



The Efficiency of Adjusted-Da-Chai-Ling-Tang in Radiation-Induced Brain Edema in Patients with Brain Tumors

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Background: Brain edema induced by radiotherapy is a common complication in patients with brain tumors, for which medical treatment is the treatment of choice. Adjusted-Da-Chai-Ling-Tang, a Chinese herbal formulation, has been confirmed to be protective against the radiation-induced edema. In this study, we investigated the efficiency of adjusted-Da-Chai-Ling-Tang in radiation-induced brain edema in patients with brain tumors. **Materials and Methods:** A total of 46 patients with brain tumors treated with radiotherapy alone or combined with surgery were enrolled. These patients were divided into two groups: The experimental group with adjusted-Da-Chai-Ling-Tang and the control group with conventional medical treatment. Clinical data including symptoms and serologic results were collected pretreatment and on the 4th, 7th and 10th day posttreatment. Magnetic resonance imaging of the brain was performed to investigate changes in brain edema. **Results:** Clinical symptoms including headache, dizziness, nausea/vomiting and fatigue significantly improved in the experimental group ($P < 0.05$). No difference in serological results was observed. Brain edema was significantly reduced in the experimental group in magnetic resonance imaging ($P < 0.05$). **Conclusion:** Adjusted-Da-Chai-Ling-Tang is effective in the treatment of radiation-induced brain edema in patients with brain tumors. No obvious side effects were observed.

Key words: Brain edema, radiotherapy, brain tumor, adjusted-Da-Chai-Ling-Tang, magnetic resonance images

INTRODUCTION

Radiation-induced edema is common in patients with brain tumors treated with radiotherapy and has been reported to contribute to neurological deficits or impaired quality of life.¹ The clinical management of radiation-induced brain edema includes surgical intervention or medical treatment, depending on the presentation and severity of the patients. Corticosteroids and osmotherapy with mannitol, glycerol, or hypertonic saline are currently considered to be effective medical therapy.² However, these medications may affect electrolyte balance and worsen renal or liver function.

Adjusted-Da-Chia-Ling-Tang, a Chinese herb formulated by Taiwanese physician Chen-yu Lee, has been proven to be effective in removing stasis, dampness, activating vitality and

restoring health to patients. However, the clinical results were lacking. Therefore, we conducted this study to investigate the effectiveness of adjusted-Da-Chia-Ling-Tang in reducing radiation-induced brain edema in patients with brain tumors using magnetic resonance imaging including T2-weighted and fluid-attenuated inversion recovery (FLAIR) images.

MATERIALS AND METHODS

Patients

A total of 46 patients with brain edema resulting from treatment for brain tumors including primary neoplasms or metastasis from other origins were enrolled in this study from July 2011 to May 2013. All of the patients were treated with radiotherapy alone or in combination with surgery. For each patient, radiotherapy with 3000 cGy for 15 sessions was prescribed 5 days a week. The exclusion criteria were:

1. Severe cortical dysfunction;
2. Diffuse multiple brain tumors;
3. Coagulopathy or bleeding tendency (prolonged prothrombin time of >3 s);
4. liver and renal function impairment;

Received: June 01, 2014; Revised: October 27, 2014;
Accepted: January 08, 2015

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5. Severe metabolic disease including diabetes mellitus or hyponatremia;
6. Psychological disease;
7. Metastasis from the lung or lymphatic system (stage IIIC or IV);
8. Pregnancy or age below 18 years; and
9. Our associated stuffs. The enrolled patients were divided into two groups: The experimental group treated with adjusted-Da-Chai-Ling-Tang; and the control group treated without adjusted-Da-Chai-Ling-Tang.

This study was approved by the Institutional Review Board and Ethics Committee of our hospital.

Regimen of adjusted-Da-chai-Ling-Tang

Adjusted-Da-chai-Ling-Tang formulation includes Chai Hu (*Bupleurum chinense* DC) 9 g, Hunag qing (*Scutellaria baicalensis* Georgi.) 15 g, Pan Xia (*Pinellia ternate* (Thunb.) Breit.) 12 g, Chi Shaoyao (*Paeonia veitchii* Lynch) 12 g, Da Huang (Radix et Rhizoma Rhei) 3 g, Zhishi (*Citrus aurantium* L.) 9 g, Hung tsao (Zizyphi Jujubae, Fructus [red date, red jujubes]) 15 g, Fuling (*Poria cocos* (Schw.) Wolf.) 30 g, Chu Ling (*Grifola umbellata* (Pers.) Pilat.) 12 g, Zer Xie (*Alisma plantago-aquatica* L.) 15 g, Chang Chu (*Atractylodes lances* (Thunb.) DC.) 12 g, Ma Huang (*Ephedra sinica* Stapf.) 9 g, Dan sheng (*Salvia miltiorrhiza* Bge) 12 g, Chuanxiong (*Ligusticum chuanxiong* Hort.) 15 g, Wu Chu Yu (*Evodia rutaecarpa* Benth.) 15 g, Tien Ma (*Gastrodia elata* Blume) 15 g, Ginseng (*Panax Ginseng*) 9 g, chuan chi (*Panax notoginseng* (Burk.) F. H. Chen) 9 g.

This prescription is actually formulated from a combination of Da-Chai-Ling-Tang and Wu-Ling Sang, replacing bai shaoyao (*Paeonia lactiflora*) with chi shaoyao (*Paeonia veitchii* Lynch), Baizhu (*Atractylodes macrocephala* Koidz. [A. ovata Thunb.]) with Chang Chu (*Atractylodes lances* (Thunb.) DC.), and the addition of Ma Huang (*Ephedra sinica* Stapf.), Dan sheng (*Salvia miltiorrhiza* Bge), Chuanxiong (*Ligusticum chuanxiong* Hort.), Wu Chu Yu (*Evodia rutaecarpa* Benth.), Tien Ma (*Gastrodia elata* Blume), Ginseng (*Panax Ginseng*), and chuan chi (*Panax notoginseng* (Burk.) F. H. Chen).

The herbal materials were selected and decocted under Dr. Lee's (Yu sheng Clinic) supervision. The medicine was decocted into a liquid, and the treatment group received 3 doses a day for 10 days.

Clinical investigation

The clinical presentations associated with brain edema including headache, dizziness, spasm, nausea/vomiting and fatigue were evaluated using a visual analog scale. Serologic studies for liver (glutamate-oxaloacetic transaminase [GOT], glutamate pyruvate transaminase [GPT], T-bilirubin) and kidney function (blood urea nitrogen [BUN], creatinine) were performed pretreatment and at 4, 7 and 10 days posttreatment. Brain edema was evaluated by

magnetic resonance imaging using sequences of T2-weighted and FLAIR images before and 3 months after treatment.

Statistical analysis

The data are presented as mean $\pm$ standard deviation. The results were compared with the Student's *t*-test. A $P < 0.05$ was considered as statistically significant.

RESULTS

Patients

A total of 46 patients were enrolled in this study. The experimental group was comprised of 22 patients (10 males and 12 females) with a mean age of 56 years (range: 40–77 years). Fifteen patients had metastatic brain tumors (12 from the lung, 1 from the colon, and 2 of unknown origin), and 7 had glioblastoma multiforme. The control group was comprised of 24 patients (14 males and 10 females) with a mean age of 57 years, of whom 18 had metastatic brain tumors (14 from the lung, 1 from the thymus, 1 from the breast, and 2 of unknown origin), and 6 had primary brain tumors (2 glioblastoma multiforme, 1 grade II glioma, 1 anaplastic astrocytoma, 1 pituitary adenoma, and 1 germinoma). There were no significant differences between the two groups.

Headache

In the experimental group, only 1 patient complained of headache at the 10th day, compared to 2 patients at the 4th day, 4 patients at 7th day and 8 patients at the 10th day in the control group. The improvement in headache was significant in the experimental group after 7 days of treatment ($P = 0.046$).

Dizziness

In the experimental group, 2 patients at the 4th day, 2 patients at the 7th day, and 1 patient at the 10th day complained of dizziness, compared to 1 patient at the 4th day, 3 patients at 7th day, and 8 patients at the 10th day in the control group. The improvement in dizziness was significant in the experimental group after 10 days of treatment ($P = 0.037$).

Spasms

No spasms occurred in any of the patients.

Nausea and vomiting

In the experimental group, 3 patients at the 4th day, 1 patient at the 7th day and 2 patients at the 10th day complained of nausea and vomiting, compared to 2 patients at the 4th day, 3 patients at 7th day and 12 patients at the 10th day in the control group. The improvement in nausea and vomiting was significant in the experimental group after 10 days of treatment ($P = 0.001$).

Fatigue

In the experimental group, 1 patient at the 4th day, 5 patients at 7th day, and 9 patients at the 10th day complained of fatigue,

compared to 2 patients at the 4th day, 10 patients at 7th day, and 18 patients at the 10th day in the control group. The improvement in fatigue was significant in the experimental group after 10 days of treatment ($P = 0.037$).

Radiation-induced brain edema

In the experimental group, a reduction in edema was noted in 8 patients [Figure 1], the same level of edema in 6 patients, and progressive edema in 10 patients. In the control group, a reduction in edema was noted in 3 patients, the same level of edema in 6 patients, and progressive edema in 15 patients. The improvement in edema area was significant in the experimental group ($P = 0.047$).

Serology index

Liver and kidney functions were evaluated with serum tests before and after treatment, and no toxic reactions to the treatment were noted (GOT, $P = 0.001$; GPT, $P = 0.002$; T-bilirubin, $P = 0.005$; BUN, $P = 0.058$; creatinine $P = 0.046$).

DISCUSSION

Radiation-induced brain edema is a well-known complication in patients with brain tumors treated with radiotherapy. With the advent of noninvasive imaging techniques and scheduled follow-up, the incidence has increased. According to the time of appearance of symptoms after radiotherapy, cerebral radiation injuries are classified as acute, early and late phase. The vasogenic edema surrounding brain tumors results from the flow of fluid into the extracellular space of the brain parenchyma through an incompetent blood-brain barrier.³ Corticosteroids and osmotherapy with mannitol, glycerol, or hypertonic saline are currently considered to be effective medical therapy.² However, despite their usefulness, these medications are associated with a high rate of complications.⁴⁻⁶ Adjusted-Da-Chia-Ling-Tang, formulated by the Taiwanese

physician Chen-yu Lee, has been proven to be effective in alleviating stasis, dampness, activating vitality and restoring health to patients. However, the effectiveness of adjusted-Da-Chia-Ling-Tang in the management of peritumoral edema in patients with brain tumors treating with radiotherapy remains unclear.

The symptoms related to a mass effect or increase intracranial pressure with peritumoral edema vary from asymptomatic to a deterioration in neurological deficits.^{1,3} In this study, the clinical presentations including headache, dizziness, nausea/vomiting and fatigue significantly improved in the patients treated with adjusted-Da-Chia-Ling-Tang. In addition, no toxic side effects were noted in liver and kidney function, suggesting that it is safe for patients with brain edema.

Peritumoral edema induced by radiotherapy was evaluated by magnetic resonance imaging in this study and was found to be significantly reduced in the treatment group. This suggests that adjusted Da-Chai-Ling-Tang performs well in constraining the development of cerebral edema and preventing brain tissue from becoming hypoxic and/or a weakening of blood vessels during radiotherapy treatment. In turn, this can decrease the possibility of brain tissue damage and prevent dissolving of cranial nerves.

CONCLUSION

Adjusted-Da-Chai-Ling-Tang showed significant efficiency in alleviating the severity of cerebral edema and its complications. Therefore, adjusted Da-Chai-Ling-Tang may be applicable for the treatment of radiation-induced brain edema in patients with brain tumors.

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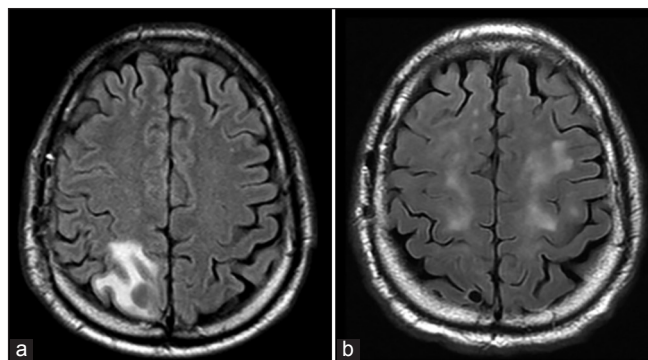


Figure 1. The magnetic resonance images of a patient with a right parietal brain tumor treated with radiotherapy revealed obvious peritumoral edema in the pretreatment phase (a) and a reduction in edema after treatment with adjusted-Da-Chai-Ling-Tang (b)