

Acupuncture relieves chemotherapy-induced refractory hiccup: A report of two cases

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Abstract

The aim of the study was to present two cases that illustrate the beneficial effects of acupuncture on chemotherapy-induced refractory hiccup in cancer patients. This report described two patients with diffuse large B cell lymphoma (DLBCL) and right upper pulmonary lobe moderate-differentiation adenocarcinoma (pT1N0M0) who experienced chemotherapy-induced refractory hiccup. Alternative treatment was administered to relieve the symptoms of refractory hiccup. The patients were treated with acupuncture 30 min prior to chemotherapy. The selected acupoints included Zusanli (ST36), Taichong (LR3), Zhongwan (CV12), Jiuwei (RN15), and Neiguan (PC6). The symptoms related to chemotherapy-induced refractory hiccup were completely relieved after treatment with 2 to 3 cycles of acupuncture. Based on our experience, we conclude that these two cancer patients benefited from acupuncture treatment, suggesting that acupuncture not only plays a role in pain control, but is also effective in relieving chemotherapy-induced refractory hiccup in cancer patients. The beneficial outcomes need large-scale studies to examine the effectiveness of acupuncture treatment for relieving chemotherapy-induced refractory hiccup in cancer patients.

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Acupuncture, a key component of traditional Chinese medicine (TCM), is traditionally used for pain control and management of body functions in patients, including cancer patients. Chemotherapy is one of the main therapeutic strategies for cancer treatment but it is usually accompanied by side effects. For example, some patients may suffer from refractory hiccup during the course of chemotherapy, for which there is no standard treatment. To explore a potential effective treatment, acupuncture was applied to treat two patients with refractory hiccups, with symptoms significantly relieved. The details are reported as follows.

Case reports

Case 1

Mr. Chen, a 78-year-old man, was hospitalized on June 14, 2016 due to multiple hypoecho nodes in his spleen after he presented with cough, hemoptysis, abdominal pain, diarrhea, fatigue, weight loss, and skin pruritus. A physical examination revealed that his

Eastern Cooperative Oncology Group (ECOG) score was 0 and there was no general superficial lymphadenectasis or any negative examination results with respect to the heart, lung, or abdomen. Chest computed tomography (CT) showed no space-occupying lesion. An abdominal CT found a space-occupying lesion in the spleen, including involvement of the splenic hilar lymph node. CT-guided splenic nodule puncture biopsy, pathological examination, and immunohistochemical analyses were performed, and the results were as follows: CD20 (+), CD79a (+), CD3 (-), CD45RO (-), BCL-2 (weak +), BCL-6 (+), CD10 (+), MUM1 (+), cyclinD1 (-), CD56 (-), CD5 (-), CD23 (-), MPO (-), Kappa (+), Lambda (-), and Ki-67 (+90%). Additionally, his lactate dehydrogenase (LDH) level was slightly elevated (298.0 U/L; reference value: 109–245 U/L). Hence, the patient was diagnosed as having diffuse large B cell lymphoma (DLBCL) [stage I; low and moderate risk; international prognostic index (IPI): 2 points; originated from a germinal center].

On June 30, 2016, the patient received R-CHOP (cyclophosphamide, doxorubicin, vincristine, and

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prednisone with rituximab) based on the general data, stage, and disease classification, and his CD20 positive status. The patient complained of a class-3 hiccup, 3 days after intravenous injection of the R-CHOP therapeutics. Although the patient was administered anisodamine (654-2) and metoclopramide, the symptom of hiccups was not relieved. Then, alternative treatment was administered to the patient. The patient received acupuncture and the symptoms of hiccups were completely relieved after 2 treatments.

Case 2

Mr. Liu, a 65-year-old man, underwent upper right pulmonary lobectomy plus systematic lymphadenectomy in the Department of Thoracic Surgery in our hospital (Sichuan Science City Hospital, Mianyang, China) on November 24, 2015, because nodules with increased FDG uptake by the right apex pulmonalis and the bilateral hilus pulmonis lymph nodes was observed on positron emission tomography-computed tomography (PET-CT). The patient was diagnosed as having right upper pulmonary lobe moderate-differentiation adenocarcinoma (pT1N0M0) based on the findings of postoperative pathological and immunohistochemical analyses. Adjuvant radiochemotherapy was not administered due to the early disease stage.

In July 2016, the patient complained of right inferior chest distress and chest pain. The chest CT showed moderate-volume pleural effusion locally in the right chest, and his epidermal growth factor receptor (EGFR) mutation status was negative. However, his circulatory tumor cell (CTC) count in the peripheral blood was higher than the normal level (the value was 8 CTCs / 3.2 mL).

Thoracocentesis catheter drainage combined with thoracic drug perfusion was performed twice. Drugs during the first perfusion included only recombinant human interleukin-2 (3 000 000 U), and those for the second perfusion contained recombinant human



Fig. 1 Corresponding points of acupuncture and moxibustion for refractory hiccup (a: Zusanli; b: Taichong; c: Jiuwei and Zhongwan; and d: Neiguan)

interleukin-2 (3 000 000 U) plus 40 mg of cis-platinum. In addition, a recombinant human endostatin injection plus PC (pemetrexed disodium injection + carboplatin) chemotherapy regimen was administered. On day 1 after the chemotherapy, the patient complained of a refractory hiccup (CTCAE: class 3), for which the symptoms were not relieved after administration of 654-2 and metoclopramide. However, the symptoms of refractory hiccup were completely relieved after 3 cycles of acupuncture.

Treatment and intervention

Acupuncture was implemented 30 min before chemotherapy. The selected acupoints included Zusanli (ST36), Taichong (LR3), Zhongwan (CV12), Jiuwei (RN15), and Neiguan (PC6). The location and depth of needle insertion are shown in Table 1.

Table 1 Location and depth of needle insertion

Acupoints	Location	Depth
Zusanli (Fig. 1a)	On anterolateral crus, one finger anterior to tibia	Perpendicular insertion for 1.0–1.5 Cun
Taichong (Fig. 1b)	Between the first and second metatarsal bones on dorsum pedis, on the anterior depression of the metatarsal bottom combination area, or an area with a touchable arterial pulse	Perpendicular insertion for 0.5–0.8 Cun
Zhongwan (Fig. 1c)	On the upper abdomen, anterior middle line, 4 Cun above the umbilicus	Perpendicular insertion for 0.5–1 Cun
Jiuwei (Fig. 1c)	On the upper abdomen, anterior middle line, 1 Cun below the xiphosternal synchondrosis	Oblique insertion for 0.5–1 Cun
Neiguan (Fig. 1d)	On the frontal area of the forearm, 2 Cun above the carpometacarpal distal transverse striation, between the tendons of the palmaris longus and flexor carpi radialis	Perpendicular insertion for 0.5–1 Cun

Note: Cun is the measuring method for acupuncture and moxibustion. 1 Cun = 3.333 cm

Discussion

Palliative treatment aims to increase the quality of life of patients with lethal diseases such as cancer. Palliative care is usually only applied to patients with fewer than 6 months of expected survival time. Palliative care for cancer not only includes treatment for cancer-related clinical symptoms such as pain, fatigue, and insomnia, but also includes treatment for radiochemotherapy-induced adverse reactions, such as nausea, vomiting, leucopenia, and hiccups^[1-2].

Hiccups are caused by sudden involuntary and intermittent constriction of the diaphragm and intercostal muscles in the early stage of glottal closure at the end of inspiration. The pathophysiology of hiccups remains elusive. One study^[3] showed that it may involve a complicated reflex arc including channels of the peripheral diaphragm, vagus and sympathetic nerves, and the central midbrain. However, the standard treatment remains controversial.

Steger *et al*^[4] systematically reviewed the treatment for 341 patients with refractory hiccup in 15 studies, and their results demonstrated that management was the most effective method under special conditions. Some drugs may be beneficial in cases where the cause of the hiccups is unclear or is irreversible. However, this review showed that all these studies were not well-designed. In a small-scale randomized placebo-controlled study, it was found that treatment with baclofen and metoclopramide was effective. An observational study reported that gabapentin and chlorpromazine were also effective. The authors of the review concluded that there were no high-quality data supporting treatments for refractory hiccup.

Although there is limited evidence regarding the clinical efficacy and safety of treatments for refractory hiccup, baclofen and gabapentin can be used as the first-line treatment for refractory hiccup, with metoclopramide and chlorpromazine as alternative choices^[4]. In some case reports, it has been reported that high-dose prokinetic agents or vinegar can relieve refractory hiccups^[5-6]. However, during chemotherapy, refractory hiccup is often induced by chemotherapeutic agents^[7] or by simultaneously administered glucocorticoids^[8]. Therefore, it is unclear regarding which drug contributes to causing hiccups during chemotherapy, and the selection of optimal treatment is also a great challenge^[5].

Acupuncture has been clinically applied for more than 3000 years in China for pain control and management of body functions^[8]. Acupuncture and moxibustion is one of the primary therapeutic methods in TCM. Increasing evidence has illustrated that TCM treatments, such as moxibustion, percutaneous electrical nerve stimulation, and acupuncture, have been widely used as palliative and support treatment for patients with cancer^[9], in which

acupuncture and moxibustion as well as related methods are applied for the treatment of different cancer-related symptoms such as nausea, vomiting, pain, and fatigue^[10-12]. However, the clinical safety and efficacy of these conventional TCM treatments continue to be debated.

Posadzki *et al*^[13] analyzed 7 randomized studies to evaluate the clinical efficacy of acupuncture as well as related methods in the treatment of cancer-associated fatigue, and they concluded that the studies all had a high risk of bias. On the contrary, Dos-Santos *et al*^[11] pointed out that acupuncture had an excellent effect on relieving fatigue based on high-quality randomized controlled studies. Furthermore, another systematic review^[2] demonstrated that acupuncture was a favorable supplement to palliative treatment for cancer, especially for clinical issues with a limited selection of routine therapies.

In this report, both cases developed refractory hiccup during chemotherapy and received TCM acupuncture after the failure of drugs such as metoclopramide and/or promethazine to relieve their symptoms. In both cases, their symptoms were markedly relieved after the initial treatment with acupuncture and the symptoms were completely relieved after 2 to 3 times of acupuncture treatment during chemotherapy.

Some studies have proven the effectiveness of acupuncture in the treatment of hiccups^[13]. The mechanism for acupuncture in the treatment of hiccup is still unclear. Most acupoints are located in related hiccup reflex arcs near the skin, such as input/output channels, secondary synapses, or ganglions^[14]. Acupuncture also has the potential to change regional blood perfusion, activate the automatic nerve system, regulate inflammatory mediators, or change axon excitability by stimulating any part of the hiccup reflex arcs, in order to treat hiccups^[15].

Some studies proposed that acupuncture could affect the central nerve system related to hiccups by regulating neurotransmitters and neurohormones, such as the secretion of serotonin, endogenous opiates, P substances, and norepinephrine^[15-16]. Sun *et al*^[17] found that needling Zusanli and Neiguan could activate the release of neurotransmitters from nucleus-isolated neurons in rats. Ji *et al*^[18] reported that mild acupuncture stimulation on Neiguan, Zhongwan, and Zusanli could effectively activate spontaneous discharges of neurons of subnucleus reticularis dorsalis in rats.

No adverse reactions or complications were reported in these two cases. Regarding acupuncture specific to chemotherapy-induced refractory hiccup, it is necessary to conduct large-scale rigorous clinical controlled trials to examine the effectiveness of acupuncture treatment for relieving chemotherapy-induced refractory hiccup in cancer patients and explore additional supplementary methods for the palliative treatment for patients with

cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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