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ORIGINAL ARTICLE

Determining the efficacy of vitamin B12 mixed oral liquid in the treatment of radiation-induced esophagitis*

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Abstract

Objective This study aimed to investigate the effects of vitamin B12 mixed oral liquid in the treatment of radiation-induced esophagitis in patients with esophageal cancer.

Methods Seventy-five patients with esophageal cancer who met the enrollment criteria were randomly divided into the vitamin B12 mixed oral liquid group (39 patients in the study group) and the gentamicin mixed oral liquid group (36 patients in the control group). The effects of the two treatment methods on esophagitis grading, pain degree, body weight loss, and Karnofsky performance status (KPS) score in patients with radiation esophagitis were observed.

Results In the control group, grade 1 radiation esophagitis accounted for 27.8% of the total patients, grade 2 accounted for 41.7%, and grades 3 and 4 accounted for 30.6%. In the vitamin B12 treatment group, grade 1 radiation esophagitis accounted for 66.7% of the total patients, grade 2 accounted for 25.6%, and grades 3 and 4 accounted for 7.7%; there was a significant difference between the vitamin B12 treatment group and control group ($P < 0.01$). Similarly, pain caused by radiation esophagitis was significantly improved in the vitamin B12 group compared with the control group ($P < 0.05$). After treatment, the average weight loss of the control group was (2.18 ± 0.36) kg, while that of the vitamin B12 treatment group was (0.90 ± 0.43) kg ($P < 0.05$). The KPS scores of the vitamin B12 group were higher than those of the control group, which were 86.2 ± 1.2 and 85.6 ± 1.5, respectively, but there was no statistical difference ($P > 0.05$).

Conclusion Vitamin B12 mixed oral liquid can effectively reduce the severity of radiation esophagitis, relieve pain, improve patients' quality of life, and increase treatment compliance.

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Key words: esophagitis; vitamin B12; quality of life; Karnofsky performance status (KPS)

Esophagitis is the common side effect of radiotherapy for esophageal cancer, which adversely affects the treatment efficacy and quality of life of patients who receive this treatment [1]. With the increasing use of radiotherapy in the treatment of thoracic tumors, despiteachieving significant results, the incidence of radiation-induced esophagitis has gradually increased. When the dose of radiotherapy reaches 20–30 Gy, different degrees of radiation esophagitis occur [2]; related studies show that the incidence of severe radiation esophagitis in lung cancer patients is as high as 15%–25% [3]. In a randomized clinical study, radiation treatment was discontinued in 21% of cancer patients owing to the occurrence of severe radiation-induced esophagitis [4].

Congestion, edema, erosion, or ulcer in the esophageal mucosa is the main pathological manifestation of radiation esophagitis. The patient with this condition may experience throatdrying, dysphagia, nausea and vomiting, and retrosternal pain. Radiation esophagitis initially occurs as an aseptic inflammation, which

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may be accompanied by infection in the later stage and further aggravates the condition. In severe cases, dehydration, electrolyte imbalance, and insufficient nutrient intake may occur. Especially when radiotherapy and chemotherapy are carried out at the same time, the symptoms are more obvious, eventually increasing the incidence of complications and affecting the radiation response of the tumor [5–6].

Therefore, the cure of radiation esophagitis is essential to the success of tumor radiation therapy. In the traditional clinical treatment of radiation esophagitis, patients are often treated with antibiotics combined with hormone therapy, are placed on liquid diet, and receive parenteral nutrition, which can partially relieve pain but cannot be used to treat radiation esophagitis. Currently, there are no available drugs that can effectively treat radiation esophagitis [2, 7]. Thus, there is a need to develop a new drug that can be used for patients with radiation-induced esophagitis.

Vitamin B12 is a water-soluble vitamin that exerts significant antioxidant effects by scavenging reactive oxygen species (ROS). It also reduces inflammatory responses by regulating the expression of cytokines and prevents immune damage in tissues [8–9]. At the same time, previous clinical trials have found that vitamin B12 can significantly reduce radiation-induced mucosal damage [10]. Over the years, vitamin B12 mixed oral liquid has proven to be an effective formula for the treatment of radiation esophagitis in our cancer treatment centers (The Second Affiliated Hospital of Medical College, Xi'an Jiaotong University, China). From January 2015 to December 2018, our department has treated 75 patients with radiation-induced esophagitis with vitamin B12 mixed oral liquid. This study aimed to determine the use and positive role of vitamin 12 mixed oral liquid during the course of radiotherapy and provide a clinical reference point on how to avoid or reduce esophageal toxicity during thoracic cancer radiotherapy.

Material and methods

General information

From January 2015 to December 2018, 78 patients with esophageal cancer who met the enrollment criteria were randomized as follows: vitamin B12 mixed oral liquid group or study group (40 patients) and control group (38 patients). One patient from the study group and two from the control group were excluded from the study. Finally, 39 patients from the study group and 36 from the control group were included in the follow-up studies. Of the total participants, 64 were men and 11 were women, aged 45–80 years. The baseline characteristics of the patients are shown in Table 1. There were no significant differences in gender, age, tumor size, and radiation dose between the two groups.

Table 1 Patients and treatment characteristics (*n*)

Group	Study group (*n* = 39)	Control group (*n* = 36)
Age (years)	65.5 ± 9.3	66.7 ± 9.5
Histology		
ESCC	37	33
EAC	2	3
Gender		
Male	33	31
Female	6	5
Marriage		
Yes	37	35
No	2	1
Grade		
G1	3	2
G2–3	36	34
Weight loss		
≤ 5%	29	28
> 5%–10%	10	8
Smoking		
Yes	25	23
No	14	13
Length (cm)		
≤ 5	13	11
> 5	26	25
KPS	81.3 ± 1.4	81.1 ± 1.5
Radiation dose (Gy)		
≤ 60	13	12
> 60	26	24

Note: $P > 0.05$. ESCC: Esophageal squamous-cell cancer; EAC: Esophageal adenocarcinoma; KPS: Karnofsky performance status

Inclusion criteria

Patients (1) with esophageal cancer confirmed by esophagoscopy biopsy; (2) who were generally in good condition, aged ≤ 80 years, with a Karnofsky performance status (KPS) score of ≥ 70, and with life expectancy of ≥ 3 months; (3) with no previous history of esophageal disease and neck and chest radiotherapy; (4) who consumed a liquid diet before treatment; (5) with no tracheal invasion and no pre-perforation signs on X-ray examination; (6) without obvious heart, liver, lung, and kidney function abnormalities and with normal electrocardiogram (ECG) findings; and (7) who had better understanding of theircondition, knew the role of the relevant treatment and adverse reactions, and voluntarily received the treatment were included in the study.

Exclusion criteria

Patients (1) whose esophageal cancer was diagnosed only based on the imaging data without pathological confirmation; (2) aged > 80 years, with poor general condition, with KPS score of < 70, and with life

expectancy of < 3 months; (3) with history of esophageal disease or neck and chest radiotherapy; (4) who did not consume a liquid diet before treatment; (5) with signs of tracheal invasion or combined esophageal perforation on X-ray; (6) with abnormal heart, liver, lung, and kidney function, and abnormal ECG findings; (7) were pregnant or lactating; and (8) who were not familiar with the treatment or refused to receive the treatment were excluded.

Treatment and radiotherapy

Patients with esophageal cancer who met the conditions were administered with a mixed oral solution every day after 20 Gy of radiotherapy. The study group received the following treatment: vitamin B12 5 mg + lidocaine 200 mg + gentamicin 320 000 U added to 500 mL of saline. The control group received the following treatment: lidocaine 200 mg + gentamicin 320 000 U added to 500 mL of saline. The patients were positioned flat on the bed while receiving the mixed oral solution, were asked to swallow the solution slowly, and were not allowed to eat or drink anything for half an hour before and after treatment, so that the drug has sufficient time to act on the esophageal mucosa. The medication was administered three times a day at a dose of 20–25 mL until the end of radiotherapy. Vitamin B12 was administered at a dose of 0.5 mg (Fangming Pharmaceutical Group Co., Ltd., China); lidocaine, 100 mg (Tiansheng Pharmaceutical Group Co., Ltd., China); and gentamicin injection, 2 mL: 80 mg (80 000 U) (Chengxin Pharmaceutical Co., Ltd., China). All treatments were carried out with a linear accelerator (Varian Medical Systems Inc., CA, USA), using 6-MV photon energies delivered in 1.8–2 Gy per fraction 5 days a week at a dose rate of 400 cGy/min. The total radiation dose administered was 50.4–66 Gy.

Diagnostic criteria

Radiation-induced esophagitis was defined as the occurrence of esophageal inflammation after radiotherapy, such as local congestion, edema, and superficial ulcer. The primary symptoms include odynophagia, dysphagia, and retrosternal pain, andthe diagnosis was made based on the history of radiotherapy and patients' symptoms [1]. According to the Radiation Therapy Oncology Group acute radiation-induced esophageal morbidity (ARIE) scoring criteria, ARIE was classified into five grades [11] (Table 2).

Observation indicators and evaluation methods

During radiotherapy, changes in the patient's radiation-induced esophagitis grading, weight, pain, and nutritional status were observed and recorded.

Table 2 Description of radiation esophagitis grade

Grade	Description
Grade 0	No change
Grade I	Mild dysphagia or odynophagia, requiring topical anesthetic, non-narcotic agents, or soft diet
Grade II	Moderate dysphagia or odynophagia. Pain drugs or pure liquid diet might be needed
Grade III	Severe dysphagiaor odynophagia with dehydration, weight loss > 15%. Nasogastric tube might be required for nutrition
Grade IV	Complete obstruction, ulceration, perforation or fistula was formed

Esophagitis pain judgment criteria

The score is measured using a 10-point visual analog scale: 0 points: no pain; 3 points or less: slight bearable pain; 4–6 points: pain affects patient's sleep but is still bearable; and 7–10 points: gradual increase in pain intensity, pain is becoming unbearable, and it affects appetite and sleep. Radiation-induced esophagitis grading and esophagitis pain scores were evaluated once a week during treatment. For statistical analysis, patients with the highest ARIE grade and the most severe pain were selected for analysis.

Evaluation criteria of quality of life

The physical condition of the patient was evaluated using the KPS established by the World Health Organization and was evaluated and recorded before and after the treatment.

Quality control

Before undertaking the study, all participants of the clinical team were trained to master the management of radiation esophagitis, including grading of esophagitis and usage of these evaluationtools. All researchers were required to strictly adhere to the standard operating procedures when performing all necessary interventions and when recording data.

Statistical analysis

Quantitative data were presented as the mean ± standard error of the mean (SEM) and analyzed by one-way analysis of variance. Statistical analyses were performed using SPSS software (version 18.0). Qualitative data was measured by χ^2 test, and a P value of < 0.05 was considered significant.

Results

Changes of radiation esophagitis grade after treatment

Two groups of patients had different levels of dysphagia or pain when swallowing during radiotherapy. In the

Table 3 The classification of radiation esophagitis after treatment (*n*)

Group	Radiation esophagitis (classification)					χ^2	*F*
	0	1	2	3	4		
Study group	0	26	10	2	1		
Control group	0	10	15	8	3	12.61	0.0056

Note: $P < 0.01$, compared with the control group

Table 4 Comparison of pain between the two groups (*n*)

Group	Grade				χ^2	*F*
	No	Mild	Moderate	Severe		
Study group	0	31	5	3		
Control group	0	18	12	6	7.223	0.027

Note: $P < 0.05$, compared with the control group

control group, 10 (27.8%) patients had grade 1 radiation esophagitis, 15 (41.7%) had grade 2, and 11 (30.6%) had grades 3 and 4. In the vitamin B12 treatment group, 26 (66.7%) patients had grade 1 radiation esophagitis; 10 (25.6%) had grade 2, and 3 (7.7%) had grades 3 and 4. There was a significant difference between the vitamin B12 treatment group and control group, indicating that the severity of radiation esophagitis was significantly reduced by vitamin B12 mixed oral solution ($P < 0.01$; Table 3).

Comparison of pain scores between the two groups

The pain scores of the two groups are shown in Table 4. None of the patients from the vitamin B12 group and control group had absence of pain. In the vitamin B12 group, 31 patients had mild pain, while 8 had moderate to severe pain. In the control group, 18 patients had mild pain, and 18 had moderate to severe pain. There was a significant difference between the two groups ($P < 0.05$).

Weight changes after radiation therapy

In the two groups, only 16.7% of the patients from the control group had an increase in body weight after the end of treatment, and the rest of the patients had different degrees of reduction in body weight. The average weight loss of the control group was (2.18 ± 0.36) kilograms. On the vitamin B12 treatment group, 41.0% of the patients had an increase in body weight, while the average weight loss was (0.90 ± 0.43) kilograms. Compared with the control group, the difference was significant ($P = 0.029$; Fig. 1).

Changes in quality of life

The KPS score was 81.1 ± 1.5 and 81.3 ± 1.4 in the control group and vitamin B12 group, respectively, at the beginning of radiotherapy. After radiation, the KPS scores of the vitamin B12 group and control group were significantly increased (86.2 ± 1.2 and 85.6 ± 1.5, respectively). There was a statistically significant difference between the post-radiation KPS scores and pre-radiation scores of each group ($P < 0.05$; Fig. 2), but there was no statistical difference between the two groups ($P > 0.05$; Fig. 2). This may be due to the fact that the increase in KPS scores of esophageal cancer patients was not only related to the improvement of radiation esophagitis, but was also related to the improvement of the disease itself.

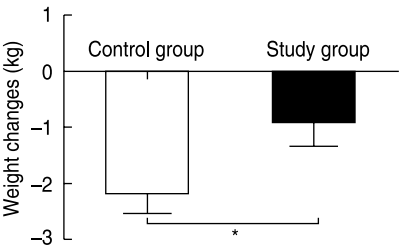

Fig. 1 Weight changes after radiation therapy. In the control group, the average weight loss was (2.18 ± 0.36) kilograms. In the vitamin B12 study group, the average weight loss was (0.90 ± 0.43) kilograms. Compared with the control group, the difference was significant ($P = 0.0442$).

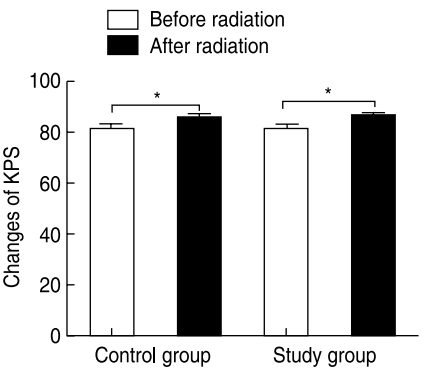

Fig. 2 KPS score changes after radiation therapy. The KPS scores of the vitamin B12 group and control group were significantly increased after radiation (86.2 ± 1.2 and 85.6 ± 1.5, respectively). There was a statistically significant difference between the post-radiation KPS scores and pre-radiation scores of each group ($P < 0.05$), but no statistical difference was observed between the two groups ($P > 0.05$).

Discussion

Radiation esophagitis is the most common side effect of radiotherapy for esophageal cancer, and it often occurs throughout the treatment period. Severe radiation-induced esophagitis can lead to pain, swallowing difficulties, depression, malnutrition, severe physical decline, and even disruption of radiation therapy, ultimately affecting the treatment of the tumor. The study found that the local tumor control rate is related to the total time of radiotherapy, and the extension of the total treatment time reduces the local control of the tumor [12].

Xu *et al* [13] found that the interrupted time (IT) of more than 4 days during intensity-modulated radiotherapy may decrease the survival outcomes of nasopharyngeal cancer patients. Moreover, IT (> 4 days vs ≤ 4 days) was found to be an independent prognostic factor for progression-free survival and overall survival.

To date, the clinical treatment of radiation esophagitis is aimed at achieving convergence, achieving anti-inflammatory effects, promoting esophageal mucosal repair, achieving analgesic effects, and promoting nutritional support. There are several treatments used to manage radiation esophagitis. These include oral glutamine, gentamicin, and procaine oral solution; epicatechin-3-gallate; and traditional Chinese medicine [14–17], and they all achieved certain clinical effects. However, there are no standard guidelines for the treatment of radiation esophagitis.

In the process of radiotherapy of tumors, radiation also acts on the esophageal mucosa not only to activate the inflammatory response, but also to decompose H_2O in the esophagus into oxygen free radicals by ionization. Oxygen free radicals generated in large amounts in local tissues can cause oxidative damage to the esophageal mucosa and produce malondialdehyde (MDA) and superoxide dismutase, which can increase the cell membrane permeability, destroy lysosomes, induce apoptosis, aggravate inflammatory response, and further cause damage to the esophagus [18–21].

Vitamin B12, or cobalamin, is an essential water-soluble vitamin that can directly scavenge ROS, especially superoxides, and exerts antioxidant properties [8]. In addition, vitamin B12 can reduce the inflammatory response by regulating the expression of cytokines and growth factors to protect against tissue damage caused by immune responses [9]. A joint study of patients with Alzheimer's disease found that patients with vitamin B12 deficiency had higher levels of interleukin-6 than those with normal vitamin B12 levels [22]. Studies of B12-deficient rats and patients with severe B12 deficiency also showed an increase in tumor necrosis factor alpha and a decreasein epidermal growth factor levels compared with controls. Other experimental results also showed that the ROS level in cobalamin-deficient melanocytes is extremely increased compared with that incontrols [23]. Previous studies further confirmed that vitamin B12 protects against oxidative stress caused by an immune response by regulating the production of cytokines and growth factors. Chen *et al* [10] found that vitamin B12 causes obvious and rapid repair and regenerationof functions on radiation-damaged mucosal epithelial cells and vascular endothelial cells, accelerating the formation of new tissues. Moreover, it can directly act on the pain receptors of the free nerve endings after being absorbed by the damaged part and has a significant peripheral and central analgesic effect.

Gentamicin is a broad-spectrum antibiotic suitable for the treatment of intestinal infections, pelvic infections, and skin and soft tissue infections caused by sensitive Gram-negative bacilli and staphylococcus. Through oral administration, gentamicin acts directly on the damaged mucosa to reduce the inflammatory reaction, so that the damaged mucosa does not delay the repair of the injury due to infection. Lidocaine has a surface anesthetic effect, which can relieve pain symptoms for those with severe pain. This oral mixture is a comprehensive treatment for the clinical symptoms of radiation esophagitis. Patients were positioned flat on bed while the mixed oral liquid was administered. They were asked to swallow the solution slowly and were not allowed to eat or drink anything for half an hour before and after administering the medication, so that the drug has sufficient time to act on the esophageal mucosa.

Our results showed that patients who were treated with vitamin B12 had higher incidence of grades 1 and 2 radiation esophagitis, while those in the control group had higher incidence of grades 3 and grade 4 radiation esophagitis. The distribution of changes in the pain scores of the two groups were similar to that of gradesin radiation esophagitis. Most of the patients in the study group experienced mild pain, and had lower incidence of moderate and severe pain than that of the control group. Changes in the distribution of radiation esophagitis and pain also affected the patients' quality of life. This study found that the quality of life of the two groups was similar to that before treatment. Moreover, the degree of weight loss in the study group was significantly lower than that in the control group after treatment, and the difference was significant. Although the quality of life in the study group improved compared with the control group, there was no statistical difference between the two groups. It may be because the increase in the KPS scores of the esophageal cancer patients was not only related to the improvement of radiation esophagitis, but was also related to the improvement of the disease itself. In addition, as the pain caused by radiation esophagitis was relieved, the radiotherapy treatment of the patients in the study group was not interrupted, which ensured the successful completion of the treatment. In the control group, two patients continued to undergo radiotherapy as their treatment was interrupted for 2–5 days due to the side effect. During the course of radiotherapy, we closely observed the patient's pain status and the changes in diet, mental, and other general conditions. If the patient experienced severe pain, which affected his or her quality of life or sleep, adjuvant treatments (such as analgesics and nutritional support), were provided. The study group did not develop toxicities associated with vitamin B12 treatment. After clinical observation, we found that the

mixed oral liquid has no toxic and side effects, is safe and reliable, and is an effective treatment for radiation esophagitis.

In summary, our preliminary results show that vitamin B12 mixed oral solution can significantly reduce the symptoms of radiation esophagitis, improve the quality of life of patients, ensure the smooth completion of treatment, and is convenient and economical. However, this study also has certain limitations. Hence, a multi-center, large-sample, double-blind clinical study is warranted.

Ethics approval and consent to participate

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Verbal consent was obtained from all participants, and the study documents were reviewed and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Medical College, Xi'an Jiaotong University, China (approval No. 2019015).

Conflicts of interest

The authors indicate no potential conflicts of interest.

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