Re-examining the Evidence in Radiation Dermatitis Management Literature: An Overview and a Critical Appraisal of Systematic Reviews

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Published

2012

Journal Title

International Journal of Radiation: Oncology - Biology - Physics

DOI

10.1016/j.ijrobp.2012.05.009

Title: Re-examining the evidence in Radiation Dermatitis Management Literature: An Overview and a Critical Appraisal of Systematic Reviews

Running Title: Re-examining the Evidence Base of Radiation Dermatitis

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Conflicts of Interest:

The authors disclose no conflicts of interest

ABSTRACT

Purpose: To provide an overview and a critical appraisal of systematic reviews (SRs) published on interventions for the prevention/management of radiation dermatitis.

Methods and Materials: We searched the following electronic databases: MEDLINE, CINAHL, EMBASE, and the Cochrane Library. We also hand-searched reference lists of potentially eligible articles and a number of key journals in the area. Two authors screened all potential articles and included eligible SRs. Two authors critically appraised and extracted key findings from the included reviews using the "A Measurement Tool to Assess Systematic Reviews" (AMSTAR).

Results: Of 1837 potential titles, six SRs were included. A number of interventions have been reported to be potentially beneficial for managing radiation dermatitis. Interventions evaluated in these reviews included skin care advice, steroidal/non-steroidal topical agents, systematic therapies, modes of radiation delivery, and dressings. However, all the included SRs reported that there is insufficient evidence supporting any single effective intervention. The methodological quality of the included studies varied, and methodological shortfalls in these reviews may create biases to the overall results or recommendations for clinical practice.

Conclusions: An up-to-date high quality SR in preventing/managing radiation dermatitis is needed to guide practice and direction for future research. Clinicians or guideline developers are recommended to critically evaluate the information of SRs in their decision making.

INTRODUCTION

Despite advances in understanding of the pathophysiology (1), radiologic techniques (2, 3) and other various interventions of radiation dermatitis, the prevalence of this condition remains high in cancer patients undergoing radical radiation treatment, with more than 90% experiencing erythema and more than 30% experiencing moist desquamation (3, 4). To date, there is a lack of conclusive evidence to inform best management and there is a large variation in the clinical management of this condition (5, 6). Although systematic reviews (SRs) have the potential to effectively inform this area of practice, no work has been conducted to evaluate the SR in this area.

Systematic reviews are increasingly used as the standard approach in summarizing health research and influence health care decisions (7). It is therefore important to ensure that the standards of SRs are maintained (8), so clinicians and policy makers can make timely and effective health care decisions (9, 10). To ensure the quality of SRs, overviews of SR are increasingly used in medicine (8, 11, 12). These overviews are intended primarily to summarise and critically appraise multiple reviews addressing the effect of two or more potential interventions for a single condition or health problem (11). From Dec 2011 to Mar 2012, we conducted an overview by reviewing the scope/ key findings of SRs published on interventions for prevention/management of radiation dermatitis; evaluating the quality of these SRs using a validated scale, and report on the direction of clinical conclusions (effectiveness); and highlighting some methodological and reporting issues of the SRs.

METHODS AND MATERIALS

Searching of relevant reviews

Systematic reviews published on prevention/management of radiation dermatitis were identified by literature search of MEDLINE, EMBASE, CINAHL, and the Cochrane Library (up to Feb 2012). The initial search strategy was designed for MEDLINE (Supp 1). The reference lists of all potentially eligible articles were reviewed for SRs. We also hand-searched a number of key journals including International Journal of Radiation Oncology, Biology, Physics, Radiation Oncology, International Journal of Radiation Oncology, Journal of Pain and Symptom Management, Journal of Integrative Cancer Therapies, and Cancer Nursing. Authors of the SRs were not contacted.

All citations were reviewed independently by two authors for inclusion in this overview. Disagreements were resolved by consensus. A citation was considered relevant for this overview using the following criteria:

- The primary aim was reviewing the efficacy of interventions for preventing and managing radiation dermatitis, and was stated in the title; abstract or the article.
- The article was described as "systematic review", "systematic overview", "quantitative review", "systematic literature review" or "meta-analysis".
- The article was published in a peer reviewed publication. Unpublished work, abstracts, letters and conference proceedings were excluded. No language exclusion was applied.

Evaluation of systematic reviews

An 11-question Measurement Tool to Assess Systematic Review (AMSTAR) was used to appraise the SRs (Supp2) (13). AMSTAR was reported to demonstrate good agreement, reliability, construct validity and feasibility (13). Two reviewers independently appraised the included reviews using AMSTAR, and judged each item as "Yes, No, Can't Answer or Not applicable". Any discrepancies were resolved by consensus. The methodological quality, the characteristics, and finding summaries of the included SRs are extracted by two authors (Table 1). Reviews achieving a score of 8-11 are deemed to be high methodological quality, 4-7 to be medium and 0-3 to be low (12).

RESULTS

The initial search yielded 1837 titles of potential interest. We reviewed abstracts of these titles and identified 105 for further consideration with full papers being obtained. We included six SRs with the objectives and outcomes of interest to this current paper (14-19) (See Table 1).

Table 1. Characteristics of the included systematic reviews

Review	PICO	Years searched	Included studies	Included study type	Language restriction
Bolderston et al 2006	P: Cancer patients with radiation induced skin reactions I: Any intervention C: Any comparison O: grading of skin reactions, pain, itchiness, burning, quality-of-life	1980 to April 2004	N=28	SRs, meta-analysis, reviews, RCTs, CCTs, and comparative studies	English only
Butcher et al 2011	P: Females with clinically diagnosed breast cancer receiving external beam photon radiotherapy to affected breast I: Use of soap, washing agent or comparative studies where no washing agents are used/ Use of creams or dressings/ Use of deodorants C: Any comparison O: post and peri-radiotherapy skin appearance	Up to September 2010	N=10	Any quantitative and qualitative studies	English only

Kedge 2009	P: Radiotherapy patients with moist desquamation I: Any intervention C: Any comparison O: wound healing time or other skin integrity measure, patient comfort, acceptability measure	Not stated	N=10	RCTs and CCTs	No restriction. However, articles that could not be translated were excluded due to financial constraint.
Koukourakis et al 2010	P: Cancer patients with radiation acute skin reactions I: Creams, ointments and dressings C: Any comparison O: Grade of acute epidermis complications	Up to September 2009	N =15	Controlled trials	English only
Savlo et al 2010	P: Cancer patients with radiation induced skin reactions I: Any intervention C: Any comparison O: grading of skin reactions, pain, itchiness,	January 2000 to October 2008	N=39	RCTs, CCTs and comparative studies	English only

	burning, quality-of-life, toxicities, patients perspective of the product, agent, or technique			
Richardson 2005	P: Cancer patients with radiation induced skin reactions I: Aloe vera gel C: Any other comparison O: Severity of radiation induced skin reactions	Up to August 2004	N=5	RCTs

Description of included reviews

All reviews (n=6) examined the efficacy of interventions for the prevention/management of radiation dermatitis (14-19). The number of included studies ranged from five studies to 39 studies in each review. These reviews varied in their scope including participants, intervention, comparison and outcomes of interest. Two reviews concerned any interventions for all cancer patients with radiation dermatitis (14, 17). One examined skin care advice in relation to the use of washing agents and other topical agents given to patients with breast cancer undergoing radiotherapy (18). One examined interventions for patients who developed moist desquamation (15). One compared aloe vera gel with other interventions for patients with radiation dermatitis (16). One examined anti-inflammatory creams in patients with post radiation acute skin reactions (19). Only one review did not have a language restriction (16). Four reviews (14, 17-19) planned to exclude non-English studies, and another one (15) planned to search for non-English studies, but did not translate some non-English studies due to financial constraint.

With regards to outcomes, the grading of skin reactions was measured in all reviews. Pain, itching, burning and quality-of-life were measured in two reviews (14, 17, 19). Other outcomes of interest included healing time (15), patient comfort/acceptability (15), patient perspectives (17). No meta-analysis was conducted in any of the included reviews. Two reviews (14, 15) provided a reason for not pooling data, due to the clinical heterogeneity of the included studies. One review planned to conduct a narrative review and not to pool data (17). The other three reviews did not provide any reasons for not pooling data (16, 18, 19).

Methodological quality of included reviews

The AMSTAR scores for the six reviews ranged from three to eight out of the total score of 11. One review scored eight (16), one scored six (17), two scored five (14, 15), and two scored three (18, 19) (see Supp 3). All reviews provided a priori design and conducted comprehensive searches with main databases searched. Three reviews performed duplicate study extraction and study selection (14, 16, 17). Three reviews used the status of publication (i.e. grey literature) as an inclusion criterion (15-17). Lists of included and excluded studies were provided in three reviews (14, 16, 17). Of the six reviews, only one listed the characteristics of participants (i.e. age, treatment sites, dosage etc) (16). Two reviews assessed the scientific quality of the included studies, and used them appropriately in formulating conclusions (15, 16). Two reviews reported that authors did not have any potential conflicts of interest (17, 19). The other four did not report any potential conflicts of interest (14-16, 18). No reviews performed/reported any assessment for publication bias.

Key findings of the included reviews

Skin care advice

Four reviews examined washing practices for preventing radiation dermatitis (14, 17-19). All four reviews concluded that gentle skin and hair washing with mild soap should not be restricted in patients receiving radiation therapy (14, 17-19). However, it was unclear how "mild" soap was defined (14, 19). Two reviews examined whether deodorants should be used in patients with radiation dermatitis (18). Bucher et al (2011) concluded

that deodorant use remained an inconclusive area. The use of non-metallic deodorants does not seem to adversely affect patient's skin reactions (18). Koukourakis et al (2010) further challenged the assumption about a potential bolus effect from metallic or non-metallic deodorants and concluded that patients could use deodorant on intact skin throughout treatment based on the results of one non-clinical study (19, 20).

Topical agents (Steroidal)

Four reviews examined the effects of steroidal topical agents (14, 17-19). These reviews reported that a number of steroidal topical agents including mometasone furoate cream, methylprenisolone aceponate cream, beclomethasone can significantly improve radiation dermatitis (14, 17-19). However, the use of steroidal agents is limited because they can cause thinning of the skin and introduce bacterial infections (18).

Topical agents (Non-steroidal)

Five reviews examined a range of non-steroidal topical agents (14, 16-19). Sucralfate/ sucralfate derivatives were reported to make no difference in severity of the reaction, when comparing with placebo or aqueous cream (14, 17, 19). Biafine cream®, an oil-in-water emulsion with non-steroidal anti-inflammatory properties, were reported by three reviews to not be superior over a number of comparators including aloe vera, Lipiderm cream® and Avene thermal spring water anti-burning gel ® (14, 17, 19). When comparing with the Biafine cream and calendula ointment, patients receiving calendula ointment had significantly fewer occurrences of dermatitis higher than grade 2, and

greater pain relief (14, 17). However, two reviews did not recommend calendula ointment due to the difficulty in application and the potential bias in the trial (14, 19).

Four reviews examined aloe vera (14, 16, 17, 19). These reviews concluded that there is no evidence suggesting aloe vera to be effective for the prevention/management of radiation dermatitis in both adults and children (14, 16, 17, 19). Further, aloe vera was less effective when comparing with an anionic phospholipid-based cream and aqueous cream (16). Xclair, an hyaluronidase-based cream, was reported by two reviews to be effective in reducing the occurrences of radiation dermatitis and burning, but not in improving pain or itching (17, 19). Two reviews reported contradictory results or uncertain benefits with regards to the use of hyaluronic acid cream (14, 19).

Systematic therapies

Two reviews examined amifostine, oral enzymes, pentoxifyiline and zinc supplements (14, 17). Amifostine, oral enzymes, pentoxifyiline and zinc supplements were reported to significantly reduce the maximum extent of radiation dermatitis at some time point during or after radiation treatment (14, 17). The results were supported by small number of trials, and further research is required. The side effects associated with oral enzymes also deserve further consideration in clinical practice and future research (14).

Mode of radiation delivery

One review examined mode of radiation delivery (17). Salvo et al (2010) reported that intensity-modulated radiation therapy (IMRT) was reported to significantly reduce moist

desquamation in patients with radiation dermatitis, compared to standard method of delivering radiotherapy. Patients receiving IMRT with light-emitting diode (LED) photo-modulation were also reported to have significantly reduced dry and moist desquamation compared to those receiving IMRT alone (17).

Dressings

Four reviews examined the use of dressings (14, 15, 17, 19). These reviews concluded that there is limited evidence investigating the efficacy of dressings (14, 15, 17, 19). Kedge suggested there may be advantages to use the moisture-vapour permeable dressing (MVPD). However, further research is necessary as there is not yet sufficient evidence supporting MVPD (15). Salvo et al (2010) reported that hydrogel dressing is not beneficial for radiation dermatitis as it had a significantly longer healing time, compared to the use of dry dressing (17). When comparing hydrogel dressing and gentian violet in the management of moist desquamation, wound size and wound pain was significantly lower with gentian violet (14, 17). However, there is no evidence supporting gentian violet in terms of healing time, pain and comfort, and there are safety and patient comfort concerns associated with its use (15). Silver-leaf nylon dressings were reported to be superior over silver sulfadiazine cream in reducing skin reactions and pain (17, 19).

DISCUSSION

This is the first overview of SRs concerning efficacy of interventions for preventing or managing radiation dermatitis. This overview confirms that there is insufficient evidence

to support the use of a particular intervention for preventing/ managing radiation dermatitis. To date, the literature in this area shows a majority of negative results. Researchers must ensure that the highest methodological standard possible is upheld for every level of research reports to avoid any bias to the results for clinical recommendations. This overview focused on the highest level of evidence (SRs) and revealed a number of methodological issues. When a review is listed to be a SR, the respective components and standards should be expected (11). Only one of the six SRs was judged to be high quality (16). However, the scope of this high quality review was limited to aloe vera use and was conducted in 2004. A number of important outcomes including pain, itching and quality-of-life were not included by some reviews, but should be incorporated in future SRs in this area. The inclusion of these important outcomes will enable the detection of any selective reporting bias in clinical trials. Shortfalls in the methodological quality of these reviews may have direct implications on the clinical conclusions made in each review. For example, Koukourakis et al (2010) set a priori decision to only include English controlled trials (19), however, this review used non-controlled studies to formulate their conclusions. In particular, despite much debate in the area of deodorant use during radiation treatment, this review (19) made a conclusion of recommending deodorant use on intact skin throughout treatment based on the results of one non-clinical study.

Further, it was unclear whether duplicate study selection was conducted in three included reviews (15, 18, 19). This could directly compromise the quality of the searching process and miss studies that fit the inclusion criteria of some of the reviews. For example, we

noticed that some controlled trials identified in the search of this overview to be appropriate, but were not included in any of the included reviews (21-23). If the review authors excluded any irrelevant studies on any grounds, they should list the excluded studies with reasons given.

The language restriction to English in the majority of the included reviews could increase the risk of reporting bias (24), because statistically significant, 'positive' results that indicate an intervention works are more likely to be published in English (24). Further, there has been an increasing evidence base for some of the complementary and alternative cancer treatments, which are more likely to be reported in a non-English language such as acupuncture (25, 26). Indeed, two RCTs with positive results were also located through the search conducted in this overview (27, 28). These articles should be taken into consideration, appraised/reviewed according to their quality. It is noteworthy that publication biases can be a significant issue that deserves investigation in all SRs (24).

An established definition of prevention/prophylaxis and treatment should be suggested for future trialists/review authors to consider. This will have enormous implications on the pooling of data across trials. We suggest that true "prevention" should be reserved for use if the trialists/review authors aim to prevent a reaction from occurring (yes/no) (29). The delaying of skin reactions may not mean that the toxicity is less severe throughout treatment and week/months post-treatment. While it may be difficult to achieve true prevention, clinicians and researchers have a responsibility to aim for this. "Treatment"

should be used to refer to any other management strategies after the onset of any graded radiation dermatitis. If the trial authors have a priori aim to prevent a particular grade of dermatitis, this should be specified clearly at the outset.

The included reviews reported a number of useful findings that deserve further investigations. However, the methodological/reporting flaws require further improvements. It is advised that a high quality over-arching SR should be conducted investigating the effects of prevention/management of radiation dermatitis. The review should include all important outcomes. This review should be updated regularly to aid timely decision making of health professionals who have to confront this medical condition on a daily basis.

CONCLUSION

There is a high variability in the quality and scope of the SRs concerning the management of radiation dermatitis. Several common methodological/reporting shortfalls in the included reviews were identified in this overview. These included the omission of duplicate selection of studies, publication bias assessment, and declaration of conflict of interest in some reviews. The methodological shortfalls identified may have created biases to the overall results or recommendations for clinical practice. This overview provides a direction for an up-to-date high quality systematic review in managing radiation dermatitis in patients with cancer to be conducted. Clinicians or guideline

developers are recommended to critically evaluate the information in the SRs in their decision making.

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