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Acupuncture for heart failure: A systematic review of clinical studies☆

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ABSTRACT

Background: Acupuncture has been used for treating heart failure mainly in combination with conventional treatments, but evidence for its effectiveness and safety has not been well established. Our aim was to review randomized controlled trials (RCTs) on acupuncture for heart failure and assess the clinical evidence.
Methods: Electronic databases such as Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and certain Chinese & Korean databases were searched until October 2015. The main outcomes assessed were mortality, New York Heart Association (NYHA) function classifications, and acupuncture-related adverse events. The details of acupuncture intervention were also investigated.
Results: Among 4107 publications, seven RCTs were included; most of them showed considerable methodological flaws. We could not conduct a meta-analysis because of the heterogeneity of the included studies. In one acute heart failure study, acupuncture shortened intensive care unit (ICU) stay by 2.2 days (95% CI 1.26, 3.14) and reduced the risk ratio of re-admission to 0.53 (95% CI 0.28, 0.99). However, mortality was not affected. Hemodynamic parameters also showed improvement. Another study reported an improved left ventricular ejection fraction by 9.95% (95% CI 3.24, 16.66). In five chronic heart failure studies, acupuncture improved exercise capacity, quality of life, hemodynamic parameters, and time domain heart rate variability parameters. Acupuncture decreased NT-pro BNP levels by 292.20 (95% CI −567.36, −17.04). No adverse effects were reported.
Conclusions: The effectiveness of acupuncture as a therapy for heart failure is currently inconclusive. Further large and rigorous clinical trials are needed to establish its clinical utility.

1. Introduction

Heart failure (HF) is defined as any structural or functional problem in the heart that causes insufficient oxygen supply to the tissues associated with metabolism [1]. About 5.7 million Americans have HF with the medical costs amounting to nearly 30 billion US dollars [2], and prevalence and medical costs are expected to rise continuously [2]. The condition is more common in older patients [3]. Common symptoms such as shortness of breath, fatigue, and chest pain are known to negatively affect the quality of life of patients with HF. As patients age, maintaining functional capacity becomes increasingly important [4]. Thus, treating debilitating symptoms in patients with HF is as important as reducing the risk of re-hospitalization due to disease exacerbation [5].

Diuretics [6,7], vasodilators [8] and anti-hypertensive [9] drugs are conventional treatments for HF and are generally recognized to be effective in relieving symptoms. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta blockers and aldosterone antagonists are known to prevent disease progression [10]. However, there are well-known adverse events (AEs) that can limit the use of conventional drugs. For example, electrolyte disturbance is the most common AE associated with diuretics [11]. Impairment of renal function, allergic reactions, and cough due to ACEi are also common [11]. In patients with chronic kidney disease, renal-angiotensin inhibition can induce severe AEs such as hyperkalemia, hypotension, or renal insufficiency [12]. Headache, flushing, leg edema, premature ventricular contraction, and bradycardia are common AEs associated with antihypertensive drugs [13–15]. Multi-drug treatment increases the risk of adverse reactions in these patients [16]. Therefore, novel and alternative treatment strategies for HF are needed.

Complementary and alternative medicine (CAM) is widely used for cardiovascular diseases like hypertension, myocardial infarction, atrial fibrillation, and ischemic stroke [17–21]. Acupuncture therapy is one such CAM treatment, and several studies support its mechanism of action in HF animal models [22,23]. Several clinical studies to treat HF with acupuncture have been conducted as well [24–30]. However, there have been no systematic reviews or meta-analyses investigating the efficacy of acupuncture for HF that might support its clinical

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relevance. The primary aim of this study was to assess the efficacy and safety of acupuncture therapy for HF via a systematic review of clinical studies. Another purpose was to analyze the current status of clinical trials on acupuncture for HF so as to improve the clinical trial protocol.

2. Methods

2.1. Search strategy and selection criteria

To evaluate the efficacy of acupuncture in HF, two independent authors (JTL, HJL) searched for RCTs in the following databases until October 2015: Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), which are English databases; the Chinese National Knowledge Infrastructure (CNKI; http://www.cnki.net) and Wanfang (http://med.wanfangdata.com.cn/), which are Chinese databases; the Research Information Service System (RISS; http://www.riss.kr), the Oriental Medicine Advanced Searching Integrated System (OASIS; http://oasis.kiom.re.kr), the National Digital Science Library (NDSL, http://www.ndsl.kr), the DBPIA (http://www.dbpia.co.kr) and the Korean Studies Information Service System (KISS, http://kiss.kstudy.com) which are Korean databases. There were no language restrictions in this review. In addition, to find gray literature, we manually searched conference proceeding lists in major Korean journals such as the Journal of Korean Oriental Internal Medicine, Acupuncture, the Korean Journal of Acupuncture and the Journal of Korean Medicine. Each search strategy was customized according to the database. Details of search strategies are described in Appendix A. The search strategy in Pubmed was as follows:

(Acupuncture OR electroacupuncture OR 'acupuncture therapy' OR ear acupuncture) AND (Heart failure OR cardiac failure OR myocardial failure OR heart insufficiency OR cardiac insufficiency OR cardiomyopathies OR ventricular dysfunction).

2.2. Eligibility criteria

Eligible participants were defined as adults with either chronic or acute HF. The primary cause of HF was disregarded except for cases due to congenital deficits, pregnancy, chemotherapy, or surgery. There were no restrictions based on gender, ethnicity, HF severity, clinical setting, left/right sided HF, systolic/diastolic HF or ejection fraction. We included the use of both manual acupuncture (MA) and electro-acupuncture (EA). Studies with ear acupuncture and pharmaco-acupuncture were excluded in this review. Interventions that stimulate acupuncture points without needle insertion such as laser acupuncture, transcutaneous electrical stimulation, or acupressure were also excluded. Control groups varied from no treatment to sham acupuncture to conventional treatments such as medication or surgery. If the same conventional treatment was used in both the intervention and control groups — and acupuncture used as an add-on therapy in the intervention group — the study was included. We excluded studies that compared two acupuncture therapies directly. We also excluded acupuncture interventions combined with alternative therapies like herbal medicine, moxibustion, or cupping.

2.3. Outcome assessment

The primary outcomes assessed were mortality and the New York Heart Association (NYHA) function classification. Secondary outcomes were metrics of general improvement including responder rate, left ventricular ejection fraction (LVEF), hemodynamic effect (mean arterial pressure, heart rate, cardiac index, stroke volume index, left ventricular working index), neuroendocrine effect, exercise capacity, re-admission rate, ICU stay length, quality of life, cost-effectiveness, diuretic use and adverse events related to the acupuncture treatment. The normal range of the cardiac index is 2.4–4.2 l/min/m^2 and stroke volume index (SI) is 35–70 ml/m^2, depending on the size of the individual. The normal range of the left cardiac work index (LCWI) is 3.4–4.2 kg/min/m^2 which is a normalized value for the amount of work per minute required for the left ventricle to pump blood [31,32]. The normal value of the LVEF is 62 ± 6% [33] and a 5% improvement is related to long term mortality [34]. Heart rate variability (HRV) information was also included as a secondary outcome measure because it is related to the mechanism of acupuncture in HF treatment that affects autonomic nervous system (ANS) tone [35]. For the responder rate, responders were defined as the patients who showed improvement in more than 50% of their symptoms.

2.4. Data extraction

Data recorded in a pre-defined extraction form included treatment country, setting, disease severity, disease duration, age, gender, intervention, outcome, effect size and adverse event. Acupuncture treatment details such as acupuncture points, EA use, stimulation method, treatment duration and frequency, retention time, and practitioner background were extracted according to the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) Checklist [36]. If there was any unclear data, we attempted to contact the authors of the study.

2.5. Assessment of risk of bias

Risk of bias (ROB) assessment was conducted by two independent authors (JTL, HJL). In the event of a disagreement while extracting data or assessing ROB, the third author (THK) resolved the discrepancy. The domains of ROB assessment are random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data, selective reporting and other biases according to the Cochrane handbook for systematic reviews [37]. ROB was graded as high, low, or unclear. When we evaluated participant and personnel blinding, we graded ROB as low even though only participants were blinded, as the practitioner cannot be blinded in an acupuncture trial.

2.6. Data synthesis and meta-analysis

Data were analyzed based on individual acute and chronic HF subgroups. Continuous data were presented with mean difference (MD) and a 95% confidence interval. Dichotomous data were presented with a risk ratio (RR) and a 95% confidence interval. Heterogeneity was assessed by I^2 statistics. If I^2 was > 50%, the random effect model was adopted for meta-analysis. Otherwise, the fixed effect model was used. Review manager version 5.3 was used for meta-analysis.

3. Results

3.1. Description of the included studies

4107 studies were identified by electrical and hand searching. Twenty-six studies were assessed for eligibility after screening and removing duplications (Fig. 1). Of these, 19 were excluded due to inappropriate intervention, population, study design and/or duplication (Appendix B). Seven studies were ultimately chosen for this review. One RCT was conducted in the US [25], one was conducted in Germany [24], and the other five were conducted in China [26–30]. Three studies were published in English [24–26] and the others were written in Chinese. The total number of patients analyzed in the review was 287 (acupuncture group, 144; control group, 143; Table 1). A summary of the included articles is presented in Table 2.

3.2. Details of the included studies and intervention

The average age of the participants ranged from 43 to 68.2 years (median, 61.6 years). Two RCTs were for out-patients [25,30], three were for in-patients [26,28,29] and two did not specify [24,27]. There were four intervention and control therapy types: 1) acupuncture with conventional therapy vs. conventional therapy alone [27,28]; 2) acupuncture vs. conventional therapy [26,29,30]; 3) acupuncture with conventional therapy vs. sham acupuncture with conventional therapy [24]; and 4) acupuncture vs. sham acupuncture [25]. Two were clinical studies for acute heart failure (AHF) [27,28], and the remaining studies were for chronic heart failure (CHF). In one AHF trial [28], disease severity was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score. Patients with an APACHE II score lower than 35 points were included. The NYHA protocol for function classification was used in all CHF trials. One of these trials included only NYHA grade I patients [26]. Another trial included grade III and IV patients [29], while another included grade II and III patients. Disease duration was not reported in AHF trials. Two CHF trials included participants who were diagnosed with HF more than three months prior to the trial [24,25]. In one trial, disease duration ranged from 8 to 120 months [29]. Other trials did not report disease duration.

EA was used in only one trial [27]. The other six used MA therapy. The chosen acupuncture point was PC6 in all seven trials. CV17 was used in four trials, and HT7 was used in three trials. Two studies allowed for the use of additional acupuncture points according to pattern identification [28,29]. The others used fixed acupuncture point combinations. All MA trials included at least one acupuncture stimulation. Needle retention time ranged from 15 to 30 min. The median value for needle retention time was 20 min. The number of treatment sessions ranged from one to 60; the median value was ten. Treatment frequency ranged from twice a day to twice a week; the median value was five times a week. Only one study reported the practitioner's background, who was a licensed acupuncturist [25] (Tables 1, 2).