they (1) were written in English, (2) were randomized controlled trials (RCTs), (3) involved patients without any active skin lesions in the irradiation area before radiotherapy for prophylactic trials or patients who had developed RD before topical agents application for treatment trials, (4) evaluated topical agents therapy versus non topical agents therapy, and (5) reported the incidence of grade 2 and higher RD for prophylactic trials or the incidence of wound healing for treatment trials.

Data extraction

The data extracted were including "authors," "publication year," "agent," "median age," "intent-to-treat (ITT) population size," "irradiation site," "with concurrent chemotherapy or not," "eligibility criteria for performance status," "the incidence of grade 2 and higher RD," and "the incidence of wound healing." The quality of all included RCTs was evaluated by Jadad score [25].

Data analysis

Overall relative risk (RR) and 95 % confidence interval (CI) for the incidence of grade 2 and higher RD or the incidence of wound healing were pooled using the random-effects model. Standard Q test and I^2 statistics were used to assess heterogeneity among trials. We considered that there was no significant heterogeneity when the P value was greater than 0.1. If the P value was less than 0.1, heterogeneity was deemed high, and sensitivity analysis was performed by excluding the trials which potentially biased the results [26]. All statistical calculations were done using STATA version 11.0.

Subgroup analysis

Trials included in prophylactic trials were divided into subgroups on the basis of "with concurrent chemotherapy or not," "type of topical agents (hormone and not hormone)," "irradiation sites (breast only and multiple sites)," and "quality of trials (Jadad score ≥4 or ≤3)." Because of the limited number of treatment trials, subgroup analysis was not conducted.

Publication bias

For meta-analyses including more than ten studies, we assessed the publication bias using Begg's test and Egger's test [27, 28].

Results

Search results

A total of 73 relevant RCTs on "RD" were obtained. Eighteen publications of them totaling 3,098 patients were eligible: 14 publications [7–10, 12, 13, 15–21, 24] totaling 2,406 patients for prophylactic trials and six publications [11, 14, 15, 22–24] totaling 692 patients for treatment trials (two publications [15, 24] evaluated both prophylactic and treatment efficiency of topical agents). The other 55 publications were excluded for some reasons. The flow chart of our selection process is shown in Fig. 1. One publication written by Williams [18] included two independent trials. Another three publications [9, 13, 20] involved two or three different topical agents in the study group, and these agents were analyzed respectively. So there were 19 trials from 14 publications for prophylactic intention and six trials from six publications for treatment intention. Characteristics of the included publications are listed in Table 1.

Efficacy of topical agents for RD (primary analysis) were as follows:

(1) Efficiency of topical agents for prophylactic intention

The total incidence of grade 2 and higher RD was 44.86 % (943/2,102) with 43.11 % (482/1,118) in the study group and 46.85 % (461/984) in the control group. There was no significant statistical difference between them (P=0.128, RR=0.90, 95 % CI=0.78–1.03). The heterogeneity was high (P=0.000, I^2=71.5 %) (Fig. 2). Sensitivity analysis showed that no single trial should be responsible for the high heterogeneity.

(2) Efficiency of topical agents for treatment intention

The total incidence of wound healing was 75.19 % (494/657) with 75.15 % (251/334) in the study group and 75.23 % (243/323) in the control group. There was no significant difference between them (P=0.784, RR=1.01, 95 % CI=0.92–1.12) but there was a high heterogeneity (P=0.067, I^2=51.5 %) (Fig. 3). Sensitivity analysis indicated that no single trial could explain the heterogeneity.

(3) Efficacy of topical agents for RD (subgroup analysis)

We divided prophylactic trials into subgroups based on "with concurrent chemotherapy or not," "hormone or not hormone," "breast only or multiple sites," "high Jadad score (≥4)

or low Jadad score (≤3).” Heterogeneity were not associated with the former three factors but could be eliminated by excluding the trials with low Jadad score (P=0.292, I^2=15.2 %). However, there was still no significant difference between the study group and control group among trials of high quality (P=0.625, RR=0.98, 95 % CI=0.89–1.07) (Table 2).

Publication bias

There was no publication bias among trials for the incidence of grade 2 and higher RD according to Begg’s test (P=0.108) and Egger’s test (P=0.232).

Discussion

Although various topical agents have been used to treat RD, there continues to be insufficient evidence to make a recommendation. This is the first meta-analysis to evaluate the efficacy of topical agents in the prevention and treatment of RD.

The primary pooled incidence of grade 2 and higher RD was 43.11 % among patients using topical agents for a prophylactic purpose, while in the control group, the incidence was higher, 46.85 %, with no significant difference (P=0.128, RR=0.90, 95 % CI=0.78–1.03). It seemed that topical agents were not efficient to prevent RD. However, the high heterogeneity (P=0.000, I^2=71.5 %) reminded us that there existed a big variation among studies. To find the source of heterogeneity, we then conducted subgroup analyses to evaluate the impact of “with concurrent chemotherapy or not,” “type of agents (hormones or others),” “irradiation sites (breast only and multiple sites),” and “quality of trials (Jadad score ≥4 or ≤3).” The results showed that the high heterogeneity came from the uneven quality among trials and could be eliminated if the trials with Jadad score less than four were ruled out (P=0.292, I^2=15.2 %). For these trials of high quality, however, there was still no significant difference between the study group and control group (RR=0.98, 95 % CI=0.89–1.07), indicating that topical agents were not an efficient way to prevent RD. In addition to prophylactic use, treatment efficacy of existing RD by topical agents was also evaluated with the result that no difference was found between the study group and control group

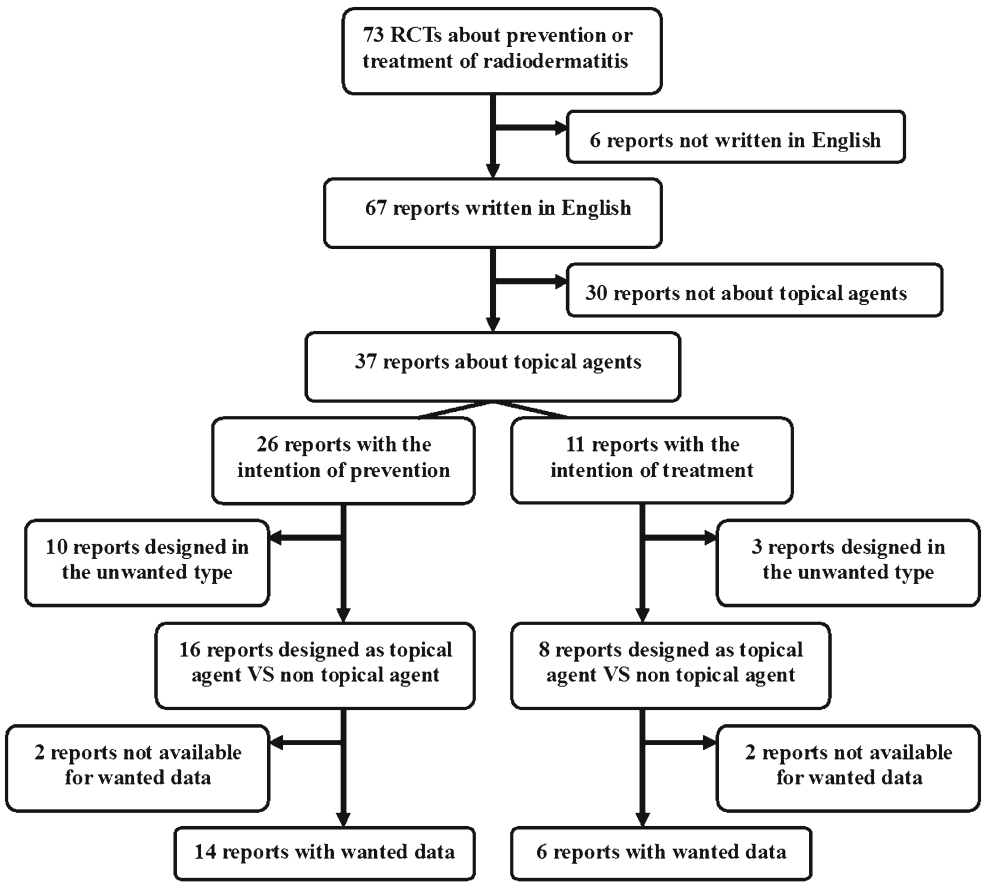

Fig. 1 Outline of selection flow chart

Table 1 Characteristics of included trials

Authors	Year	Agent	Age (T/C)	Size	Site	Chemo	PS criteria	Jadad score	Intention
Robert et al. [7]	2010	0.1 % Mometasone furoate	60/57	176	Breast	No	ECOG ≤2	5	Prevention
Bostro et al. [8]	2001	Mometasone furoate	58/60	49	Breast	No	NA	5	Prevention
Omidvari et al. [9]	2007	0.1 % Betamethasone /petrolatum	NA	51	Breast	No	NA	5	Prevention
Shukla et al. [10]	2006	Beclomethasone	44.6/45.9	60	Breast	Yes	KPS ≥70	3	Prevention
Mak et al. [11]	2000	Gentian violet	NA	42	Multiple	Yes	NA	3	Treatment
Masferrer et al. [12]	2010	3 % Urea	NA	272	Breast	Yes	NA	3	Prevention
Rizza et al. [13]	2010	Formulation A/formulation B	48/50 52/50	68	Breast	No	NA	5	Prevention
Gollins et al. [14]	2008	Gentian violet	NA	33	Multiple	No	NA	3	Treatment
Ma et al. [15]	2007	Lianbai liquid	43/39	126	Multiple	No	KPS ≥80	2	Prevention
			41/43	92					Treatment
Liguori et al. [16]	1997	Hyaluronic acid	NA	152	Multiple	No	NA	5	Prevention
Schmuth et al. [17]	2002	0.5 % Dexpanthenol	44/55	36	Breast	Yes	KPS ≥70	5	Prevention
Williams et al. [18]	1996	Part I: *Aloe vera*	NA	194	Breast	No	NA	4	Prevention
		Part II: *Aloe vera*		108				3	
Heggie et al. [19]	2002	*Aloe vera*	56/60	225	Breast	Yes	NA	5	Prevention
Gosselin et al. [20]	2010	Biafine/aquaphor /radiacare	NA	208	Breast	No	KPS ≥80	5	Prevention
Fisher et al. [21]	2000	Biafine	62/62	185	Breast	No	KPS ≥70	3	Prevention
Mak et al. [22]	2005	Gentian violet	NA	146	Nasopharyngeal	Yes	KPS >30 %	3	Treatment
Delaney et al. [23]	1997	10 % Sucralfate	67/63	39	Multiple	NA	ECOG: 0–4	5	Treatment
Elliott et al. [24]	2006	Trolamine	NA	331	Multiple	Yes	Zubrod <2	3	Prevention
				340					Treatment

T/C treatment group/control group, *Chemo* chemotherapy, *PS* perform status, *NA* not available

for the incidence of wound healing (P=0.784, RR=1.01, 95 % CI=0.92–1.12). But we could not draw a firm conclusion from this result because of the high heterogeneity (P=0.067, I^2=51.5 %), and subgroup analysis

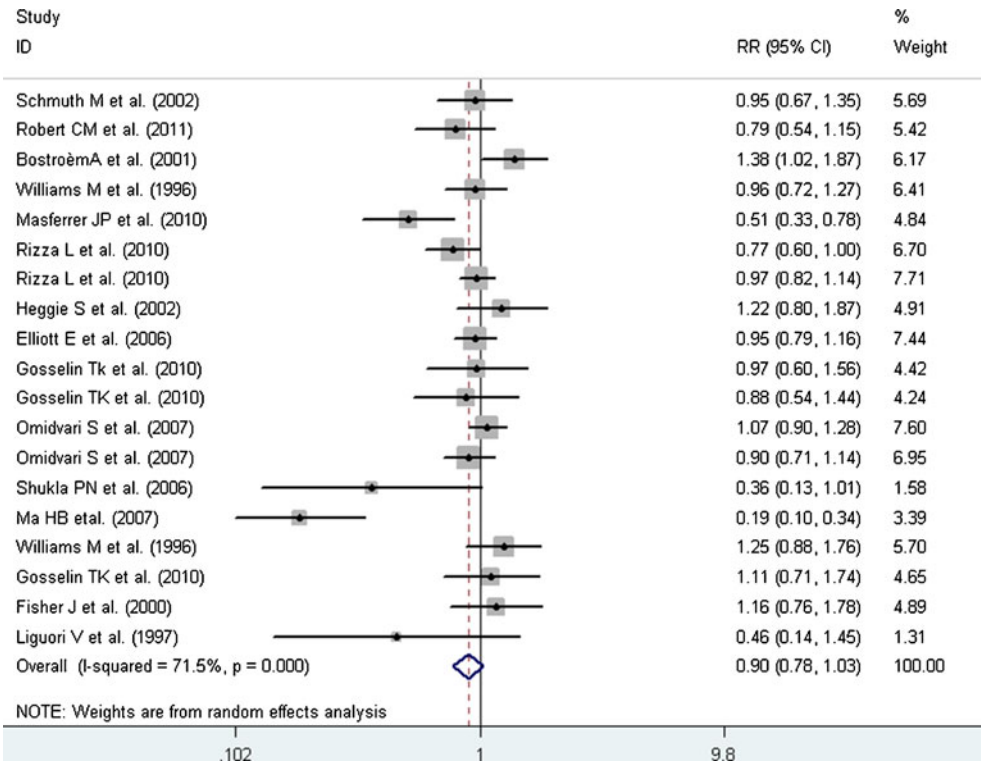

Fig. 2 Forest plot of RRs for the incidence of grade 2 and higher radiodermatitis

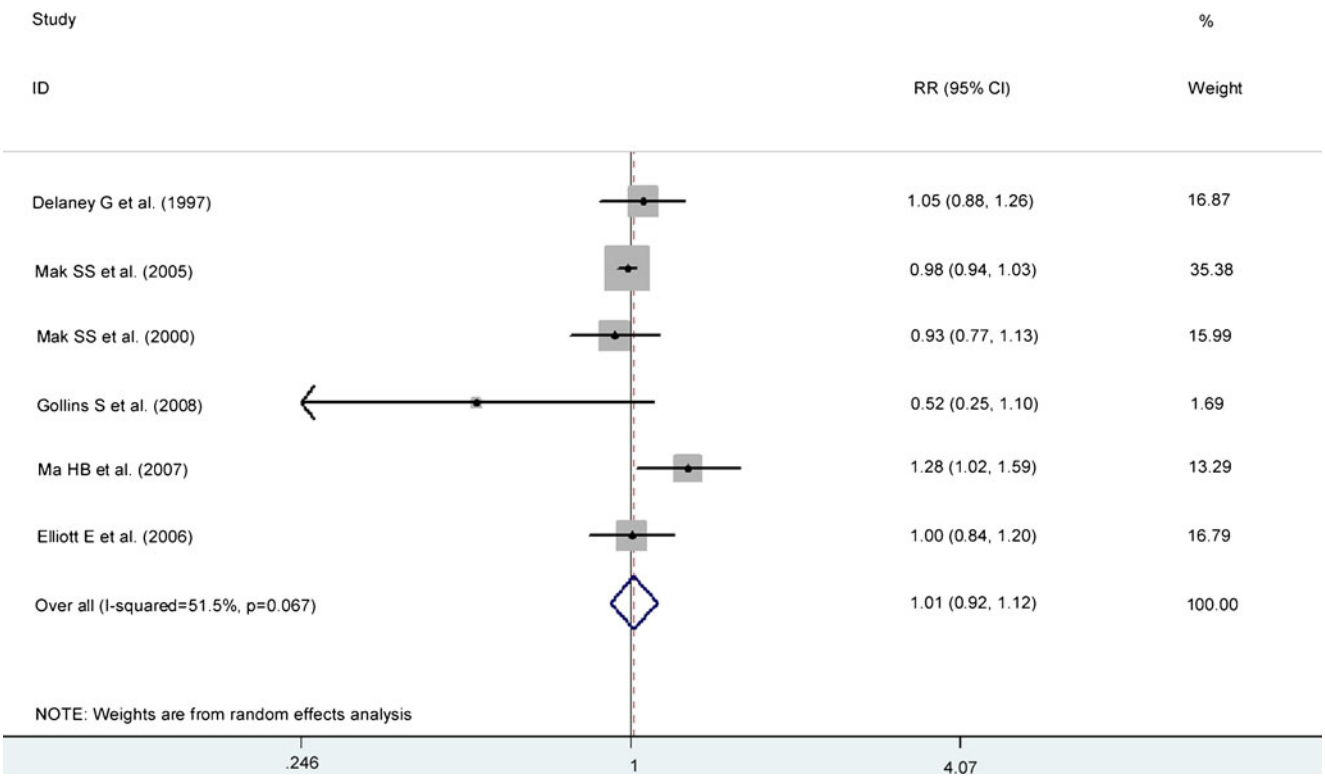

Fig. 3 Forest plot of RRs for the incidence of wound healing

was inappropriate to be conducted in consideration of the few number of trials (only six).

The reason of the disappointing results calculated above was probably that the topical agents chosen in these trials were blinded, not according to the pathophysiology of RD. RD was caused by a complicated process involving DNA damage and alteration of proteins, lipids, or carbohydrates that caused the injury of skin and its appendage, especially the destruction and depletion of basal cells. Without enough basal cells migrating towards the surface to compensate for the shedding stratum corneum, desquamation occurred [29–32]. Thus, the candidate agents should be with the function of repairing the damaged macromolecules, especially DNA and proteins, or promoting the cell proliferation. Among the studied topical agents in the included trials, the pharmacological mechanism of corticosteroids such as methylprednisolone and mometasone furoate was best elucidated. Corticosteroids were used in the case of RD because of their function of anti-inflammation [33]. However, as mentioned previously, RD was caused mainly by decompensation for cell death, and inflammation herein should be defined as a protective attempt to initiate the wound healing [34]. Corticosteroids treatment would inhibit migration of neutrophils and macrophages to the wound bed. These recruited inflammatory cells remove damaged tissue and produce chemoattractants and growth factors to drive collagen synthesis and wound contraction which, however, would be delayed by corticosteroids [35–37]. As for the other topical agents, including *Aloe vera*, trolamine, sucralfate, gentian violet, urea, mixture of oil and aqueous, vitamin C, and hyaluronic acid, all of them

Table 2 Subgroup analyses for the incidence of grade 2 and higher radiodermatitis (prophylactic trials)

Factor	Status	RR (95 % CI)	*P* value	Heterogeneity
Chemotherapy	Yes	0.82 (0.60–1.13)	0.229	I^2=68.9 %, *P*=0.012
	No	0.91 (0.77–1.08)	0.299	I^2=73.4 %, *P*=0.000
Hormone	Yes	0.93 (0.70–1.23)	0.614	I^2=65.3 %, *P*=0.021
	No	0.88 (0.74–1.05)	0.148	I^2=74.7 %, *P*=0.000
Site	Breast	0.96 (0.86–1.08)	0.521	I^2=47.4 %, *P*=0.018
	Multiple	0.44 (0.12–1.56)	0.204	I^2=93.1 %, *P*=0.000
Jadad score	≥4	0.98 (0.89–1.07)	0.625	I^2=15.2 %, *P*=0.292
	≤3	0.65 (0.40–1.06)	0.084	I^2=88.4 %, *P*=0.000

RR relative risk, *CI* confidence interval

just have the function of moistening the skin or even mild anti-inflammation. So the direction of agent selection should be changed.

Recently, various growth factors emerged as promising topical agents in the prevention and treatment for RD, such as platelet-derived growth factor, granulocyte–macrophage colony-stimulating factor and epithelial growth factor. These growth factors act as signaling molecules that bind to specific receptors on the surface of their target cells and consequently stimulate cellular growth, proliferation, and differentiation [8, 38–41]. So theoretically, they are good choices to be used as anti-RD agents. Yet more clinical trials are needed to explore their efficacy.

In summary, corticosteroids and other conventional topical agents proved to be useless in the prevention and treatment of RD. New type of agents, such as growth factors, may be considered to be applied on RD.

Limitation

Most studies available concentrated on patients of breast cancer. In addition, the study about single topical agent is not sufficient, and we fail to do subgroup analysis for each cream; so, more RCTs are needed.

Conflict of interest None

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