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ORIGINAL ARTICLE

Study of Qingre Liyan Decoction (清热利咽汤) in Treating and Preventing Acute Radioactive Oral Mucositis*

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ABSTRACT **Objective:** To study the effect of Qingre Liyan Decoction (清热利咽汤, QRLYD) in the prevention and treatment of acute radiative oral mucositis (AROM), and to explore the mechanism of QRLYD by detecting epidermal growth factor (EGF) and T lymphocytes (CD3, CD4, and CD8). **Methods:** Sixty patients conforming with the standard were randomly assigned to two groups, 30 patients in each group. Patients in the trial group were treated with QRLYD, and those in the control group were treated with Dobell's solution, both groups receiving conventional radiation treatment. The treatment course for both groups was 6 weeks on average. Blood routine test, CD3, CD4, and CD8 in the peripheral blood and EGF in the saliva were detected one day before and on the 14th and 28th day of radio-therapy. **Results:** Patients in the trial group were in good condition with normal spirits and intake of food and drinks. The incidence of AROM is lower and the effect in preventing AROM is higher in the trial group than those in the control group (P<0.05). The EGF in saliva, and CD4 and CD8 in the blood of patients in the trial group were higher than those in the control group (P<0.05). **Conclusion:** QRLYD can cure and prevent AROM. The mechanism may be related with its effects in enhancing body immunity and promoting salivary EGF.

KEY WORDS Qingre Liyan Decoction, acute radiative oral mucositis, epidermal growth factor, T lymphocytes

Malignant tumors in the head-neck region account for 10%-30% of all kinds of malignant tumors. The incidence of the disease is 14.39 in 100 thousands in males and 10.65 in 100 thousands in females in China. Among these tumors, nasopharyngeal carcinoma is the most common. Statistics show that 80% of nasopharyngeal carcinoma patients in the whole world came from south China, especially in Guangzhou and its neighboring areas. Its incidence in south China is 30-80 in 100 thousands (mostly in males). The ratio between male and female is 2-4:1[1,2].

The application of radio-therapy (RT) on carcinoma in the head-neck region is becoming increasingly important. The cure rate on cancer of stage Ⅰ-Ⅱ is 90% and 70% respectively. However, its clinical efficacy is greatly affected by radiation injury. Acute radiative oral mucositis (AROM) is the most commonly encountered acute side-toxic effect in applying RT for head-neck carcinoma, and the incidence of severe cases reaches 33%-49%, which usually made it necessary to discontinue the treatment and reduce its effectiveness. Therefore, all scholars at home and abroad are seeking methods to prevent and cure AROM, but so far there is still no widely acknowledged effective one.

In this clinical trial, Qingre Liyan Decoction (清热利咽汤, QRLYD) was used to prevent and cure AROM and a certain clinical efficacy has been achieved by making use of its function in clearing heat to expel toxin, nourishing yin and supplementing qi, and activating blood circulation to remove blood stasis.

METHODS

Inclusion Standard

The selected cases had to conform to the diagnostic standard of head-neck carcinoma and be suitable for RT, with no severe functional abnormality in the heart, liver and kidney and no remote metastasis of carcinoma. Also, they had to strictly abide by the doctor's instructions and

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cooperate with the physicians in treatment and medical check-ups.

Exclusion Standard

Excluded were patients not conforming with any item of the above-mentioned standards of inclusion, or with severe diseases of the cardio-vascular, pulmonary, renal or nervous system.

General Data

Sixty patients, hospitalized from February 2004 to February 2006 in Shaanxi Oncology Hospital, their condition conforming to the inclusion standard, were selected and randomly assigned to two groups equally by lot-drawing method, the trial group was treated with QRLYD and the control group was treated with Dobell's solution. All the patients in both groups received conventional RT.

In the trial group, there were 15 males and 15 females, their age ranging from 42-62 years, the average age was 52.0±5.6 years; the group included 13 cases of nasopharyngeal carcinoma, 3 of tongue carcinoma, 3 of tonsillar carcinoma, 1 of maxillary carcinoma, 2 of parotid carcinoma, 1 of buccal carcinoma, 2 of laryngo-carcinoma, and 5 of cervical malignant lymphoma; their Karnofsky Performance Status (KPS) score was 68.0±7.5 on average.

In the control group, there were 17 males and 13 females, aged between 34-64 years, average age of 49.0±7.7 years; there were 10 cases of nasopharyngeal carcinoma, 2 of tongue carcinoma, 2 of maxillary carcinoma, 1 of parotid carcinoma, 2 of gingival carcinoma, 3 of laryngo-carcinoma, and 10 of cervical malignant lymphoma; their KPS score was 69.0±5.3 on average.

Statistical analysis showed that there was insignificant difference in the clinical data of age, gender, KPS score and total dosage of radiation applied between the two groups (P>0.05), and so they were comparable.

Methods of Treatment

RT was performed in the conventional sectioning method, with linear-accelerator 6MV X-ray, radiation on the face-neck combined traverse field, or facio-buccal front-lateral field with wedge-shaped plate, or neck tangent line or bilateral neck traverse field, 10-14 m^2 in area, 36-40 Gy of dosage. To avoid the spinal cord for some cases, the RT could be modified to radiation on the scruff or supra-middle portion of the neck with 8MV X-ray, 14-24 Gy. The total dosage applied was 50-70 Gy, with the median of 60 Gy.

In the whole course of RT, the patients in the trial group took QRLYS 200 mL daily, which was provided by Puji Pharmacy, Shaanxi Province, consisting of Flos Lonicerae 15 g, Rhizoma Belamcandae 15 g, Lasiosphaera seu Calvatia 9 g, Radix Astragali 30 g, Radix Glehniae 30 g, Radix Ophiopogonis 30 g, Radix Trichosanthes 15 g, Radix Scrophulariae 15 g, Rhizoma Ligusticum wallichii 15 g, Herba Agrimoniae 20 g, Rhizoma Imperatae 9 g, and Radix Glycyrrhizae 10 g.

Patients in the control group were treated by gargling with Dobell's solution, supplied by the preparation room of the First Hospital Affiliated to Xi'an Jiaotong University, batch No. 040122, 040603, 041211, 050423, 051025. The gargling was implemented 5 to 8 times daily, by keeping the solution in the mouth for 3-5 min first, and then swallowed slowly.

Items of Observation

Epidermal growth factor (EGF) in saliva was tested at the stated time points, i.e. one day before (T0), the 14th (T1) and 28th day (T2) of RT by radio-immune assay with the test kit bought from Beijing Huaqing Institute of Biochemistry Technique, batch No. 200509/200511.

T-lymphocyte subsets were determined on the same time points as EGF by enzyme-linked immunosorbent assay, with the test kit bought from Dalian Fanbang Chemical Technique Development Co., Ltd., batch No.050607.

Liver function, kidney function, and blood routine tests were examined, and changes of clinical symptoms were observed.

Grading of AROM

According to Radiation Therapy Oncology Group (RTOG) 2.0[3], the severity of AROM

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was graded into 5: Grade 0: no change; Grade Ⅰ: hyperaemia with mild pain but no need of analgesic; Grade Ⅱ: flaky mucositis bloody secretion, moderate pain and need of analgesic; Grade Ⅲ: fused fibrinous mucositis with severe pain and need of narcotics; Grade Ⅳ: ulcerative mucositis with bleeding, and necrosis.

Standard of Efficacy Evaluation

The efficacy of the treatment was evaluated as markedly effective when there was only slight hyperaemia on the oral membrane with pain disappearing completely or reduced to mild degree and the patient can take normal food of any kind; as effective when there was oral-pharyngeal hyperaemia but with no leukoplakia or erosion, with moderate pain, and the patient was able to take a semifluid diet; and as ineffective when there was still oral membranous hyperaemia, with leukoplakia or erosion and severe pain, and the patient is only able to take fluid food[4].

Statistical Analysis

Data was expressed as $\bar{x} \pm s$, analyzed by *t*-test and *Ridit* test for two independent samples with SPSS 13.0 Software.

RESULTS

Occurrence of AROM and Clinical Efficacy

After treatment, the different grades of AROM that occurred in the trial group were Grade 0 in 1 case, Grade Ⅰ in 10, Grade Ⅱ in 14, Grade Ⅲ in 5, and Grade Ⅳ in 0; while in the control group they were Grade 0 in 0, Grade Ⅰ in 4, Grade Ⅱ in 13, Grade Ⅲ in 12 and Grade Ⅳ in 1. By *Ridit* test, there was a significant difference between the two groups ($P<0.05$). Therapeutic efficacy in the trial group was markedly effective in 11, effective in 14 and ineffective in 15, with the total effective rate of 83.3%; while that for the control group was markedly effective in 4, effective in 13 and ineffective in 13, with the total effective rate of 56.7%. Comparison between the two groups showed significant difference in total effective rate ($P<0.05$).

Comparison of WBC and PLT Counts

The results are shown in Table 1. There was no significant difference between the two groups before treatment and after treatment ($t=0.76$, $t=1.73$, $P>0.05$). WBC and PLT counts all increased after treatment, which might be due to the injection of colony-stimulating factor when the patient's WBC count decreased during RT.

Table 1. Changes of WBC and PLT Count in the Two Groups ($\bar{x} \pm s$)

Group	Case	Time	WBC ($\times 10^9$/ L)	PLT ($\times 10^{12}$/ L)
Trial	30	Pre-treatment	4.68 ± 1.92	14.77 ± 5.79
		Post-treatment	5.73 ± 1.91	17.36 ± 5.82
Control	30	Pre-treatment	4.51 ± 1.98	15.23 ± 6.10
		Post-treatment	4.71 ± 1.73	16.59 ± 6.35

Comparison of EGF and T-lymphocyte Subsets between the Two Groups

The results are shown in Table 2. Before treatment, there was no significant difference between the two groups in the level of EGF ($P>0.05$). An insignificant difference remained after 14 days of treatment ($t=0.423$, $P>0.05$), but significant difference was shown after 28 days of treatment ($t=2.327$, $P<0.05$), indicating that QRLYD initiated and exhibited its effects in repairing membranous injuries and promoting local EGF production in about one month.

Comparison of CD4 and CD8 between the two groups after treatment also showed significant difference ($t=2.293$ and 3.991, $P<0.05$). For the reader's reference, the normal value of CD3, CD4 and CD8 are 70.96 ± 5.5%, 41.3 ± 5.6% and 26.4 ± 4.6% respectively.

Adverse Reaction

No adverse reaction on liver function or kidney

Table 2. Comparison of EGF and T-lymphocyte Subsets ($\bar{x} \pm s$)

Group	Case	Time	EGF (pg/mL)	CD3 (%)	CD4 (%)	CD8(%)
Trial	30	Pre-treatment	974.830 ± 526.200	60.5 ± 4.1	35.2 ± 2.3	20.5 ± 3.1
		Post-treatment 28 d	938.800 ± 477.217*	65.1 ± 12.5	37.2 ± 4.3*	21.6 ± 3.4*
Control	30	Pre-treatment	916.533 ± 540.408	60.6 ± 7.2	34.4 ± 3.1	21.1 ± 2.8
		Post-treatment 28 d	689.433 ± 341.596	62.0 ± 6.8	39.9 ± 4.9	25.1 ± 3.4

Note: *$P<0.05$, compared with the control group post-treatment

function was found in either group.

DISCUSSION

It is believed in modern medicine that the oral mucous membrane is constituted of multi-layer flat squamous epithelium, which renovates quickly, and is sensitive to radiation. In the early stage of radiation diseases, the reactive dilatation of the capillary on the radiated site would result in local congestion, and the basal cells of oral membranous epithelium will be denaturalized and sloughed, part of them even becoming putrescent. When the disease reach the stage of climax, extensive epithelial exfoliation and bleeding of the oral membrane would happen and ulceration and continuously expanding putrescence under the ulcer would happen too in severe cases. The patients may have such clinical symptoms of total exhaustion as fever, poor appetite, and so on. In the final stage, atrophic membrane and extinction of glands accompanied with a certain degree of fibrosis would appear, and the patients will be intractably dry in the mouth, and in case muscular fibrosis exists, it would be hard to open the mouth or dysphagia, etc[5-10].

Repairing of the skin or mucous membrane is decided by the speed of cell growth and proliferation in the affected location[11]. Medical immunologic and molecular cytobiologic studies show that the healing of a wound is controlled by the growth factor and polypeptides including EGF, which possesses effects in promoting the growth of various kinds of cells like squamous epithelial and vascular endothelial cells and in regulating the synthesis of protein, so as to accelerate the healing as well as to improve the quality of healing and effect of the treatment. Its mechanism is probably by way of the combination of EGF with the membranous calcium channel, and the energy offered by ATP to activate tyrosine proteinkinase in the cytoplasm of the channel to make changes in its structure through phosphorylation of the two subunit 5 500 and 170 000, thus increasing the membrane DNA of calcium influx.

This experiment indicated that QRLYD can improve the concentration of EGF in the saliva, and stimulate oral membranous epithelium and, through the biologic effect of EGF, to accelerate the repairing process of radiation injury, promote the auto-renewal of the membrane, increase the salivary secretion and reduce the chance for the oral cavity to get microbial infection. Comprehensively, it could reduce or alleviate AROM. Obviously, the QRLYD-induced elevation of EGF level is certainly beneficial to the repairing of radiation injuries. So the increase of EGF content is of course one of the mechanisms of QRLYD.

Normally, immunity is maintained through mutual actions between T-lymphocyte subsets. Disordered T-lymphocyte subsets would raise immune disturbance and a series of pathological changes. This trial showed that QRLYD could increase the peripheral T-lymphocyte subsets. As to why the increase of CD3 was of no statistical significance, errors in the process of experiment cannot be ruled out. The increase of CD4 and CD8 was definitely of statistical meaning, showing that TCM can improve the patients' immunity.

Generally, the strengthening of the body's immunity could serve, in one aspect, to mobilize integrally the positive regulating function of the body, enhance its endurance against radiation, and decrease adverse reaction; and in another aspect to increase immunity, especially that of cellular immunity, and kill cancer cells to a certain extent, thus limiting their multiplication and invasion. Both of the effects are favorable to prevention and treatment of AROM. So, the immunity enhancing effect of QRLYD is also regarded as one of its acting mechanisms.

Currently, traditional Chinese medicine (TCM) holds that X-ray is a substance of a hot nature, its invasion could consume yin-jin (阴津, body fluid), and further scathe qi-blood. As a hot natured lethal agent, RT-induced radiation injuries are actually yin damages by excessive evil heat. Along with the increasing of dosages of RT applied, the accumulated heat will be converted into toxin, which damages yin-jin and directly burn the oral membrane to form AROM. So the treatment should be mainly for clearing heat, removing toxic substances and nourishing yin. Yu, et al[12] held that X-ray is hot and toxic in nature, liable to burn and consume Jin-ye to cause qi-blood

stagnancy and blood stasis accumulation, which is difficult to dissolve. They suggested that the way of cure should be, on the basis of activating blood circulation, to remove stasis, and in combination with supplementing qi to make qi fluent for promoting blood circulation, thus enhancing the power in dissolving stasis. Zhao, et al[13] suggested that the TCM syndrome of AROM was dryness in Fei (肺) with damage of Yin-ye, and the treatment should be nourishing yin, moistening the dryness and producing Jin-ye.

In clinical practice, patients after RT usually seriously suffer from the symptoms of dry-heat damaging Jin with qi-deficiency and blood stasis syndrome, such as dry sensation in the nose and mouth, sore throat that is hard to relieve by water-intake, difficulty in swallowing, ulcer in the mouth and throat, anorexia, weakness, and dark-red-colored tongue. So, in the prescription of QRLYD, Flos Lonicerae and Radix Scrophulariae were used as the dominant medicine, which were assisted by Radix Glehniae, Radix Trichosanthes, Rhizoma Belamcandae and Lasiosphaera seu Calvatia for clearing heat and toxic substance, used in cooperation with Radix Ophiopogonis and Radix lehniae for nourishing yin and moistening dryness, and supported by Radix Astragali and Rhizoma Ligusticum wallichii, etc., as auxiliary agents for supplementing qi, activating blood circulation and removing stasis; all their effects were harmonized by Liquorice. QRLYD was medicated by being kept in the mouth first for about 3-5 min to bring about a local effect and then slowly swallowed so as to affect a permanent or radical cure.

In sum, QRLYD can treat and prevent AROM to a definite degree, and is worthy of further clinical studies.

REFERENCES

1. Gu XZ, Yin WB, Liu TF, et al. eds. Radiation therapy of tumor. 2nd ed. Beijing: Beijing Medical University and Peking Union Medical College Press, 1994:356.
2. Hao XS, ed. Compendious oncology. 1st ed. Beijing: People's Medical Publishing House, 2002:305.
3. Shen WJ, Wang LH, eds. Therapeutic radiation injury. 1st ed. Beijing: China Medico-Pharmaceutical Sciences and Technology Publishing House, 2002:116-121.
4. Huang GX, Zhang P, Qiu HJ, et al. Chinese medicinal prevention and treatment of acute radiation oropharyngitis in patients with nasopharyngeal carcinoma. J Sun Yat-sen Univ (Med Sci) (Chin) 2003;24(1):54.
5. Yu JM, Xu ZF, eds. General clinical lesson of oncology. 1st ed. Jinan: Shandong Sciences and Technology Publishing House, 2004:300-329.
6. Beetz A, Messer G, Oppel T, et al. Induction of interleukin 6 by ionizing radiation in a human epithelial cell line: control by corticosteroids. Int J Radiat Biol 1997;72:33-43.
7. Asa B, Henrik L, Carl S, et al. Potent corenterold cream (mometason furoate) significantly reduces acute Nacliating dermatitis: results from a double-blind randomized study. Radiat Oncol 2001;59:257-265.
8. Wong ZG. Current state and expectation on research of skin radiation injury. Chin J Radiat J Med Prod (Chin) 1996;16:(4)218-219.
9. Halperin EC. Gaspar L, George S, et al. A double-blind randomized prospective trial to evaluate topical vitamin C solutind for the prevention of radiation dermatitis. Int J Radiat Oncol Biol Phys 1993;26:413-416.
10. Li SY, Gao L, Yin WB, et al. Effect of Gene time on acute radiation mucositis and dermatitis. Chin J Radiat Oncol (Chin) 2002;11(1):30-33.
11. Ren BZ, ed. Biochemistry and clinic medicine. 1st ed. Changsha: Hunan Technology Publishing House, 1993:315,361-362.
12. Yu RC, ed. Traditional medicinal oncology. 1st ed. Beijing: Science Publishing House, 1985:1-16.
13. Zhao T, Wei HB, Li X, et al. Observation on preventing and controlling mouth mucositis of 41 cases with therapy of nourishing yin to produce body fluid after radiotherapy of nasopharyngeal cancer. Beijing Univ Tradit Chin Med (Clinical Medicine) (Chin) 2003;10(3):16-17.

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