Clinical Trial/Experimental Study

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Randomized, self-controlled, prospective assessment of the efficacy of mometasone furoate local application in reducing acute radiation dermatitis in patients with head and neck squamous cell carcinomas

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Abstract

Background: Acute radiation dermatitis (ARD) is a common adverse effect in patients undergoing radiotherapy. Mometasone furoate cream (MMF) was reported to significantly reduce ARD, especially in breast cancer. Clinically, ARD is more critical and more difficult to prevent in patients with head and neck squamous cell carcinoma (HNSCC) than in those with breast cancer, because a higher dose of radiotherapy is required in HNSCC cases. The aim of this study was to evaluate the effect of MMF local application on radiation dermatitis in patients with HNSCC.

Methods: HNSCC patients scheduled for bilateral radical radiotherapy to the neck with identical radiation doses were enrolled. One side of the neck skin (test groups) of the patients were randomized to apply a thin layer of MMF once a day from the date of first radiotherapy until either 2 weeks after end of radiotherapy or until the test side skin developed ARD lesions, while the other side of neck (control groups) didn't apply any medication. The severity of ARD was evaluated weekly by using the modified radiation therapy oncology group score, pain intensity, and itch stages.

Results: Forty-one patients (82 targets) were analyzed. There was a significant difference between the ARD scores on the test side and the control side. MMF reduced the stages of ARD when the radiotherapy dose was <6000 cGY ($P = .01$) but showed no improvement when the dose was ≥6000 cGY ($P = .699$). Compared to the control side, local application of MMF significantly reduced the itch and pain scores of the test side skin regardless of the radiotherapy dose and ARD stage ($P < .001$) during radiotherapy.

Conclusions: This study showed that MMF inunction after high-dose radiotherapy (>50 Gy) can prevent ARD, especially when the radiation dose is <6000 cGY.

Abbreviations: ARD = acute radiation dermatitis, HNSCC = head and neck squamous cell carcinomas, MMF = mometasone furoate cream, PTV = primary target volume, RTOG = radiation therapy oncology group.

Keywords: acute radiation dermatitis, head and neck squamous cell carcinomas, mometasone furoate cream

1. Introduction

Radiation dermatitis is a subcutaneous and vascular adverse effect of radiotherapy, affecting approximately 95% of the patients receiving radiotherapy for cancer.[1–3] Acute radiation dermatitis (ARD) remains one of the most commonly observed adverse effect of radiotherapy, which leads to complications such as super infection or treatment disruption.[4] ARD is defined as dermatitis that occurs 8 to 20 days after exposure to radiation, regardless of the doses and number of treatment cycles. Researchers have confirmed that it results from immediate structural tissue damage, generation of short-lived free radicals, irreversible double-stranded breaks in the nuclear and mitochondrial DNA, and initiation of an inflammatory response in the epidermis and dermis.[5,6] This deleterious effect of the severe skin reaction has a profound impact on the patients' quality of life and can lead to interruption of radiotherapy, especially in patients with breast cancer, lung cancer, and head and neck cancer because a higher radiation dose is required in such cases.[7] Therefore, many agents have been used to treat or prevent radiation dermatitis.

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Topical application of anti-inflammatory drugs such as corticosteroids, aloe veragel, honey, and homeopathic remedies is the most common treatment for ARD.[2,7] However, the results are not always satisfactory. In this setting, innovative approaches to treat ARD are welcome. Recently, some studies showed that local application of mometasone furoate cream (MMF) significantly reduced ARD.[8,9] MMF is a synthetic corticosteroid and has 3 potential advantages over other topical corticosteroids. First, it is a potent corticosteroid with a low risk of overt cutaneous atrophy.[10] Second, the local application has been claimed to have a prolonged effect, lasting for 24 hours, and thus requires only once-a-day application.[9] Third, it has been confirmed that MMF has a strong inhibitory effect on IL-6 activity, both on the transcriptional and protein levels, during radiotherapy.[11] A previous study showed that MMF can reduce ARD in patients receiving radiotherapy for breast cancer.[8] The total radiation doses for breast cancer and head and neck squamous cell carcinomas (HNSCC) are usually 46 to 50 Gy and >=50 Gy, respectively. It is well known that skin reactions increase with an increase in the radiation dose. Whether MMF can reduce ARD in patients receiving higher radiation doses (>50 Gy) is not clear. In this study, patients with HNSCC were enrolled to confirm the effect of MMF on ARD.

The objective of this study was to assess whether MMF can protect HNSCC patients from ARD during radiation, the extent to which it can reduce the patients' radiation therapy oncology group (RTOG) ARD scores, and its efficacy in reducing the accompanying symptoms of radiotherapy such as pain and itching.

2. Materials and methods

2.1. Study design

This was a prospective, randomized, open, self-controlled trial. All the enrolled patients were treated with intensity-modulated radiotherapy. The photon energy was 6 MV, and the radiation doses of the primary target volume (PTV) were identical on both sides of the neck. The neck was demarcated into the left and right half, with the midline of the neck considered as the dividing line. The cranial boundary was the lower mandibular margin and lower border of the ear pinna. The lower boundary was the proximal edge of the clavicle.[12] One side of the neck skin (left or right) of the eligible patients was randomized into the test group, while the other side was used as a control (control group) in accordance with a computer-generated randomization chart. One side of the neck skin (test groups) of the patients were randomized to apply a thin layer of MMF once a day from the date of first radiotherapy until either 2 weeks after end of radiotherapy or until the test side skin developed ARD lesions, while the other side of neck (control groups) did not apply any medication. Daily washing with perfume-free soap and tap water was recommended. Patients using MMF were asked to allow the application to remain on the neck for at least 18 hours per day during these weeks and the use of any other topical agents over the irradiated area was forbidden.

Two doctors assessed the ARD independently, every Friday during radiotherapy and for 2 consecutive Fridays after completion of radiotherapy. The assessment included symptoms on both sides of the neck, such as pain, itching, and the RTOG scores for ARD. If the assessments of 2 doctors were different, the scores were recorded by consensus. We used the RTOG scale for the classification of ARD as follows[87]: 0 = no visible change; 1 = follicular, dark erythema with hair loss, dry peeling, and less sweating; 2 = tender or bright erythema with or without moist desquamation, but with patchy moist desquamation with moderate edema; 3 = confluent moist desquamation with pitting edema of the unfold skin; 4 = necrotic, ulcer and bleeding. We divided the pain and itch scores on the part of skin subjected to radiotherapy into 3 stages as follows: 0 = no pain or itch; 1 = little pain or itch that did not affect daily sleep; and 2 = serious pain and itch that affected sleep. Application of MMF was discontinued if the skin developed ARD signs. We retrieved the patients' radiotherapy plan, outlined skin target (skin and subcutaneous 0.5 cm) of the neck on the completed radiotherapy plan,[13] and calculated the average dose of the skin target.

Table 1

Characteristics of patients.

Characteristics of the patients	
Age, mean ± SD (range), yr	53.39 ± 12.64 (from 19 to 74)
Tumor	
Nasopharyngeal carcinoma	29
Neck esophageal cancer	8
Hypopharyngeal carcinoma	4
Treatment	
Chemotherapy	38
No chemotherapy	3
Skin dose, cGy	
<6000	30
≥6000	11
Skin dose, mean ± SD (range), cGy	
Right neck	5866.36 ± 235.41 (from 5326 to 6372)
Left neck	5871.87 ± 239.81 (from 5377 to 6308)
Miss times, mean ± SD (range)	1.53 ± 1.41 (from 0 to 4)

Miss times: Missed times: times MMF was not applied for various reasons.
MMF = mometasone furoate cream, SD = standard deviation.

The study was approved by the institutional ethics review board of Mianyang Central Hospital (s2015013). Consent was obtained from all the patients, and signed copies of the consent form were provided to each of the patients. It was approved by the Clinical Trials Board and the identifier on Clinicaltrials.gov is NCT02495064.

2.2. Patient selection criteria

Patients eligible for enrollment in this study were adults (age ≥18 years) with histological evidence of a primary HNSCC, scheduled for regular fractionated definite radiotherapy to the primary site and both sides of the neck with the same accelerator, with the same radiation dose on both sides. Patients who were pregnant or lactating, and had hormone allergy, skin infection, or ulceration at the radiation site were excluded from the study. Elderly people with skin atrophy and allergies were also excluded.

Table 2

ARD score.

	RTOG ARD score				
	1	2	3	4	*P*-value
Test group (n)	25	10	4	2	.039
Control group (n)	13	23	3	2	

ARD = acute radiation dermatitis, RTOG = radiation therapy oncology group.

Table 3

Pain and itch score.

	Pain score			Itch score		
	1	2	*P*-value	1	2	*P*-value
Test group (n)	40	1	<.001	40	1	<.001
Control group (n)	3	38		11	30	

Table 4

ARD score of skin radiotherapy dose <6000 cGy and ≥6000 cGy.

	<6000 cGy			≥6000cGy				
ARD score	1	2	*P*-value	1	2	3	4	*P*-value
Test group (n)	23	7	.001	2	3	4	2	.952
Control group (n)	10	20		3	3	3	2	

ARD = acute radiation dermatitis.

2.3. Statistical analysis

At a bilateral test 0.05 significance level and a power of 80%, presuming a dropout rate of 10%for each group, expected incidence of 40% for a RTOG score of 3 and 4 in the control group and 16.7% in the test group, the estimated sample size was 120 (60 patients).

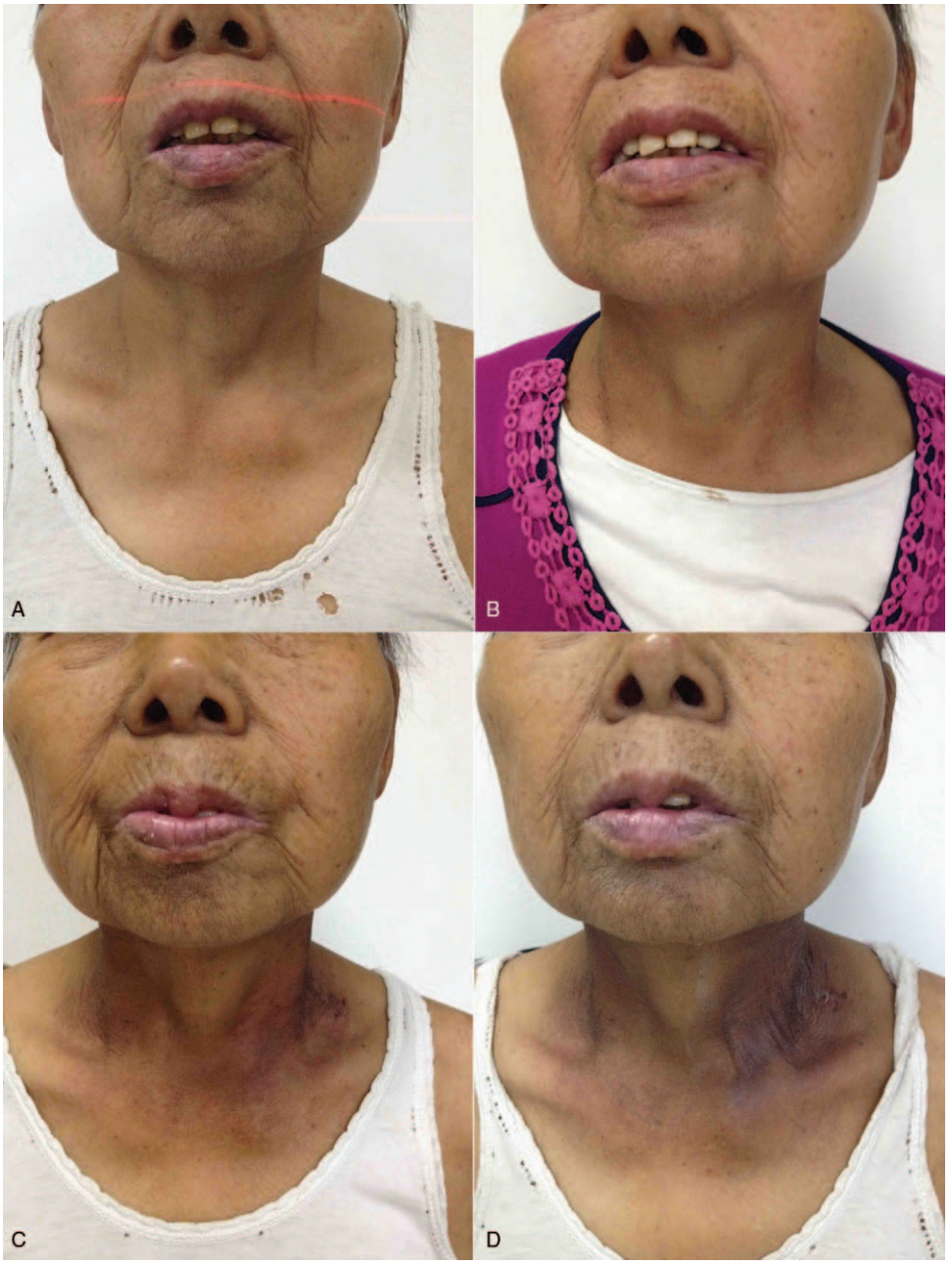

Figure 1. Acute radiation dermatitis in a patient who received radiotherapy on the right and left sides of the neck at doses of5519 and 5487cGy/30fractions, respectively. MMF was applied to the right side of the neck (the test side), and the left side of neck was used as a control, with nothing applied to the skin. (A) 3 wk after radiotherapy; (B) 4 wk after radiotherapy; (C) 5 wk after radiotherapy; and (D) 6 wk after radiotherapy. MMF = mometasone furoate cream.

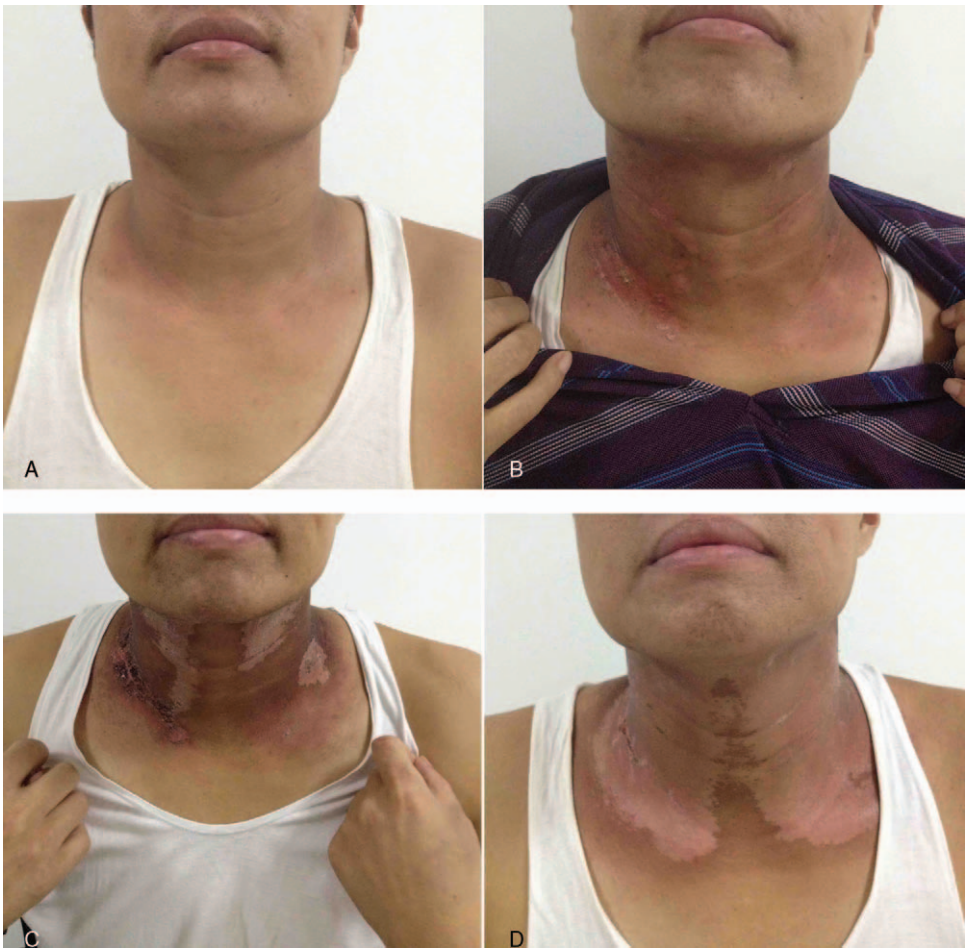

Figure 2. Acute radiation dermatitis in a patient who received radiotherapy on the right and left sides of the neck at doses of 6283 and 6242 cGy/33 fractions, respectively. The skin on the left side of the neck was treated with MMF (the test side), and the right side of neck was used as a control, with nothing applied to the skin. (A) 4 wk after radiotherapy; (B) 5 wk after radiotherapy; (C) 6 wk after radiotherapy; and (D) 7 wk after radiotherapy. MMF = mometasone furoate cream.

The primary efficacy analysis measured the maximal RTOG score, pain severity, and itching stages as mentioned above. We documented the severity of ARD based on RTOG scores for both sides of the neck, for each patient. The Mann–Whitney *U* test was used for all statistical comparisons of the RTOG ARD score and the pain and itch scores. All the *P*-values were 2-sided, and *P*-values of $<.05$ were considered significant. Statistical analyses were performed using the SPSS 21.0 software.

3. Results

Sixty patients with HNSCC were enrolled at the Mianyang Central Hospital from February 2015 to July 2016. Nineteen patients withdrew from the study because of lesser itch and pain on the test side than on the control side and they used MMF on both sides of the neck. Thus, 41 patients (Table 1), 82 subjects were included in the final analysis. Eighteen of the 41 patients received cisplatin chemotherapy every 3 weeks concurrently with radiotherapy, 19 patients received cisplatin plus paclitaxel chemotherapy every 3 weeks concurrently with radiotherapy, while 4 patients received only radiotherapy.

The doses of radiation to the right and left sides of the neck were 5326 to 6372 cGy and 5377 to 6308 cGy, respectively, in 28 to 33 fractions for 6 to 7 weeks, 5 days per week. The radiotherapy doses of the skin were calculated after radiotherapy.

Of the 82 subjects, 38 had a ARD RTOG score of 1, 33 patients' scores were 2, and scores of 3 and 4 were seen in 7 and 4 patients, respectively. All 82 subjects complained pain and itching on the neck. There was a significant difference between the ARD scores on the test side and the control side ($P = .039$; Table 2). We observed that if the ARD score was 1 or 2, the score on the MMF test side was usually 1, while the score on the other side was 2 (Table 2). However, when the ARD score was 3 or 4, using MMF after radiotherapy did not reduce the ARD. Since the ARD stage is positively related to the radiotherapy dose, we analyzed the differences in the ARD scores according to the radiotherapy dose (Table 3). It was seen that using MMF reduced the ARD when the skin radiotherapy dose was <6000 cGY ($P = .01$; Table 4 and Fig. 1). When the dose was ≥ 6000 cGY, using MMF showed no significant improvement ($P = .952$; Table 4 and Fig. 2).

In our study, patients developed pain and itching on both sides of the neck. However, Compared to the control side, local

application of MMF significantly reduced the itch and pain scores of the test side skin regardless of the radiotherapy dose and ARD stage ($P < .001$) during radiotherapy (Table 3).

4. Discussion

Clinically, ARD occurs more frequently in patients with breast, lung, and head and neck cancers because of the higher radiation doses required.[14,15] This has a profound impact on the patients' quality of life and can even lead to interruption of radiotherapy. In 2013, the Multinational Association for Supportive Care in Cancer skin toxicity study group suggested a possible reduction in ARD with the use of potent steroids.[16] In 2014, a systemic review by Chan RJ arrived at the same conclusion.[17] Subsequently, betamethasone and MMF were tested in several clinical trials.[7,8,18–20] Several randomized clinical trials of MMF showed a reduction in the symptoms of dermatitis in patients of breast cancer. The N06C4 trial showed that using MMF could reduce erythema, pigmentation, itching, and burning.[19] However, these published research studies provided no definite clinical recommendations since ARD is greatly influenced by individual factors.

Usually, the severity of ARD depends on both, treatment-related and individual or patient-related factors. Researchers could control the treatment factors, but not the individual factors such as the individual's usual skincare routine, medications, diabetes, renal failure, old age, chronic sun exposure, smoking, and environmental conditions.[21] Pain and itch are subjective feelings, and each individual has a different sensitivity to itching and pain, which is influenced by subjective emotions, past experiences, lifestyle, and so on.[22–24] Hence, a self-comparative trial might be the best solution. Therefore, a self-comparative approach was used to observe the efficacy of MMF in reducing ARD in patients with HNSCC, who usually receive higher radiation doses (>50 Gy), but identical doses for PTV on both sides of the neck.

In our study, we found that the patients benefitted from the MMF therapy. Our results prove that MMF inunction after radiotherapy can prevent ARD; however, further research is necessary. Several factors affect skin reactions, such as radiation dose and volume, radiotherapy technique, surgery at the same site before radiotherapy, history of smoking, and previous and concurrent chemotherapy.[25,26] Concurrent chemotherapy causes more severe ARD; however, the effects of different drugs were not considered in our trial. Especially 5-fluorouracil, which is commonly used in head and neck cancers, has toxic adverse effects on the skin and mucosa. ARD occurs after radiotherapy. The self-contrast design of this study excluded most of the aforementioned reasons.

During the period of our study, we came across a paper from the Edinburgh Cancer Centre published in July 2016.[21] Based on the years of clinical experience in this center, the researchers divided the risk of radiation dermatitis into 4 grades. In this study, they concluded that MMF is equally effective as betamethasone in reducing ARD for patients.

During the experiment, we observed that the ARD cases occurred in different seasons, which has rarely been mentioned in previous studies. In winter, patchy dry peeling of the skin occurred after MMF application, while wet desquamation increased significantly in summer. We infer that the difference in results was due to the wide variation in ambient temperature.

The limitation of this study was that 19 patients withdrew from the study. Since these 19 patients benefitted from the application of MMF on the test side, they requested to be allowed the use of MMF on the control side as well.

5. Conclusion

This study showed that MMF inunction after high-dose radiotherapy (>50 Gy) can prevent ARD, especially when the skin dose is <6000 cGY.

Author contributions

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Supervision: Tangzhi Dai.
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