Meta-analysis of Chinese Medicines for prevention and treatment of radiation esophagitis

LU Jun-zhang, ZHANG Lei, CAO Xiu-tang, YANG Ming-hui, ZHAO Hong, LIU Yi

OBJECTIVE: To systematically assess the clinical effectiveness of Chinese medicines for prevention and treatment of radiation esophagitis by meta-analysis.

METHODS: The articles were mainly retrieved from the "CHKD (China Hospital Knowledge Database) periodical full text databank", the "China periodical full text databank", the "CHKD doctor's and Master's degree student full text databank", and the "China doctor's degree student thesis databank", and they were selected according to the literature selection standard. The effects of Chinese medicines and Western medicines on radiation esophagitis were compared by meta-analysis.

RESULTS: Based on 13 articles, we found that the effectiveness of Chinese medicines for prevention and treatment of radiation esophagitis was superior to Western medicines, with no obvious side effects. Meta-analysis showed that the total odds ratio was 0.426 and the 95% confidence interval was 0.368, 0.493.

CONCLUSION: Chinese medicines are superior to Western medicines in preventing and treating radiation esophagitis. However, some methodological problems in the literature may have affected the authenticity of the results. Therefore, more rigorous, multi-central, randomized controlled trials with a large sample size should be designed to obtain a more reliable conclusion.

Key words: Radiation esophagitis; Meta-analysis; Traditional Chinese Medicine therapy.

INTRODUCTION

The morbidity of malignant tumors has tended to increase yearly in these 10 years. Radiotherapy is one of the main therapeutic treatments for tumors in the chest, such as lung cancer, carcinoma of the esophagus and mediastinal tumors, and it plays an important role in controlling the advance of malignant tumors. However, in radiotherapy of tumors in the chest, the radiation field unavoidably often spreads to the esophagus, inducing acute esophagitis. This mainly manifests as odynophagia, which affects food intake. For patients with mild esophagitis, food intake is not sufficient and for severe cases, it leads to malnutrition and electrolyte disturbance, even when treatment is suspended, affecting the therapeutic effect of the radiotherapy. In recent years, clinically, chemotherapy has been commonly combined with radiotherapy to treat cancers of the...
esophagus and lung to achieve better anti-cancer effects. However, according to statistical results, 20%-30% of patients suffer from severe acute esophagitis, limiting the treatment and severely influencing the patient’s quality of life, even leading to or accelerating death. Presently, Western medicine adopts expectant treatment with the digestive tract mucosal protective agent, Smecta, as well as anti-inflammatory agents and analgesics, such as antibiotics, anesthetics, and glucocorticoid hormones. Unfortunately, because of side effects, such as inhibition of immune function, aggregating or inducing infection, colonial imbalance, and hemorrhage of the digestive tract, they are unfavorable for the clinical population and long term use. Chinese medicines can be used as an auxiliary treatment. These medicines can prevent radiation esophagitis and can strengthen resistance of the body and have anti-cancer effects, increasing the patient’s quality of life and prolonging the survival period, which conforms to the total goal of combined treatment of tumors. However, it is unclear whether Chinese medicines can be used as standard medicines for preventing and treating radiation esophagitis, and their therapeutic effect and safety are not well understood. Therefore, the authors adopted the method of evidence-based medicine (meta-analysis) to investigate these issues.

METHODS

Retrieval tactics
The research range was limited to medical literature publically published in medical periodicals in China between January 1999-December 2010, including the "CHKD periodical full text databank", the "China periodical full text databank", the "CHKD doctor’s and Master’s degree student full text databank", and the "China doctor’s degree student thesis databank". "Radiation esophagitis" was used as a key word or title for the first retrieval, and then "prevention and treatment", "treatment", "Chinese drugs", "treatment with Chinese drugs", and "treatment with Chinese medicine and drugs" were used as key words for the second retrieval.

Inclusive criteria
Inclusive criteria included the following: 1) main intervenient measures were clinically randomized controlled trials of Chinese medicines for prevention and treatment of radiation esophagitis; 2) there were generally recognized criteria for diagnosis; 3) forms of prepared Chinese drugs, including decoctions and pill capsules, and administration methods, including oral administration and enema, were not limited; 4) there were generally recognized criteria for assessing therapeutic effects.

Exclusive criteria
Exclusive criteria included the following: 1) reports with no cases of a control group; 2) Western medicines were used for the treatment group and Chinese medicines were used for the control group; 3) Chinese drugs were used in the treatment group and placebo was used in the control group; 4) in the treatment group, there were complex factors, such as acupuncture; 5) descriptive research without statistical analysis.

Quality assessment of methodology
The trials included in this study were assessed by the Jadad scale. The clauses and subclauses in the scale were involved in assessment of randomization and methods, blind methods (double blind/single blind), and detailed reports on excluding research subjects. A total score of 1-2 was regarded as research of low quality and 3-5 was regarded as high quality.

Methods for assessment of therapeutic effects
With regard to RTOG (Radiation Therapy Oncology Group) and EORTC radioactive toxicity criteria, scaling criteria for acute radiation esophagitis were divided into 0-4 grades as follows: 0: no symptoms; 1: mild dysphagia or odynophagia, and superficial anesthesia, non-anesthetic analgesia or a semiliquid diet was necessary; 2: moderate dysphagia or odynophagia, and anesthetic analgesia or a semiliquid diet was necessary; 3: severe dysphagia or odynophagia, complicated by dehydration or a body mass decreasing over 15%, and supplement of nutrition by nasal feeding or venous transfusion was necessary; and 4: complete obstruction, and ulcer and perforation or fistulous formation. Among them, grades 0 and 1 were regarded as mild inflammation and grades 2, 3, and 4 as moderate and severe inflammation. The occurrence rate of moderate and severe inflammation was used for determining therapeutic effects.

Statistical method
RevMan 4.2 software package supplied by the Cochrane co-network was used for data analysis. For the enumeration data, RR (Risk Ratio) was selected for calculation of the 95% CI, and Chi-square analysis was used for heterogeneity of various test results. If there was no heterogeneity, a fixed effect model was selected for meta-analysis. Conversely, a randomized effect model was selected for meta-analysis. Potential publishing deviation was analyzed with an inverted funnel plot.

RESULTS

Analysis of the literature and assessment of quality
Seventeen papers possibly conforming to the inclusive criteria were assessed by reading abstracts of the literature. The full text was then read and 4 papers were excluded. Finally, 13 papers were included in the study (Table 1). The reasons for excluding the literature were...
as follows: intervening measures had mixed factors in 2 studies\(^a,^5\); chemotherapeutic drugs and treatment duration in the treatment group were greatly different to other previous literature in 1 study\(^6\); and 1 study\(^7\) was replicated in the literature. All of the 13 papers selected were ≥2 points in the Jadad scale, and the grouping method was "random" and the treatment duration began from radiotherapy to the end of radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Mild Inflammation</th>
<th>Moderate-severe Inflammation</th>
<th>Total cases</th>
<th>Mild Inflammation</th>
<th>Moderate-severe Inflammation</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>LU JZ, et al(^9)</td>
<td>Modified Zhuye Shigao Decoction</td>
<td>Smecta</td>
<td>68</td>
<td>12</td>
<td>80</td>
<td>19</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>XU LC, et al(^10)</td>
<td>Modified Qige San</td>
<td>Procaine, dexamethasone, gentamicin</td>
<td>20</td>
<td>8</td>
<td>28</td>
<td>7</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>WU D, et al(^11)</td>
<td>Chinese drugs for clearing away heat and toxic material</td>
<td>Saline, sodium bicarbonate, lidocaine</td>
<td>34</td>
<td>2</td>
<td>36</td>
<td>23</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>YAO WH(^12)</td>
<td>Shenhan Maidong Decoction</td>
<td>Saline, gentamicin, lidocaine</td>
<td>28</td>
<td>12</td>
<td>40</td>
<td>16</td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>CHEN ZM, et al(^13)</td>
<td>Shuangdi Mixureal.</td>
<td>Procaine, dexamethasone, gentamicin</td>
<td>29</td>
<td>11</td>
<td>40</td>
<td>15</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>HE FX(^14)</td>
<td>Shunshi Decoction</td>
<td>Saline, lidocaine, dexamethasone, gentamicin</td>
<td>127</td>
<td>10</td>
<td>137</td>
<td>86</td>
<td>44</td>
<td>130</td>
</tr>
<tr>
<td>FANG P, et al(^15)</td>
<td>Yangxin Jiedu Decoction</td>
<td>Vitamin C tablet, prednisone tablet, amoxicillin capsule</td>
<td>25</td>
<td>5</td>
<td>30</td>
<td>8</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>CUI DL, et al(^16)</td>
<td>Method for nourishing yin and removing toxic material</td>
<td>Gentamicin, mannitol</td>
<td>20</td>
<td>17</td>
<td>37</td>
<td>13</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>ZENG BR, et al(^17)</td>
<td>Yangxin Qingre Shengji Decoction</td>
<td>Saline, gentamicin, lidocaine</td>
<td>17</td>
<td>13</td>
<td>30</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>ZHAO JB, et al(^18)</td>
<td>Yingqiao Qingdai Decoction</td>
<td>Saline, lidocaine, dexamethasone, gentamicin</td>
<td>32</td>
<td>10</td>
<td>42</td>
<td>14</td>
<td>45</td>
<td>59</td>
</tr>
<tr>
<td>HUANG Y, et al(^19)</td>
<td>Chinese drugs</td>
<td>Mannitol, dexamethasone, gentamicin</td>
<td>15</td>
<td>23</td>
<td>38</td>
<td>5</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>WANGXZ(^20)</td>
<td>Decoction and soft extract of Chinese drugs</td>
<td>Vitamin C tablet, gentamicin</td>
<td>87</td>
<td>3</td>
<td>90</td>
<td>58</td>
<td>32</td>
<td>90</td>
</tr>
<tr>
<td>ZHOU X, et al(^21)</td>
<td>extract of Chinese drugs</td>
<td>Saline, lidocaine, dexamethasone, gentamicin</td>
<td>16</td>
<td>29</td>
<td>45</td>
<td>12</td>
<td>31</td>
<td>43</td>
</tr>
</tbody>
</table>

### Assessment of therapeutic effects of Chinese drugs for preventing and treating radiation esophagitis

The 13 papers all reported the effects of Chinese drugs and Western drugs for preventing and treating radiation esophagitis, and the results were compared between the 2 groups by meta-analysis (Figure 1). Statistical analysis showed that the heterogeneity test was \(P<0.0001\) which suggested that there was heterogeneity among the results of the studies. This difference was mainly induced by differences in the follow-up time, treatment dosage and dosage form of the drug. A random effects model was then selected. \(RR = 0.426, 95\% CI = 0.368, 0.49\), and the total effectiveness was hypothesized tested and it was found that \(Z=11.40 (P<0.0001)\). These results indicated that Chinese drugs had a significantly better effect than Western drugs in preventing and treating radiation esophagitis.
Lu JZ et al. Meta-analysis of Chinese Medicines for prevention and treatment of radiation esophagitis

Publication bias
The essence of meta-analysis is that it is a type of observational research, and drawing a funnel plot can help determine publication bias. In this study, a funnel graph was drawn with the ratio (RR) of the synthetic therapeutic effects of the treatment group to that of the control group in the 13 studies as the horizontal coordinate, and the reciprocal of RR as the vertical ordinate (Figure 1). We observed that the reversed funnel-shape plot was asymmetrical, indicating that the inclusive literature in this study showed publication bias. The main cause of this publication bias is that studies with negative results are difficult to publish. In addition, low quality of the methodology, differences between the test group and the control group in basic data, and other factors could also lead to asymmetrical distribution of the inverted funnel plot.

DISCUSSION
This study showed that Chinese medicine for preventing and treating radiation esophagitis was significantly better than Western medicines, with no significantly adverse effects. Previous research has indicated that the basic pathogenesis of radiation esophagitis is "invasion of heat toxicity, injuring both Qi and yin", accompanied by blood stasis, blood-dryness, phlegm-dampness, failure of descending of the stomach-Qi and disorder of the stomach-Qi. The principle of treatment is clearing away heat and toxic material, nourishing yin and promoting production of body liquids. Auxiliary treatment includes activating blood circulation and removing blood stasis, removing heat from the blood and moistening, resolving phlegm and removing dampness, regulating the stomach, and lowering the reverse flow of Qi. Commonly-used recipes are Zhuye Shigao Decoction, Qige Decoction, Shashen Maidong Decoction, and Shunshi Decoction. Commonly-used Chinese drugs for clearing away heat and material include Zhuye (bamboo leaf), Shigao (Gypsum Fibrosum), Luzen (Rhizoma Phragmitis), Jinyinhau (Flos Lonicerae), and Lianqiao (Fructus Forsythiae). Drugs for supplementing Qi and nourishing yin include Renshen (Radix Ginseng), Maidong (Radix Ophiopogonis), Shengdi (Radix Rehmanniae), Shashen (Radix Adenophorae Strictae), Xuanshen (Radix Scrophulariae), and Tianhuafen (Radix Trichosanthis). Drugs for eliminating dampness and resolving phlegm, lowering the reverse flow of Qi, and stopping nausea and vomiting include Chuanbei (Bulbus Fritillariae Cirrhosae) and Banxia (Rhizoma Pinelliae). Drugs for promoting circulation of Qi and blood circulation include Yujing (Radix Curcuma) and Danshen (Radix Salviae Militiorrhizae). Drugs for clearing away heat and toxic material and anti-cancer effects include Baihua Sheshē Cao (Herba Hedyotis Diffusa) and Banzhi (Herba Scutellariae...
Barbatae). TCM aims to “prevent diseases” at the beginning of radiation treatment. Simultaneous preventive administration can significantly decrease the morbidity of moderate-severe radiation esophagitis, achieve good prevention and treatment effects, obtain successful completion of radiotherapy, and improve the quality of life of the patient.

Our study has the following limitations. 1) Because the quality of most of the studies included in our meta-analysis was low, and meta-analysis itself also has certain shortcomings, our conclusion needs to be confirmed. In the future, scientifically designed clinical research programs, with multi-central, randomized, double blind, controlled trials with a large sample size should be performed to provide more convincing evidence. 2) In our study, the inverted funnel plot was clearly asymmetric, indicating that the included literature showed publication bias. The main cause of this bias is that studies with negative results are difficult to publish. In addition, the low quality of methodology and a small sample size are causes leading to this asymmetric distribution. 3) The heterogeneity test showed that 0.05, which is possibly caused by problems in the implementation of randomization and other aspects, with a lack of balance between the treatment group and the control group. Additionally, basic treatments of the two groups had more changes, there were differences in drug dosage and therapeutic course in the control group, and the characteristics of the studies, including age, sex proportion, duration of illness, patient’s condition and complications, were also important factors of variance. 4) In all of the studies, there were no adverse reactions in the Chinese drug group. Because of a less test about our study, our results need to be confirmed. In the future, studies should focus on the safety of medicines, with more detailed observational reports and more systematical assessment.

While our meta-analysis showed that Chinese drugs for preventing and treating radiation esophagitis had a good clinical effect and no obvious adverse reactions were found, the quality of the inclusive literature was low, with publication bias. Therefore, potential therapeutic effects remain to be shown by well designed, randomized double blind, placebo, controlled trials. Future studies need to be of good scientific research design with a large sample size, contain multi-central clinical cases, have systematic syndrome differentiation and assessment of radiation esophagitis, and establish methods and criteria of syndrome differentiation typifying conforming to TCM syndrome differentiation theories and clinical practice. Strengthening exploration of objectification and standardization of TCM for preventing and treating radiation esophagitis are required to provide more convincing evidence for clinical therapeutic effects of Chinese drugs.

REFERENCES

4 Duan YL, Fan XH, Shi ZZ, Sun ZX, Liu LP, Liu GL. Preventing and treating action of single Xue Jie on radiation esophagitis. Chin J Radiomedicine & Prevention 2006; 459
6 Wei HZ, Wei L, Gu XJ, Wang ZA, Xu DT, Fan SH. Clinical study on Fan Shi-huai’s Shunshi Decoction for preventing and treating radiation esophagitis induced by radiotherapy of esophagus cancer. Chin Tumor Clinic 1999; 26: 152
7 Wang XZ. Observation on clinical therapeutic effects of Chinese medicine and drugs in preventing and treating radiation esophagitis. Sichuan J Chin Med 2010; 80-81
10 Xu LC, Zou CL. Clinical observation on Modified Qi Ge San for preventing and treating radiation esophagitis. Chin Emergency Tradit Chin Med 2010; 19: 929-930
12 Yao WH. Observation on therapeutic effect of Modified Sashen Maimendong Decoction for prevention and treatment of radiation esophagitis. Chin J Radiomed & Prevent 2004; 24: 376
14 He FX. Clinical study on Shunshi Decoction for prevention and treatment of acute radiation esophagitis. Drugs & Clinic 2007; 4: 36-38
17 Zeng BR, Li W. Clinical observation on Yangyin Qingre Shengji Decoction for prevention and treatment of acute ra-
Lu JZ et al. Meta-analysis of Chinese Medicines for prevention and treatment of radiation esophagitis

diation esophagitis. Hunan J TCM University 2004; 29: 60, 61, 79
18 Zhao JB, Li ZJ, Zhang TX, Li YZ, He YX, Hong P. Yinqiao Qingdai Decoction for prevention and treatment of acute radiation esophagitis in 60 cases. Chin J Chin Med Information 2008; 15: 69
19 Huang Y, Qian SY, Hu YH. Clinical study on Chinese drugs for prevention and treatment of radiation esophagitis. Liaoning JTCM 2004; 31: 1005-1006