

Scientific Article

Efficacy of Lvpao Powder on Radiation Therapy –Induced Mucositis: A Retrospective Study of 114 Patients With Head and Neck Carcinoma



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Purpose: To compare the efficacy and safety of Kangfuxin solution and lvpao powder on mucositis induced by radiation therapy in head and neck carcinoma patients. We retrospectively analyzed 114 patients with head and neck malignant tumors in our center.

Methods and Materials: Patients were given Kangfuxin solution to rinse the mouth or Lvpao powder sprayed on oral mucosa after the solution use. The side effect was evaluated by Common Terminology Criteria for Adverse Events version 4.0.

Results: The grade 3 mucositis occurred in 32.9% (23/70) and 11.4% (5/44) in Kangfuxin solution group and Kangfuxin solution + lvpao powder group, respectively ($P = .009$). The pain score of the Kangfuxin solution group was significantly higher than that of the Kangfuxin solution and lvpao powder group, with 4.26 ± 0.81 versus 3.75 ± 1.03 ($P = .007$). The time of symptom relief in the combined group was significantly shorter than that in the single drug group, with 3 days versus 6 days ($P = .000$). The weight loss of the former groups was bigger than that of the latter group (6.67 ± 1.20 kg vs 5.95 ± 0.94 kg; $P = .001$). There was no statistical difference in the limitations in mouth opening ($P = .164$).

Conclusions: Lvpao powder is safe and effective as a mucosal repair drug in accelerating the recovery of patients and reducing their body weight.

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Introduction

Radiation-induced oral mucositis is one of the most common and severe complications of radiation therapy for head and neck cancer.¹ It usually occurs when the

dose of radiation therapy reaches 30 Gy, and symptoms include congestion, erythema, erosion, ulcer, and fibrosis of oral mucosa, resulting in pain, dehydration, dysgeusia, and malnutrition.^{2,3} More than 80% of patients diagnosed with head and neck carcinoma will suffer radiation oral mucositis, and half of them will even undergo grade 3 to 4 oral mucositis. Once this complication happens, radiation therapy may be interrupted because of the intolerable side effects, leading to poor prognosis.^{4,5} The occurrence of radiation-induced oral mucositis prolongs hospital stays and increases economic burdens,⁶ so reducing mucosa injury and improving patient quality of life has always been a focus of radiation therapy doctors.^{7,8} During

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radiation therapy, it is recommended to quit smoking tobacco and drinking alcohol, drink plenty of water, and avoid hot, acidic, and spicy foods. Maintaining oral hygiene can also help prevent and reduce radiation oral mucositis. Patients are advised to have an oral examination and improve oral hygiene before radiation therapy. A soft toothbrush is recommended, and saline or alkaline (sodium bicarbonate) mouthwash can be used to gently clean the mouth. Once a patient suffers from side effects, several steps are taken. For patients diagnosed with grade 1 to 2 mucositis, maintaining oral hygiene is important, and nutritional support is recommended for those with eating difficulties. For grade 3 or definite infection, local or systemic antibiotics and hormones may be used. If grade 4 radiation oral mucositis occurs, radiation therapy, concurrent chemotherapy, or cetuximab treatment should be delayed until the mucositis is reduced to less than grade 2.⁹

Present research has found that there are many factors related to radiation oral mucositis. Patient factors include poor oral hygiene, history of periodontal disease, smoking, and malnutrition.¹⁰⁻¹² Other treatment-related factors such as radiation therapy technology, radiation therapy fraction mode, dose and radiation therapy site, chemotherapy drugs, and targeted drugs also affect the severity of mucositis.^{13,14} Kangfuxin solution is a polyalcoholic compound extracted from the American cockroach, which has the ability to remove decay and regenerate muscle, promoting the proliferation of granulation tissue, improving the microcirculation of gastrointestinal mucosa, and accelerating the repair and regeneration of damaged tissues. It also reduces inflammatory response and promotes cellular immune function.¹⁵ Lvpao powder, a traditional Chinese medicine with the effects of inhibiting or killing various pathogenic bacteria, accelerating the absorption of exudates, which is beneficial to the growth of granulation tissues. The Lvpao powder is directly applied to the ulcer surface, allowing a larger concentration of medicine to cover the lesion area and avoiding side effects caused by systemic medication.

The efficacy and feasibility of treatment of mucositis were evaluated by comparing the patients treated with lvpao powder and Kangfuxin solution with those treated with Kangfuxin solution alone.

Method and Materials

Patients enrollment

This study retrospectively analyzed 114 patients with head and neck malignant tumors from August 2019 to August 2022. We collected patient information such as diagnosis, age, smoking history, performance status score (PS score), radiation dose, concurrent therapy including chemotherapy, and targeted therapy from the electronic

medical record system. The inclusion criteria included (1) patients diagnosed with head and neck malignant tumor proved by pathology or histology, (2) age ranging from 18 to 70 years old, (3) patients who received head and neck radiation therapy with or without concurrent chemotherapy and targeted therapy, (4) a performance status score of 0 to 1, and (5) an expected survival time greater than 1 year. Exclusion criteria included (1) patients allergic to Lvpao powder, (2) patients who receive a radiation therapy dose less than 60 Gy, (3) oral or throat mucosa inflammation caused by other reasons, and (4) patients with diabetes mellitus and poor blood glucose control. This retrospective study was carried out using the opt-out method for the case series of our hospital. The study was approved by the Human Research Ethics Committee and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was waived by our institutional review board because of the retrospective nature of our study.

Treatment

Dental and gingival conditions evaluated by dentists were recorded for all patients before radiation therapy. All patients must complete dental cleaning and periodontal scaling. Dental caries must be extracted to reduce oral complications during radiation therapy. Intensity modulated radiation therapy was applied with doses ranging from 60 to 70 Gy, and the conventional fraction radiation mode was adopted (2 Gy per fraction, 5 fractions per week). Oral care was given immediately after the start of radiation therapy, including drinking more water, gargling before meals, brushing teeth with soft bristles after meals, and wiping the oral cavity with cotton balls dipped in normal saline in the morning and evening. Patients in the Kangfuxin group were given Kangfuxin solution to rinse the mouth 3 times a day, while patients in the Lvpao powder group sprayed the powder on oral mucosa after the Kangfuxin solution use. The patients were asked to not eat or drink within 30 minutes of using the drugs. During treatment, if oral mucosal reaction gets worse or the patient experiences fever or other symptoms, oral mucositis should be considered as a coinfection. Oral mucosal swabs then need to be sent for bacterial and fungal cultures, and drug sensitivity tests should be performed before treatment because prophylactic application will not be performed. There were no antifungal medications involved in our research. Because the patients received the radiation therapy from Monday through Friday, they were asked to visit their doctors at least 3 times a week to elevate the side effects.

Outcome

The main outcome measures included oral pain score, the incidence and grade of radiation mucositis, and time

to symptom relief. The secondary outcome measures are body weight loss and limitation of mouth opening.

Evaluation criteria

In this study, the radiation therapists are responsible for grading the mucositis according to the Common Terminology Criteria for Adverse Events version 4.0. Oral pain is scored by a numerical rating scale, with 0 to 10 representing different degrees of pain. The distance between the upper incisor and the lower incisor was used to assess limitation of mouth opening. Mild mouth opening limitation is 2 to 2.5 cm, moderate mouth opening limitation is 1 to 2 cm, and severe mouth opening limitation is more than 1 cm.

Statistical analysis

Statistical analysis was performed with SPSS 26.0 software. The counting data were expressed as percentage

(%), the comparison between groups was expressed by χ^2 test, the measuring data were expressed by mean \pm SD, and the comparison between groups was expressed by T test. $P < .05$ for the difference was statistically significant.

Results

A total of 114 patients were enrolled in this study with diseases including nasopharyngeal carcinoma (73 patients), parotid gland cancer (20 patients), oral malignant tumor (14 patients), and buccal mucosa cancer (7 patients). There were 84 males and 30 females. Seventy patients were enrolled in the Kangfuxin solution group, and 44 patients were enrolled in the Kangfuxin solution + Lvpao powder group. Basic patient information is shown in Table 1.

All patients eventually received a radiation dose more than 60 Gy. One hundred fourteen patients had different degrees of mucosal injury, but no patient experienced grade 4 toxicity. Grade 2 mucositis occurred 67.1% (47/

Table 1 Patients' basic information and characteristics

Characteristics	Kangfuxin solution group	Kangfuxin solution and lvpao powder group	P
Sex			.613
Female	19	11	
Male	51	33	
Smoking			.689
Yes	49	30	
No	21	14	
Age	43-68	43-69	.968
ECOG			.195
0	42	29	
1	28	15	
Primary tumor			.058
Nasopharyngeal carcinoma	43	30	
Parotid gland cancer	12	8	
Oral malignant tumor	11	3	
Buccal mucosa cancer	4	3	
Current treatment			.294
Chemo and target therapy	35	25	
Chemotherapy	23	12	
None	12	7	
Radiation dose			.134
60-66 Gy	26	14	
60-70 Gy	44	30	

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2 Analysis of primary and secondary outcome

Complications	Kangfuixi solution group	Kangfuixi solution and lvpao powder group	P
Pain score (mean \pm SD)	4.26 \pm 0.81	3.75 \pm 1.03	.009
Incidence of oral mucositis (%)			.007
Grade 3	32.9%	11.4%	
Grade 2	67.1%	88.6%	
Time to symptom relief (d)	6.0 \pm 0.558	3.0 \pm 0.206	.000
Body weight loss (kg)	6.67 \pm 1.20	5.95 \pm 0.94	.001
Limitation of mouth opening (%)			.164
Mild limitation	72.9%	84.1%	
Moderate limitation	27.1%	15.9%	

70) and 88.6% (39/44) in the Kangfuxin solution group and the Kangfuxin solution + Lvpao powder group, respectively, while grade 3 mucositis occurred in 32.9% (23/70) and 11.4% (5/44) of the 2 groups, respectively. The rate of grade 3 acute radiation mucositis in Kangfuxin solution group was significantly higher than that in Kangfuxin solution + Lvpao powder group ($\chi^2 = 6.376$; $P = .009$). The details are shown in [Table 2](#).

For pain caused by mucositis, we adopted the numerical scoring method to evaluate the patient's pain, recording their maximum pain then conducting statistical analysis. After statistical analysis, the pain score of the Kangfuxin solution group was 4.26 ± 0.81 , and the pain score of the Kangfuxin solution + lvpao powder group was 3.75 ± 1.03 . The pain score of the Kangfuxin solution group was significantly higher than that of the Kangfuxin solution + lvpao powder group after comparative analysis ($P = .007$).

Patients in the 2 groups began to feel pain, and some of them even suffered ulceration of the oral mucosa 12 to 16 days after the initiation of radiation therapy. We recorded the remission time of mucositis symptoms such as pain relief and decrease in the size of ulcer after the 2 different treatments. The recovery time was 6 days in the group with Kangfuxin solution and of 3 days in the group with Kangfuxin solution + lvpao powder group. The time of symptom relief in the combined group was significantly shorter than that in the single drug group, indicating that the use of lvpao powder can further reduce side effects and improve patient quality of life.

In addition, previous studies have shown that due to the pain caused by acute radiation mucosal injury, some patients had difficulty opening the mouth which caused poor dietary intake and poor nutrition, resulting in treatment interruption, further affecting the efficacy of the cancer treatment. We analysed mouth opening limitation in the 2 groups. The mild limitation rate was 72.9% (51/70) and 84.1% (37/44) in the Kangfuxin solution group and the Kangfuxin solution + lvpao powder group, respectively. The moderate limitation was 27.1% (19/70)

and 15.9% (7/44) in the 2 groups, respectively. The probability of moderate limitation in Kangfuxin solution alone group was higher than that other group, but there was no statistical difference ($\chi^2 = 1.937$; $P = .146$).

We also compared the weight loss of the patients before and after treatment. The weight loss of the Kangfuxin solution group decreased by 6.67 ± 1.20 kg, and the weight of the Kangfuxin solution + Lvpao powder group decreased by 5.95 ± 0.94 kg. The weight loss of the former groups was bigger than that of the latter group ($P = .001$).

Discussion

Radiation mucositis, the main acute reaction after radiation therapy for head and neck cancer, has always been a concern of clinicians.^{16,17} Because of the special location of head and neck tumors, radiation therapy is the main treatment, and chemotherapy can aggravate side effects.^{18,19} Once acute mucositis occurs, it seriously affects the daily life of patients.²⁰ These side effects not only burden the patients but also reduce the treatment efficacy.²¹

Radiation transmission oral mucositis is an inflammatory and ulcerative lesion of the oral mucosa caused by direct radiation damage to the DNA strands and chromosomes of the mucosal epithelial cells as well as a decrease in the protective effect of mucus secreted by salivary glands, such as the parotid gland. Secondary bacterial and fungal infections can occur, causing malnutrition and decreased resistance, reducing the tolerance of radiation therapy. Mucosal damage caused by radiation therapy may lead to local or even systemic infections, which may exacerbate the severity of mucosal damage. Local or systemic antibiotics are highly involved for grade 4+ radiation transmission oral mucositis,²² and appropriate antibiotics should be selected according to the results of the bacterial or fungal cultures and the results of sensitivity tests.

In our research, no patient experienced grade 4 toxicity. Therefore, we have not addressed antibiotic use. Previous studies have found that Kangfuxin solution promotes granulation tissue growth and angiogenesis, accelerates the shedding of necrotic tissue, and repairs a variety of ulcers and wound surfaces.^{23,24} It is also safe and effective in the treatment of radioactive mucositis.

Grade 2 mucositis occurred 67.1% and 88.6% in the Kangfuxin solution group and the Kangfuxin solution + lvpao powder group, respectively, and grade 3 mucositis occurred in 32.9% and 11.4% of the 2 groups, respectively. The rate of grade 3 acute radiation mucositis in Kangfuxin solution group was significantly higher than that in Kangfuxin solution + lvpao powder group in our research. The probability of mucositis reaches 100% in head and neck tumors,²⁵ and the lvpao powder significantly reduces the incidence of grade 3 or higher mucositis, which is why the probability of grade 2 mucositis in the lvpao powder group is higher than that in the Kangfuxin solution alone group. In this study, after gargling with the Kangfuxin solution, the local use of lvpao powder accelerates the oral mucosal epithelial cell proliferation and repair, reducing the patient's pain. In addition, lvpao powder has no odor, is easily accepted by the patients, and is not absorbed by the gastrointestinal tract. We did not observe the obvious toxic side effects.

During treatment, pain is the most common manifestation of radiation mucositis, which affects the patient's eating and psychological state. The combination of lvpao powder + Kangfuxin solution greatly reduced the patient's score of the numerical rating scale. Avoiding the use of opioid painkillers and their possible side effects also reduces the economic burden of patients, and improve the patient's degree of cooperation, reducing the risk of radiation therapy interruption.

Radiation dysphagia, also known as radiation temporomandibular joint dysfunction, mainly manifests as difficulty in opening the mouth or clenching the teeth after receiving radiation therapy, which is also a serious complication and sequelae of radiation therapy after radical radiation therapy for nasopharyngeal carcinoma. In this study, there was no significant difference in the degree of difficulty in opening the mouth between the 2 groups. Considering that difficulty in opening the mouth is a long-term complication and that the follow-up period of this study is too short, we will continue to follow-up this group of patients.

This study retrospectively analyzed the occurrence and treatment of radiation mucositis in patients after radiation therapy in our center. The results showed that after the use of lvpao powder, the incidence of grade 3 mucositis and pain in patients were decreased compared with those in the Kangfuxin solution group. Meanwhile, the remission of mucositis symptoms was accelerated. The improvement of the above conditions also decreased the weight loss of patients. During the treatment, the use of

lvpao powder reduced the toxicity and side effects, reduced the use of off-site nutrition and painkillers, reduced the economic burden of patients, and greatly improved patient life of quality.

By now, there is no effective drug for mucosal injury.^{26,27} Kangfuxin solution has been 1 of the main drugs for the recovery of mucositis.²⁸ In recent years, with the development of traditional Chinese medicine, more and more traditional Chinese medicine is widely used in clinical practice.^{29–32} Previous studies have shown that lvpao powder has good efficacy in healing oral ulcers. Lvpao powder also achieved good clinical efficacy for mucosal injury caused by radiation, suggesting that lvpao powder may be considered as an option for the treatment of mucositis in the future.

However, as a retrospective study, this study still has some defects. Although the baseline characteristics of the 2 groups were relatively balanced, some patients were also treated with nimotuzumab, which has been reported to aggravate mucosal damage. In addition, although 68.4% of patients had nasopharyngeal carcinoma, some patients with parotid gland cancer and oral cancer were enrolled. Considering that the target volume and dose were still a major factor, there was still a bias, though we limited the dose (>60 Gy). A larger clinical trial with more patients can provide us more accurate conclusions.

Conclusion

This study retrospectively analyzed 114 patients with head and neck cancer treated in our center. We found that the combination of lvpao powder and Kangfuxin solution had some advantages over Kangfuxin solution alone in the treatment of radiation-induced mucosal injury, mainly in the reduction of the occurrence of grade 3 mucositis and the control of pain. It is suggested that lvpao powder is safe and effective as a mucosal repair drug in accelerating the recovery of patients and reducing their body weight.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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