

Acupuncture Treatment for Persistent Hiccups in Patients with Cancer

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Abstract

Objective: The objective of this study was to investigate the effects of acupuncture treatment for persistent hiccups in cancer patients.

Design: The study design was a retrospective case series.

Settings/location: The study setting was the Clinical Research Center of the National Institutes of Health.

Subjects: The subjects were 16 adult male patients ages 27–71 with cancer, with persistent hiccups.

Interventions: There were one to three acupuncture sessions over a 1–7-day period.

Outcome measures: Treatment efficacy was measured using a hiccup assessment instrument pre- and post-treatment. The effects of acupuncture on common symptoms reported by all patients were also evaluated.

Results: Thirteen (13) patients experienced complete remission of persistent hiccups ($p < 0.0001$); 3 patients experienced decreased hiccups severity. Significant improvement was observed in discomfort ($p < 0.0001$), distress ($p < 0.0001$), and fatigue ($p = 0.0078$).

Conclusions: This case series demonstrates that acupuncture may be a clinically useful, safe, and low-cost therapy for persistent hiccups in patients with cancer.

Introduction

HICCUPS ARE THE REPEATED, involuntary, spasmodic contractions of the diaphragm and inspiratory muscles, followed by sudden closure of the glottis.^{1,2} Some scientists believe there may be an evolutionary connection between human hiccups and a protective reflex in amphibians such as tadpoles.³ Most bouts of hiccups are short-lived and not pathologic. Persistent hiccups are defined as lasting longer than 48 hours. They can have a detrimental impact on quality of life, with consequences that include disturbed sleep, disruption in eating and drinking, speech difficulties, pain, gastrointestinal reflux, anxiety, fatigue, and depression.⁴

Persistent hiccups have been linked to drug-related causes, including chemotherapies and anesthetics, as well as many other conditions, such as nervous system disease, infection, and metabolic disorders.^{5,6} Pharmacologic approaches including baclofen, gabapentin, chlorpromazine, haloperidol, metoclopramide, lidocaine, valproic acid, and nifedipine, have been used with varying degrees of effectiveness^{7,8} but have not proved consistently effective.^{9–11} Some remedies used to treat hiccups can actually induce them, while other agents that cause hiccups appear to be

useful in treatment.¹¹ In addition, drug therapies for hiccups have been reported to cause adverse reactions in terminally ill patients.² Although acupuncture has long been used to treat hiccups in Asian countries,¹² in the United States we found only a single case report of the use of acupuncture for persistent hiccups in a patient without cancer.¹³ In this article, we present a case series of acupuncture treatment for persistent hiccups in 16 patients with cancer, with supporting data analysis. Also, this is the first report of the utilization of an assessment instrument to measure hiccups severity.

Materials and Methods

Patients

From March 6, 2002 to December 8, 2008, 16 adult male patients, ages 27–71, with varied cancer diagnoses were referred to the Acupuncture Consult Service of the National Center for Complementary and Alternative Medicine, the National Institutes of Health (NIH) for treatment of persistent hiccups at the Clinical Research Center. These cancer patients were enrolled in protocols of the National Cancer Institute (NCI) and the National Heart, Lung, and Blood

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Institute (NHLBI). The research protocols, which were approved by the Institutional Review Boards of NCI and NHLBI, cover cancer surgery, oncology therapy, and stem cell transplantation. Our study was approved by the NIH Office of Human Subjects Research (OHSR Exempt #4469). Oral informed consent was obtained and recorded in the medical record for each patient.

Acupuncture

In accordance with Traditional Chinese Medicine theory, acupuncture points were selected as follows: BL 17 (*Geshu*), GV 14 (*Dazhui*), CV 12 (*Zhongwan*), PC 6 (*Neiguan*), ST 36 (*Zusanli*), BL 20 (*Pishu*), BL 21 (*Weishu*), and LR 14 (*Qimen*) (Table 1).^{14,15} A 30-minute acupuncture session was administered. Standard sterilization procedures were followed prior to insertion of disposable 32-gauge, 0.25×40-mm (diameter×length) sterile steel needles. Acupuncture was performed with the patient lying in the lateral recumbent position. Moderate hand manipulation was employed and no electric stimulation was applied. The acupuncture needles were manipulated (lifting and thrusting, twirling or rotating) until the patient reported that they felt the *de qi* (needling sensation), characterized by soreness, numbness, heaviness, a feeling of distention, and pressure-like sensations. *De qi* is an important indicator for the treatment. All patients received the same acupuncture protocol.^{14,15}

Measurements

A Hiccups Assessment Instrument (HAI) was devised to measure hiccup severity. Patients were asked to rate the severity of their hiccups on a 0–10 numerical scale, ranging from 0 for “no hiccups” to 10 for “worst hiccups.” Patients were informed that a rating of 1–3 would be considered “mild” hiccups, that is, nagging, annoying, but interfering little with Activities of Daily Living (ADL); 4–6 would be considered “moderate” hiccups, that is, interfering significantly with ADL; and 7–10 would be “severe” hiccups, that is, disabling and unable to perform ADL. The HAI was administered immediately before and after each acupuncture treatment. A follow-up evaluation using the HAI was conducted 1–3 days later. During the follow-up, if the patient reported hiccups severity greater than 0, he received further

acupuncture treatment. If the patient reported that hiccups severity was 0, he received no further acupuncture treatment. The number of treatment sessions depended on the individual patient’s condition and ranged from 1 to 3 treatments within a 7-day period.

Discomfort, distress, and fatigue, reported by all subjects, were also measured on a 0–10 numerical rating scale adopted from the Neuropathic Pain Scale, Brief Fatigue Inventory, and National Comprehensive Cancer Network Distress Thermometer.^{16–18} An evaluative questionnaire was administered pre- and post-treatment.

Data analysis

The primary objective was to compare the hiccups scores before and after acupuncture treatment. Absolute and percentage score changes were statistically analyzed using the Wilcoxon signed rank test.¹⁹ Data collected on discomfort, distress, and fatigue underwent the same statistical analysis.

Results

The 16 case series patients were all male; age range of 27–71 years; 14 were white, 2 were black. They came from diverse sociodemographic backgrounds with respect to religion, ethnicity, nationality, employment, marital status, and education. There were 13 inpatients and 3 outpatients, including 9 referred from the Surgery Branch of NCI; 5 referred from the Oncology Branch of NCI; and 2 from the Stem Cell Transplant Branch of NHLBI. All patients presented with persistent hiccups lasting longer than 48 hours prior to treatment. The range of duration of hiccups was 48 hours to 144 hours and the average was 70 hours.

The 16 patients included 6 patients with severe hiccups (7–10), 6 with moderate hiccups (4–6), and 4 with mild hiccups (1–3), as determined by the HAI. The mean hiccups severity was 5.2, or moderate, which indicated a significant impact on ADL.

Of 16 patients, 13 had complete remission of hiccups after acupuncture treatments, as indicated by a score of 0 on the HAI. Of the 13 patients who experienced complete remission, 8 patients achieved these results after one treatment session; 2 patients required two sessions; and 3 patients required three sessions. Three (3) of the 16 patients experienced

TABLE 1. ACUPUNCTURE POINTS FOR HICCUPS

Point	Location	Depth
BL 17 (<i>Geshu</i>)	1.5 <i>cun</i> ^a lateral to lower border of spinous process of 7th thoracic vertebra	Puncture obliquely 0.5–0.8 <i>cun</i>
GV 14 (<i>Dazhui</i>)	Below spinous process of 7th cervical vertebra	Puncture obliquely upward 0.5–1 <i>cun</i>
CV 12 (<i>Zhongwan</i>)	4 <i>cun</i> above umbilicus	Puncture perpendicularly 0.8–1.5 <i>cun</i>
PC 6 (<i>Neiguan</i>)	2 <i>cun</i> above transverse crease of wrist	Puncture perpendicularly 0.5–1 <i>cun</i>
ST 36 (<i>Zusanli</i>)	3 <i>cun</i> below ST 35, one finger-breadth from anterior crest of tibia	Puncture perpendicularly 1–1.5 <i>cun</i>
BL 20 (<i>Pishu</i>)	1.5 <i>cun</i> lateral to lower border of spinous process of 11th thoracic vertebra	Puncture obliquely 0.5–0.8 <i>cun</i>
BL 21 (<i>Weishu</i>)	1.5 <i>cun</i> lateral to midpoint on line joining spinous process of 12th thoracic and 1st lumbar vertebra	Puncture obliquely 0.5–0.8 <i>cun</i>
LR 14 (<i>Qimen</i>)	Directly below nipple in 6th intercostal space	Puncture horizontally 0.5–1 <i>cun</i>

^a*Cun* is a measurement used for acupuncture point locations. One *cun* is the distance between the two medial ends of the creases of the interphalangeal joints of the patient’s flexed middle finger.

TABLE 2. CHARACTERISTICS OF PATIENTS WITH CANCER WITH HICCUPS

No. of subjects (M/F)	16 (16/0)
Age in years: median (range)	56 (27–71)
Cancer diagnoses, no. (%)	
Melanoma	4 (25)
Lymphoma	3 (18.7)
Leukemia	2 (12.5)
Adenocarcinoma	2 (12.5)
Other ^a cancers: Desmoplastic small round cell, esophageal, lung, mesothelioma, multiple myeloma	5 (31.3)
Symptoms, ^b no. (%)	
Hiccups, discomfort, distress, fatigue	16 (100)
Nausea/vomiting	11 (68.8)
Pain	5 (31.3)
Dysphagia	4 (25)
Insomnia	4 (25)
Weakness	4 (25)
Breathing difficulties	3 (18.7)
Anxiety/depression	2 (12.5)
Constipation	2 (12.5)
Cough	2 (12.5)
Other ^a symptoms: abdominal distension, confusion, dehydration, diarrhea, dry skin, fear, headache, numbness, anorexia, slow speech, heartburn	11 (68.8)

^aIn the other categories, 1 patient presented with each of the cancers or symptoms listed.

^bAll patients presented with multiple symptoms. M, male; F, female.

reduction of hiccups symptoms following the first acupuncture session but were dropped from the study due to medical conditions that precluded further treatment. Two (2) of these 3 patients reported hiccups severity scores reduced from 4 to 2 following one acupuncture treatment, but did not continue treatment due to neutropenia and the possibility of infection. The third patient reported reduced hiccup severity scores from 7 to 4 but was discharged to hospice care.

In addition to hiccups, the patients also complained of 23 other symptoms, and all 16 patients reported discomfort, distress, and fatigue symptoms (Table 2). Among these symptoms, some physical and mental symptoms showed interesting changes following acupuncture treatment. There were significant reductions in discomfort, distress, and fatigue in all 16 subjects. Following the disappearance of their hiccups, patients also reported cessation of symptoms that might be related to hiccups, such as difficulties in swallowing (4 patients), sleeping (2 patients), breathing (2 patients), and speech (1 patient), as well as pain in the diaphragm area (1 patient), cough (1 patient), and nausea/vomiting (1 patient). None of the subjects in this study reported any adverse effects from the acupuncture, as evaluated by the NCI Common Terminology Criteria for Adverse Events v4.0 (grade 0).²⁰

The difference in hiccups severity pre- and post-acupuncture treatment was highly significant ($p < 0.0001$) (Table 3). This result was seen for individual sessions, as well as for the average of all treatments ($p < 0.0001$). There were also statistically significant findings for reduction of distress ($p < 0.0001$), discomfort ($p < 0.0001$), and fatigue ($p = 0.0078$) after the first treatment (Table 3, Fig. 1).

TABLE 3. RESULTS OF ACUPUNCTURE TREATMENT FOR HICCUPS

Symptoms	N	Mean	SD	Change from baseline		p-Value
				Absolute mean	Percent	
Hiccup severity–1st AT						
Before	16	5.2	2.5			
Immediately after	16	1.0	1.8	–4.3	–82.5	<0.0001
Follow-up	16	1.4	1.6	–3.8	–70.8	<0.0001
Hiccup severity–2nd AT						
Before	5	3.3	0.8			
Immediately after	5	0.2	0.3	–3.1	–94.6	<0.0001
Follow-up	5	1.9	1.7	–1.4	–45.0	<0.0001
Hiccup severity–3rd AT						
Before	3	3.2	0.3			
Immediately after	3	0.0	0.0	–3.2	–100.0	<0.0001
Follow-up	3	0.0	0.0	–3.2	–100.0	<0.0001
Hiccup severity–AAAT						
Before	24	4.7	2.1			
Immediately after	24	0.7	1.2	–3.9	–84.5	<0.0001
Discomfort–1st AT						
Before	16	6.4	2.1			
Immediately after	16	2.2	0.9	–4.2	–62.8	<0.0001
Distress –1st AT						
Before	16	6.4	2.3			
Immediately after	16	2.3	1.4	–4.1	–62.7	<0.0001
Fatigue–1st AT						
Before	16	5.9	2.1			
Immediately after	16	5.0	1.6	–0.9	–12.6	0.0078

SD, standard deviation; AT, acupuncture treatment; AAAT, average of all acupuncture treatments.

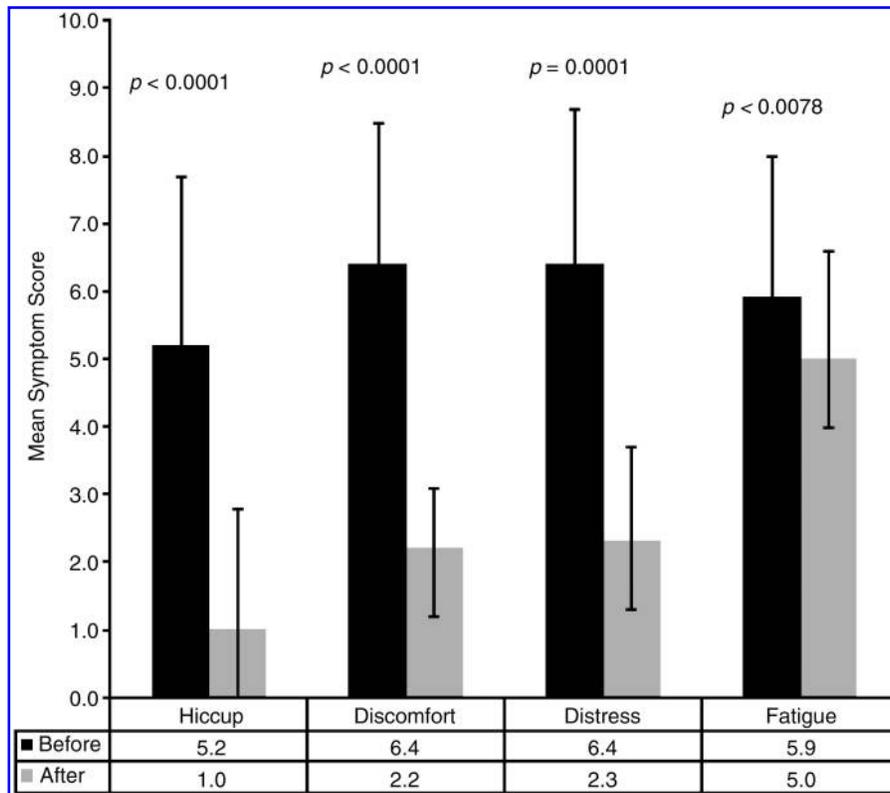


FIG. 1. Statistical analysis of first acupuncture treatment for hiccups in patients with cancer. $N=16$. Hiccups: 0 = No hiccups, 10 = Worst hiccups. Discomfort: 0 = No discomfort, 10 = Extreme discomfort. Distress: 0 = No distress, 10 = Extreme distress. Fatigue: 0 = No fatigue, 10 = Fatigue as bad as you can imagine.

A questionnaire administered prior to the first treatment assessed patients' expectation of success. Ten (10) patients "did not know" whether treatments would be successful and 6 thought success was "likely," including 4 patients who had previous acupuncture experience. In the post-treatment assessment, all 16 subjects "agreed" or "strongly agreed" that the acupuncture treatment was helpful; that they would use acupuncture again; and that they would recommend acupuncture to others.

Discussion

This case series demonstrated significant relief for persistent hiccups, as well as significant reductions in discomfort, distress, and fatigue after acupuncture therapy. The effect of acupuncture for persistent hiccups in patients with cancer was measured using the HAI. This article presents a preliminary validation of the HAI and demonstrates its usefulness as a clinical and research instrument. The HAI was simple to administer, and the 0–10 numerical scale was familiar and easily understood by patients. To our knowledge, this is the first report of the use of a measurement instrument for hiccups severity. In repeated measurements, HAI responses indicated variability and significant change following acupuncture interventions. Thus, the HAI was not only useful in evaluating the patient's condition, but also provided evidence of the positive change in symptoms in response to acupuncture treatments.

The mechanisms for acupuncture's efficacy in treating hiccups remain unclear. Most acupoints for hiccups are

located near dermatomes related to afferent/efferent pathways, secondary synapses, or nuclei involved in the hiccup reflex arc.²¹ Acupuncture might modulate any portion of the hiccup reflex arc locally by changing blood perfusion, activating the autonomic nervous system, regulating inflammatory mediators, or altering axonal excitability.²² It is also possible that acupuncture influences the hiccup center by modulating the secretion of neurotransmitters and neurohormones, such as endogenous opioids, norepinephrine, serotonin, substance P, and γ -aminobutyric acid.^{22,23}

Sun et al. observed that acupuncture at ST36 and PC6 could activate discharges of the nucleus tractus solitarius neurons in the rat, and Ji et al. reported that moderate acupuncture stimulation of PC6, CV12, and ST36 could effectively activate discharges of the subnucleus reticularis dorsalis neurons in the rat.^{24,25} These same acupoints were also utilized in our study.

Acupuncture has been in clinical practice for over 3000 years in China, and its popularity in the United States and other parts of the Western world has been increasing since the late 1970s.²⁶ Acupuncture's acceptance by non-Asian patients was also investigated in this study, and the results of the post-treatment evaluative questionnaire indicated that acupuncture was favorably viewed by all 16 subjects with varied sociodemographic backgrounds.

The Acupuncture Consult Service is open to all NIH patients with a wide range of diseases and symptoms. There was no referral bias from the requesting physicians. The subjects were all male patients with cancer receiving chemotherapy at the

time of the study, and most had undergone surgery or stem cell transplantation as well. This suggests that there might be an association of persistent hiccups with cancer and cancer-related procedures or therapies, and that the male patients are more susceptible to persistent hiccups. These observations were confirmed in other reports.^{27,28} The occurrence of hiccups has a reported range of 30%–0.39% in patients with cancer undergoing chemotherapy with different drugs. The total incidence was much higher in males than in females.²⁹

In this study, the mean hiccups severity score of 5.2 indicates that the patient's ADL were significantly impacted and highlights the need for medical attention. However, pharmacologic interventions might not succeed, might cause adverse effects, or might not be permitted by the research protocols. Acupuncture was therefore considered a better intervention. The patients enrolled in our study did not receive any interventions for hiccups for 24 hours prior to acupuncture treatment. In 1997, an NIH Consensus Development Conference on Acupuncture concluded that dental pain and nausea could be successfully treated with acupuncture.³⁰ Statements issued in 2003 by the World Health Organization and in 2004 by the American Academy of Medical Acupuncture provided a longer list of indications for acupuncture, including hiccups.²⁶

This study demonstrated that acupuncture treatment not only completely resolved persistent hiccups but also reduced fatigue, discomfort, and distress. Patients reported that hiccup-related symptoms also improved. Pharmacologic approaches for hiccups are not necessarily successful in related symptoms control and may even cause adverse effects.²² For example, 1 patient in our study was referred for acupuncture treatment because baclofen, a popular remedy for hiccups,¹¹ had to be discontinued, due to side-effects of weakness, vomiting, and increased fatigue. After acupuncture therapy, the hiccups stopped and some of his other symptoms improved.

The safety of acupuncture was also evaluated in the study, and no serious adverse events occurred. Two (2) previous articles—one a study of the adverse effects of 32,000 acupuncture consultations and the other a prospective audit of acupuncture treatments of 1848 professional acupuncturists—have demonstrated that acupuncture is safe.^{31,32} Our evaluation showed that one to three acupuncture treatments resolved persistent hiccups completely in all patients who were able to complete the study. The same result was reported in two prior studies. However, those studies were limited to 1 and 2 patients, respectively.^{13,23} The rapid effectiveness of acupuncture also suggests that it is a cost-effective therapy for hiccups. Another previous study reported that acupuncture may provide long-term relief from hiccups through changes in neuronal gene expression that result in neuronal input modulation.³³ A longer follow-up period than provided in our case series is needed to evaluate this finding. Case series with observational outcomes inherently have methodological limitations and confounding factors. Future randomized, blinded, controlled studies are needed to better understand the mechanisms of action.

Conclusions

Based on the outcomes of 16 observational cases, acupuncture may be a useful, safe, and low-cost therapy for persistent hiccups in patients with cancer.

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Disclosure Statement

No competing financial interests exist.

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