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Topical use of Jiawei Simiao Yongan Gao to prevent radiodermatitis in patients with head and neck cancer

A retrospective cohort study

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Abstract

Radiodermatitis is a common side effect of radiotherapy, but currently there is no standard treatment for its prevention. This study aimed to observe the effect of topical application of a paste based on traditional Chinese medicine, Jiawei Simiao Yongan Gao, on radiodermatitis caused by radiotherapy for patients with head and neck cancer.

This was a retrospective cohort study of 40 patients with head and neck cancer evaluated during their radiotherapy. Of these, 20 patients were treated with Jiawei Simiao Yongan Gao on the irradiated skin from the beginning of radiotherapy (JSY group). The other 20 patients were given standard nursing (standard group). Acute skin reactions were classified according to the radiation-induced skin reaction assessment scale (RISRAS) and American radiation therapy oncology group (RTOG) acute toxicity grading criteria every 2 weeks, and adverse effects were recorded until the end of the radiotherapy.

The two groups showed differences in severity of radiodermatitis. At 0 to 30 Gy, the skin reactions were similar in the two groups, while above 40 Gy the skin reactions were significantly lower grade in the JSY group ($P < .05$). At 0 to 20 Gy, there was no statistical significance ($P > .05$); but above 30 Gy they were lower in the JSY group ($P < .05$).

Jiawei Simiao Yongan Gao effectively alleviated acute radiodermatitis caused by radiotherapy of head and neck cancer patients compared with standard nursing.

Abbreviations: JSY = Jiawei Simiao Yongan Gao, KPS = Karnofsky performance score, PTV = planning target volume, RISRAS = Radiation-Induced Skin Reaction Assessment Scale, RT = radiation therapy, RTOG = American Radiation Therapy Oncology Group, TCM = traditional Chinese medicine, UICC/AICC = Union International Central Cancer/American Anticancer Institute.

Keywords: Cohort study, head and neck neoplasms, Jiawei Simiao Yongan Gao, radiodermatitis

1. Introduction

Many patients with carcinoma of the head and neck, particularly those patients with locally advanced disease, receive radiotherapy. About 80% to 90% of all patients with head and neck cancer undergoing radiotherapy develop radiation dermatitis,[1] whereas severe skin reactions occur in ~25% of these patients.[2]

Acute dermatitis is the most common radio-induced side effect during treatment for head and neck cancer.[3] Several factors may potentially affect skin toxicity. Both treatment- and patient-related risk factors can affect the degree of radiation-induced skin changes that occur.[4]

Radiotherapy-related factors such as total dose, fractionation, radiation energy, volume of treated regions,[5] treatment duration, boost application, and treatment site have been suggested.[1] Patient-related factors depend on age, comorbid conditions, skin phototype, and genetic predisposition.[5] Furthermore, the combination of radiotherapy and chemotherapy increases skin reactions, resulting in severe xerosis, inflammation, skin thinning, and necrosis of the upper dermis and epidermis.[6] Patients with head and neck cancer are commonly treated with radical radiotherapy or chemoradiotherapy,[7] which increases the likelihood of acute skin toxicity.[5,7]

The side effects may both reduce the patients' compliance and quality of life. Skin barrier function may be disturbed, resulting in folliculitis (skin rash), xerosis, pruritus, hyperpigmentation, and erythema. Additionally, the skin becomes more sensitive to allergens and prone to infection, and becomes more sensitive to ultraviolet radiation.[8–13]

Up to now, despite the use of a wide variety of different topical agents, there has been no generally accepted treatment for the

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prevention of the acute skin reactions resulting from head and neck cancer treatment.[3] In traditional Chinese medicine (TCM), acute radiation dermatitis belongs to the category of furuncles. "Yang Ke Gang Yao" records: "sores and ulcers are external diseases, external treatment is particularly important; all light symptoms rely on external treatment, can achieve full success; and dangerous ulcers, especially depend on external treatment, two of the above refer to each other, this is the theory of Yangyi." The TCM Jiawei Simiao Yongan Gao is a combination of ingredients in a paste that may help prevent or improve the symptoms of skin reaction due to RT. All the ingredients are used to treat irradiated skin reaction by clearing heat and toxicity, activating the blood, dissipating nodules, and relieving pain.

According to TCM, the manifestation of acute radiodermatitis is a skin reaction, so clear and light drugs which can enter the lung meridian directly are often used for treatment. Honeysuckle, which is the key medicine for carbuncles, can dispel pungency and release bitterness, clear away heat and toxic materials, to dissipate the carbuncle.[14] Angelica Sinensis can nourish and activate the blood, and relieve pain through promoting coronary circulation. Radix Scrophulariae can purge fire and eliminate toxins, and nourish the kidney-yin.[15] Raw Glycyrrhiza clears heat and toxicity. Raw Astragalus is added on the basis of the original prescription, and replenishes qi.[16] Forsythia promotes qi circulation by relieving yingfen. In addition, Forsythia is considered to be "the best medicine for sores," because it belongs to heart meridian, and as The Yellow Emperors Internal Classic said—"all pains and itches belong to the heart," forsythia can eliminate cardio pyrexia and dissipate heat and detoxify and dissipate nodules and detumescence.[17] Dandelion dissipates heat and detoxifies and dissipates nodules and Lithospermum can expel heat from the blood, activates the blood, dissipate carbuncles, and clear toxicity.[18,19] Borneol adds a transdermal effect.[14]

We found that use of the TCM Jiawei Simiao Yongan Gao as a topical agent on the skin where RT is used to treat head and neck cancer could reduce the occurrence of skin reaction. Therefore, the aim of this study was to retrospectively analyze the occurrence of radiodermatitis in patients with head and neck cancer treated with Jiawei Simiao Yongan Gao during RT in comparison to standard skin care.

2. Materials and methods

2.1. Patients

Patients with head and neck cancer who had received RT (or concurrent RT and chemotherapy) in the oncology department of the Third Hospital affiliated to Beijing University of Chinese Medicine during January 2013 to October 2018 were included. The inclusion criteria were:

1. Patients with head and neck malignant tumors confirmed by pathology;
2. Over 18 years old, male or female;
3. Received radiotherapy for the first time and did not receive radiotherapy within 1 month;
4. Karnofsky performance score (KPS) > 60;
5. Completed the full course of radiotherapy.

The exclusion criteria were:

1. Severe heart, lung, liver, and kidney dysfunction;
2. Critically ill or dying patients;
3. Pregnant or lactating women;
4. Damage or infected skin in the radiotherapy area;
5. Severe skin allergy;
6. Patients who participated in other clinical studies.

The study was approved by the ethics committee of the Third Hospital affiliated to Beijing University of Chinese Medicine Third Affiliated Hospital. The consent was obtained from the patients.

2.2. Radiotherapy

Radiotherapy was delivered to patients with a 6mv-X Intensity Modulated Radiation Therapy Elekta linear accelerator (Elekta, Sweden). The radiotherapy region included the tumor area and drainage area of the lymph nodes of the neck (one side or both sides). The first target area, planning target volume (PTV1) received a 66 to 70 Gy dose; the second target area (lymph node drainage area) PTV2 received approximately 60 Gy, 200 cGy/f, 5 times per week. When the treatment reached 30 times, only PTV1 was treated and radiotherapy for PTV2 stopped.

2.3. Interventions

A total of 40 patients undergoing normal routine treatment were retrospectively documented in this trial. Of these 40 patients, 20 patients were treated with Jiawei Simiao Yongan Gao for external use on irradiated skin after given standard nursing from the beginning of radiotherapy and were assigned to the JSY group. In addition, 20 patients were given only standard nursing and were assigned to the standard group. Because of the small number of patients in the study, the cases were matched 1:1 in terms of gender, age, cancer stage, tumor location, radiation dose, and presence or absence of cervical lymph node metastasis.

The JSY group was given Jiawei Simiao Yongan Gao for external use in the irritation region of neck skin from the beginning of RT. The paste was evenly applied to the radiotherapy area and 1 cm beyond the radiotherapy area, at a moderate thickness, twice a day with an interval of 6 h. It should be noted that any residual drug on the skin was wiped off before RT. The treatment lasted until the end of the RT regimen.

The drugs were smeared immediately after RT, but overexertion should be avoided. Wearing clothes made of soft material was suggested to decrease skin friction. Attention was given to observe any skin reaction every time the paste was used. If a rash or other reaction occurred, such as ulceration after smearing, the patient stopped using Jiawei Simiao Yongan Gao.

The standard group was given standard nursing. This followed a strict regimen during the radiotherapy. Irritated skin was kept clean and dry, especially the neck crease, which was scrubbed gently with warm water and a soft towel, no tape, iodine, tincture, alcohol, or other stimulants were used. A hot-water bag was forbidden, and direct exposure to sunlight was avoided.

2.4. Preparation of Jiawei Simiao Yongan Gao

The ointments for external use were made in the hospital. The ingredients for the Jiawei Simiao Yongan Gao treatment were 90 g Radix Scrophulariae, 90 g Honeysuckle, 60 g Angelica Sinensis, 30 g Raw Astragalus, 30 g Lithospermum, 30 g Forsythia, 30 g Dandelion, and 10 g raw Glycyrrhiza. Each ingredient was rubbed into a powder and mixed together into formula granules by the hospital's pharmacy. Then, 10 g Borneol was added and mixed with heated Vaseline, which was mixed into a paste with the TCM granules.

2.5. Data collection

The tumor staging referred to the diagnostic and staging criteria of the Union International Central Cancer/American Anticancer Institute (UICC/AICC) 7th revisional edition.[20]

According to the radiation therapy oncology group (RTOG) acute radiation toxicity scoring system,[6] the clinical classification of acute radiodermatitis was evaluated as follows: grade 0: there is no change; grade 1: follicle dark erythema/alopecia/asteatotic desquamation/hypohidrosis; grade 2: haphalgesia or erythema, flaking moist desquamation/moderate edema; grade 3: fusion moist desquamation outside skin folds, pitting edema; grade 4: ulcer, hemorrhage, necrosis. The degree of radiodermatitis was recorded every 2 weeks. At T2, 2 weeks after treatment start, until T14, 14 weeks after treatment start.

The patient symptoms were recorded using the classification standards of the radiation-induced skin reaction assessment scale (RISRAS),[21–23] as shown in Table 1. The Chinese version of the scale was used with a reliability and validity coefficient of 0.80. The patients' subjective symptoms were recorded every 2 weeks (T2–T14).

2.6. Statistical analysis

Data analysis was performed using SPSS version 22.0 (IBM SPSS, IBM Corp). Continuous data with normal distribution are expressed as means ± standard deviation (SD). Categorical data are expressed as frequencies and percentage. To describe the data, *t* test was applied for measured data, the ANOVA test was used for counting data. To exclude confounding factors, a multivariate regression analysis was performed. A *P*-value $<.05$ was considered statistically significant for all tests.

3. Results

A total of 40 patients were evaluable. Demographic and clinical characteristics of the patients are shown in Table 2. The median age of the patients in the JSY group was 58 years with a range of 30 to 75 years in the standard group the median age was 57 years with a range of 33 to 78 years. Male patients were 65% of the JSY group and 60% of the standard group. The most common location was nasopharyngeal in both groups and the majority of patients were clinical stage III. The planning target volume of both groups was similar. The two groups were similar in respect to the baseline data.

The whole radiotherapy treatment was completed in both groups. So, all patients were included in the analysis. In all cases, treatments were performed according to the observational protocol.

3.1. Skin reactions

The RTOG scores are shown in Figure 1. Until the T2 treatment time point, the RTOG criteria were assessed as normal for all patients. From T4 (20 Gy) to T6 (30 Gy), the proportion of radiodermatitis in both groups was shown as grade 1, and it was not statistically different in the two groups ($P > .05$). However, from T8 (40 Gy) to T14 (70 Gy), the results were markedly different ($P < .05$). The reaction of the JSY group was lower compared to the standard group. From T12 to T14, grade 3 reactions were observed in the standard group, while no grade 3 reactions were observed in the JSY group. The reactions were grade 1 principally in the JSY group, and grade 1 toxicities were increased in the JSY group compared to untreated controls.

Table 1

Scoring the patient's subjective symptoms according to the radiation-induced skin reaction assessment scale (RISRAS).

Symptom	Grade of symptom as assessed by the patient			
	Not at all	A bit	Some	Very
Do you feel any tension, discomfort, or pain in the skin of the radiation region?	0	1	2	3
Do you feel itchy at the radiation region?	0	1	2	3
Do you feel burning at the radiation region?	0	1	2	3
How much do you think the skin reaction caused by radiotherapy affects your daily activities?	0	1	2	3

Table 2

Clinico-demographic characteristics of the patients.

Clinical and demographic features	JSY group (n = 20)	Standard group (n = 20)	*P*
Age (years)	58.20 ± 12.73	56.85 ± 12.47	.737
Sex			
male	13 (65%)	12 (60%)	1.000
female	7 (35%)	8 (40%)	
Tumor localization			
Nasopharyngeal	10 (50%)	8 (40%)	.917
Hypopharyngeal	3 (15%)	4 (20%)	
Oropharyngeal	3 (15%)	4 (20%)	
Laryngeal	4 (20%)	4 (20%)	
Clinical stage			
III	16 (80%)	15 (55%)	1.000
IV A	4 (20%)	5 (25%)	
Planning target Volume 1	67.19 ± 1.71	67.26 ± 1.69	.901
Planning target Volume 2	57.01 ± 1.45	56.73 ± 1.22	.572

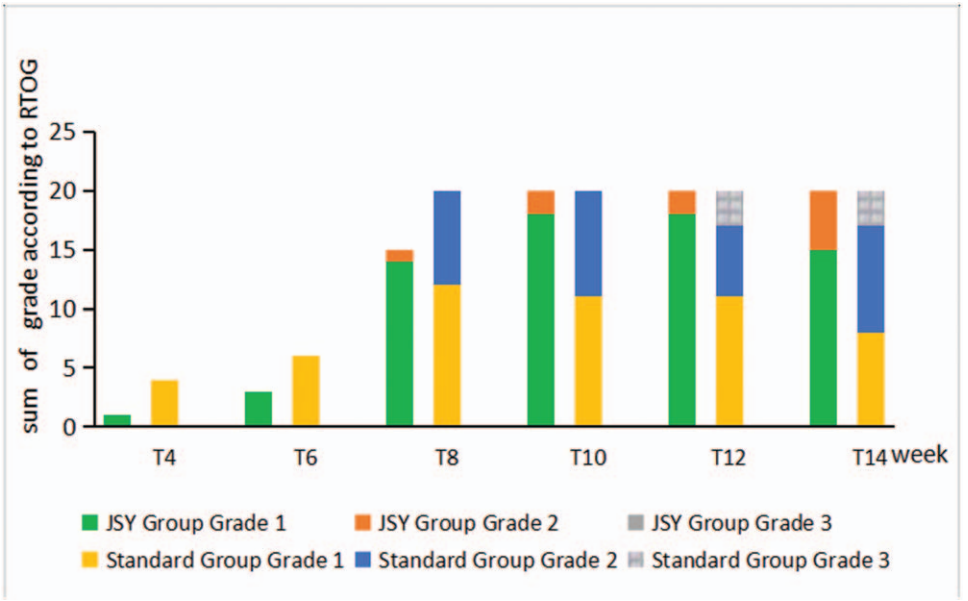

Figure 1. Graph representing the proportion of dermatitis as monitored by the radiation therapy oncology group (RTOG) acute radiation toxicity scoring system. T on the *x*-axis represents the time after radiotherapy started. The *y*-axis represents the percentage of cases.

3.2. RISRAS score

The results of the skin reactions were in line with the symptoms of the patients as assessed by the RISRAS scores. The sum of the RISRAS scores is shown in Figure 2. The findings showed that the JSY group and the standard group had similar symptoms from T0 to T4 ($P > .05$). From T6, the results show a significant benefit for Jiawei Simiao Yongan Gao over standard care during RT ($P < .05$). Amelioration of symptoms was obvious in the JSY group, because the subjective feelings of patients in the JSY group were better than that the standard group (Table 3).

3.3. Multivariate analysis

Multivariate regression analysis was conducted on the variables involved in the study which included Age, Sex, Tumor localization, and Clinical stage. The test of the analysis model had a P value of .09 ($P > .05$), which had no significance indicating that the variables had little influence on the results.

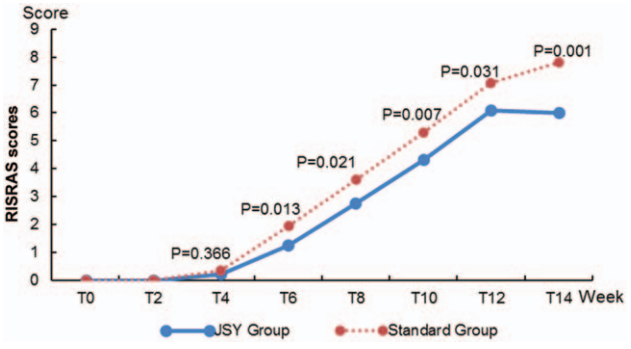

Figure 2. Graph showing the sum of the radiation-induced skin reaction assessment scale (RISRAS) scores. The time after the start of radiotherapy is shown as T on the *x*-axis, the *y*-axis shows the sum of RISRAS scores.

4. Discussion

The aim of this study was to retrospectively analyze the occurrence of radiodermatitis in patients with head and neck cancer treated with Jiawei Simiao Yongan Gao during RT in comparison to standard skin care. The results showed a clear difference in severity of radiodermatitis; after 8 weeks of RT when the skin reactions were significantly lower grade in the JSY group. The symptoms experienced by the patients reflected the decreased incidence of skin reactions as the RISRAS scores were significantly lower in the JSY group from 6 weeks after RT started. So, these results suggest that topical application of Jiawei Simiao Yongan Gao alleviated skin reactions during RT treatment.

Radiotherapy is the main treatment for head and neck cancer and acute radiodermatitis is one of the most common acute reactions in the process of radiotherapy. There have been many different approaches to try and alleviate acute radiation dermatitis in patients with head and neck cancer. Triethanolamine cream is commonly used in the clinic as a kind of oil-in-water anti-inflammatory drug, which can stimulate fibroblast proliferation, increase collagen synthesis,[24] improve skin tolerance, improve late and mild reactions to radiotherapy, and prevent irradiated skin injury.[25] However, it is ineffective for irradiated skin injury above degree 2.[26] Investigation into other agents in a systemic review suggested there was no strong evidence that indicates differences between topical pharmacological interventions or non-pharmacological topical controls.[27] Meta-analysis suggested that topical agents could not prevent or treat radiodermatitis.[28] However, these two studies investigated a wide range of agents, which may have hidden the results of small studies that were using effective agents. A small study on 94 patients with nasopharyngeal carcinoma suggested that intervention with simple olive oil was effective in decreasing the rate of skin injury during chemoradiotherapy.[29] While study of calendula, a topical agent derived from a plant of the marigold

Table 3

Sum of radiodermatitis grade between the two groups.

	JSY group (n = 20)				Standard group (n = 20)				*P*
	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total	
T4	1 (5%)	0	0	1 (5%)	4 (20%)	0	0	4 (20%)	
T6	3 (15%)	0	0	3	6 (30%)	0	0	6 (30%)	
T8	14 (70%)	1 (5%)	0	15 (75%)	12 (60%)	8 (40%)	0	20 (100%)	.048
T10	18 (90%)	2 (10%)	0	20 (100%)	11 (55%)	9 (45%)	0	20 (100%)	.031
T12	18 (90%)	2 (10%)	0	20 (100%)	11 (55%)	6 (30%)	3 (15%)	20 (100%)	.040
T14	15 (75%)	5 (25%)	0	20 (100%)	8 (40%)	9 (45%)	3 (15%)	20 (100%)	.037

($P < .05$, suggests the radiodermatitis grade is statistically different between the two groups).

family, has shown convincing evidence in the laboratory supporting calendula's mechanism of action in preventing radiation induced skin toxicity but clinical studies have demonstrated mixed results.[30] The results of this study suggest that an approach based on TCM may be effective in alleviating radiodermatitis. Patients treated with Jiawei Simiao Yongan Gao had significantly lower grade of skin reactions and reported symptoms than those undergoing standard care.

The reaction of the skin to ionizing radiation is complex and depends on many factors, such as the fraction of radiation, the segmentation method, the total dose, the type of radiation, the prescription volume and the treatment of radiation side effects.[31] During the RT process, with the accumulation of radiation dose, the skin capillaries in the irradiation field expand and hyperemia occurs, furthermore, erythema, pigmentation, skin erosion even ulceration can occur. These reactions may increase the pain of patients, cause important loss of life quality and patient compliance[32] with a potential negative impact on RT treatment efficacy,[33] which may prolong hospitalization time, and interrupt treatment in order to promote the healing of injured skin as soon as possible. Therefore, effective methods to prevent or treat radiodermatitis are important.

In TCM, acute irradiated skin injury is characterized as steamed skin with fire and toxin, and the lung governs the skin and fur, therefore, acute irradiated skin injury is closely related to lung-heat, while the lung governs qi and breathing, lung is responsible for administration and regulation, facing hundreds of veins. As a result, the collaterals of the lung are closely related to the lung. For acute radiation-induced skin injury, its evolution is characterized by gas-fire heat junction in the early stage and collateral stasis blockage in the later stage,[34] which is consistent with the pathogenesis of "Chronic Diseases Transforming to Collaterals." As a consequence, the principles of treating acute irradiated skin reaction should be clearing heat and activating blood and removing blood stasis and relieving pain. The application of the Jiawei Simiao Yongan Gao can guide the drugs directly to the station of illness. The results of this study confirmed the beneficial effects of Jiawei Simiao Yongan Gao in reducing skin reactions during RT.

This study has some limitations. The study was based in a single center, so the sample size was quite small. Despite this demonstration of clinically significant activity, the results may be related to several factors, such as the unblinded, non-randomized study design. There was no placebo standard group or comparison with another topical agent. Therefore, larger scale randomized controlled trials are needed to fully evaluate the efficacy of Jiawei Simiao Yongan Gao in prevention of radiodermatitis.

In conclusion, topical application of Jiawei Simiao Yongan Gao resulted in lower grade skin reactions and patient symptoms of acute radiodermatitis caused by radiotherapy for head and neck cancer patients. So, we recommend using Jiawei Simiao Yongan Gao when RT is regularly used in the future. We would also use it on other types of cancer not just head and neck cancer patients. However, we are aware that this data is from a nonrandomized study and further randomized trials and larger multicenter studies are needed to support the use of Jiawei Simiao Yongan Gao in clinical practice.

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