

ACUPUNCTURE IN TREATING HEPATIC FIBROSIS: A REVIEW WITH RECOMMENDATION FOR FUTURE STUDIES

Jue ZHOU, Ph.D.,^{1*} Yi LIANG Ph.D.,^{2*} Xian-Ming LIN M.D.,²
Rui-Jie MA, Ph.D.,² Jian-Qiao FANG, Ph.D.,^{2**}

¹ College of Food Science and Biotechnology, Zhejiang Gongshang University, Hangzhou, Zhejiang, China, ² The Third Clinical College of Zhejiang Chinese Medicine University, Hangzhou, Zhejiang, China; ** Professor of Acupuncture, Vice-President, Zhejiang Chinese Medicine University; Binwen Road 548, Hangzhou, 310053, China.

**E-mail: fjqtcem@163.com

Abstract

Hepatic fibrosis, as a major medical problem, is characterized with significant morbidity and mortality. Acupuncture has potential advantages in treating hepatic fibrosis as acupuncture functions well to reduce Qi and Blood stagnation, resolve stasis and enhance body immunity, which are important factors in treating hepatic fibrosis. The aim of this review was to appraise the current limited evidence of acupuncture in treating hepatic fibrosis from both animal experiments and clinical trials by using both Chinese and western databases and to provide recommendations for future studies.

Key words: Acupuncture; hepatic fibrosis; review

Introduction

Hepatic fibrosis, as a major medical problem, is characterized with significant morbidity and mortality (Tsukada et al., 2006). Hepatic fibrosis is caused by chronic damage to the liver in conjunction with the accumulation of extracellular matrix (ECM) proteins, a characteristic of most types of chronic liver diseases (Friedman, 2003). In China, hepatic fibrosis is mostly caused by hepatitis B viral (HBV) infection, whereas hepatitis C viral (HCV) infection and alcohol are the key factors in the United States, Europe and Japan (Koike, 2006; Seeff and Hoofnagle, 2002). Hepatic fibrosis may progress into liver cirrhosis and other complications coupled with carcinogenesis (Perz et al., 2006).

As hepatic fibrosis was historically thought to be a passive and irreversible process due to the collapse of the hepatic parenchyma and its substitution with a collagen-rich tissue (Popper and Uenfriend, 1970; Schaffner and Klion, 1968), it received little attention until the 1980s, when hepatic stellate cells (HSCs), formerly known as lipocytes, perisinusoidal cells, were found as the main collagen-producing cells in the liver (Friedman et al., 1985). This cell type, first described by von Kupffer in 1876, undergoes a dramatic phenotypic activation in chronic liver diseases with the acquisition of fibrogenic properties (Geerts, 2001). Hepatic fibrosis regression in model systems can be stimulated with drugs that target the activities of fibrogenic HSCs, during which, the established fibrosis may be susceptible to regression and possibly even reversion (Ellis and Mann, 2012). Although blood markers and instrumental methods have been proposed for the noninvasive assessment of hepatic fibrosis in HCV, they are not recommended by international guidelines due to the unsatisfactory accuracy and incomplete validation (Sebastiani and Alberti, 2012), however, semiquantitative histological staging and morphometry could be used as a complementary techniques for monitoring fibrosis (Cales et al., 2009).

The treatment for hepatic fibrosis should avoid the complications of chronic liver disease when its cause cannot be treated. In the treatment of hepatic fibrosis, cause, comorbidity and fibrosis are the main therapeutic endpoints, in which, reduction of fibrosis course, reversion of fibrosis, and reversion of cirrhosis should be fully considered (Daneshpour et al.,

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2011; Efe et al., 2012; Gietka, 2011; Shaker et al., 2011; Wong et al., 2011), however, the most effective and ideal strategy is to cure the underlying disease process before further fibrosis has developed (Ellis and Mann, 2012; Friedman and Bansal, 2006). The major limitation of the existing treatment for hepatic fibrosis is the prolonged natural history of fibrosis compared with that in experimental models, and difficulties in accurate noninvasive fibrosis assessment (Noll et al., 2011). Moreover, many patients are asymptomatic even when fibrosis is already advanced, which requires not only prevention of evolution in cirrhosis but also reversal of established fibrosis in a cirrhotic liver (Ellis and Mann, 2012).

In recent years, many researches on the effects of complementary and alternative treatments on hepatic fibrosis have been conducted (Batey et al., 2005; Feng et al., 2009; Ferrucci et al., 2010; Schuppan et al., 1999; Seeff et al., 2001).

According to the classic theory of traditional Chinese medicine (TCM), hepatic fibrosis belongs to the syndrome of “Qi stagnation and Blood stasis” and “Deficient healthy energy”. Chinese herbal medicine (CHM) has eminent efficacy in treating hepatic fibrosis, which is based on reducing Qi and Blood stagnation, resolving stasis, eliminating toxins and enhancing body immunity (Feng et al., 2009). According to a recent systematic review and meta-analysis of randomized controlled trials (RCTs), CHM alone and CHM combined with Western medicine showed significant improvements in serum hyaluronic acid, laminin, procollagen type III, type IV collagen, compared with Western medicine alone (Cheung et al., 2012). However, large RCTs using standardized Chinese medicine syndrome diagnosis and CHM formulae with longer follow-up are required for further evaluation (Cheung et al., 2012).

Acupuncture is an important part of TCM, which functions to regulate Yin and Yang, promote Blood circulation to remove stasis, dredge meridian and collateral, replenish Deficiency syndrome, and eliminate excess syndrome. In the early stage of hepatic fibrosis, the main pathogenesis is Qi stagnation and Blood stasis, which should be treated with the principle of dispersing stagnated liver Qi and promoting Blood circulation to remove stasis and strengthen vital Qi. Acupuncture functions well to reduce Qi and Blood stagnation, resolve stasis and enhance body immunity, which are important factors in treating hepatic fibrosis (Feng et al., 2009; Ishikawa et al., 2012; Rong et al., 2011).

Acupuncture has potential advantages in treating hepatic fibrosis (Zhao and Qiu, 2000), although there are not so many animal experiments and clinical trials conducted on it. The aim of this review was to appraise the current limited evidence from both animal experiments and clinical trials by using both Chinese and western databases and to provide recommendations for future studies.

Animal experiments

As early as in 1998, acupuncture at Zusanli (ST 36) and Guanyuan (CV 4) was found to markedly decrease swelling of liver cells and improve the hepatic microcirculation in model rats with hepatic fibrosis (Zhu and Sun, 1998). In another study conducted in 2005, acupuncture at Zusanli acupoint only was also found to mitigate damages of model rats' hepatic cells and decrease the serum levels of hyaluronic acid and procollagen III, indicating the acupuncture at Zusanli acupoint only can lower degrees of hepatic fibrosis of the model rats (Wang et al., 2005). Acupuncture at Ganshu (BL 18) and Yanglingquan (GB 34) acupoints was found to effectively treat hepatic fibrosis of the model rats by decreasing procollagen III levels (Chen, 2002) and inhibiting ECM components expression (Chen, 2003). Min et al (Min et al., 2008) conducted an animal experiment to explore the effects of electroacupuncture on the histopathological changes and serum indexes of the model rats with hepatic fibrosis and investigated the underlying mechanism. In their study, the rat models of hepatic fibrosis were induced with carbon tetrachloride. Then, the rats were divided into electroacupuncture group, medicine group, and model group. The liver collagen expression and the serum hyaluronic acid, laminin, procollagen III, and collagen IV levels were detected with morphologic methods and radioimmunoassay. The rats in the electroacupuncture group were fixed and punctured at Ganshu (BL 18) and Zusanli (ST 36) with needles of 0.30 mm in diameter and 13 mm in length. The results showed that the collagen was hyperplasia in the liver tissue, and the serum hyaluronic acid, laminin and procollagen

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III levels were higher than those of the model group. In the rats of electroacupuncture group, the collagen area of liver tissue and the serum hyaluronic acid and laminin levels were lower than those of the model rats, demonstrating electroacupuncture has positive effects in preventing and treating hepatic fibrosis, and the effects were obtained by inhibiting synthesis of extracellular matrix, and promoting the breakup of collagen (Min et al., 2008).

Curcumin and curcumol are main bioactive components in *Curcuma Wenyujin*, which has been used as a common traditional Chinese medicinal herb to remove Blood stasis and to alleviate pain in some Asian countries (Zhou et al., 2010). Curcumin was found to inhibit liver cirrhosis in rodent models and to exert multiple biological effects in HSCs (O'Connell and Rushworth, 2008). A recent study was aimed to evaluate the effects of acupuncture combined with curcumin in attenuating hepatic fibrosis (Zhang et al., 2012). In the study, 60 Sprague-Dawley male rats were randomly divided into control, model, sham, acupuncture, curcumin and combination therapy groups, in which Taichong (LR 3), Qimen (LR 14), Ganshu (BL 18) and Zusanli (ST 36) were selected as the acupoints (Zhang et al., 2012).

After treatment, pathological indexes, histology for hepatic injury and fibrogenesis, and ECM components were detected. Acupuncture combined with curcumin was found to markedly reduce the serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, hyaluronic acid, laminin and procollagen III. It also inhibited ECM expression such as α -smooth muscle actin, fibronectin and $\alpha 1$ collagen, and lead to significant liver histological improvements, indicating acupuncture treatment could significantly enhance the antifibrotic efficacy of curcumin on CCl₄-induced hepatic fibrosis in rats and a combination of acupuncture with curcumin may be exploited for the prevention of hepatic fibrosis (Zhang et al., 2012). The results were consistent with those of another study published in 2011 (Wu, 2011), which had the same study design.

Clinical trials

Xue et al applied combined therapy to treat hepatic fibrosis caused by chronic HB (Xue and Shao, 2007). The combined therapy included Ganlixin injection and injection of Danshen (*Salvia miltiorrhiza*) on the Zusanli (ST 36) acupoint. They finally demonstrated that combined therapy significantly decreased the serum hyaluronic acid, laminin and collagen IV levels, compared with the Ganlixin injection alone. Long-term administration of Danshen was also found to ameliorate hepatic fibrosis in rats (You et al., 2007). A clinical trial including 102 patients was also conducted to explore the effects of injecting oxymatrine at Ganshu (BL18), Sanyinjiao (SP 6) and Zusanli (ST36) acupoints on the liver function and the serum levels of hyaluronic acid, laminin, procollagen III, and collagen IV of the patients with hepatic fibrosis caused by chronic HBV (Tang, 2007). After treatment of 3 months, compared with the controls, the liver function and the serum levels of hyaluronic acid, laminin, procollagen III, and collagen IV of patients in treatment group were significantly improved. Similar results were obtained in another trial, in which, the researchers injected tanshinone at Ganshu (BL18), Sanyinjiao (SP 6), Qimen (LR14) and Zusanli (ST36) acupoints (Jiang et al., 2007). Tanshinone is the main bioactive constituent of Danshen, which is a traditional medicine used to improve blood circulation and treat chronic hepatitis and hepatic fibrosis (Kim et al., 2003). Matrine, as an alkaloid found in *Sophora* plants in Leguminosae, can markedly reduce serum-driven proliferation and collagen synthesis of HSCs (Zhang et al., 2001). A recent clinical trial (Jin et al., 2011) including 72 patients was to explore the effects of injecting matrine injection at Zusanli (ST 36) acupoint on liver function of patients with hepatic fibrosis caused by chronic HBV. They were randomly divided into matrine point injection group (treatment group) and Fufang Biejia Ruangan tablets group (control group), with 36 in each group. All patients were given basic treatment using vitamin C and inosine. Sixty-nine patients completed the course of treatment. After treatment of 3 months, compared with the controls, the symptoms and liver function of patients in treatment group were significantly improved, which showed that injection matrine at Zusanli (ST 36) can improve liver function, reduce liver inflammation and alleviate or delay the progress of hepatic fibrosis of patients with hepatic fibrosis caused by chronic HBV.

Recommendation for future studies

1. To conduct multi-centre clinical trials:

Multi-center trials using the same study design may reduce the variation caused by the different protocols for treatment and differences in baseline indicators observed between different hospitals. For the patients with hepatic fibrosis, the treatment may include basic treatment and acupuncture and/or CHM treatment. For different hospitals, there exist differences on the protocols of the basic treatment for hepatic fibrosis, which would lead to various results. Among all the clinical trials on the effects of acupuncture on hepatic fibrosis, none was conducted in multi-centers.

2. To provide the detailed information on the acupuncture practitioners

As we know, the education, training and practice of acupuncture practitioners will influence the nature of the acupuncture treatment given and is therefore a variable that may significantly affect the outcome. The acupuncture practitioners may include: TCM doctors or practitioners, trained examiners, trained nurses, physicians, and traditional acupuncturists. The duration of relevant training, length of clinical experience, and details of expertise in treating the specific condition being evaluated, as well as practical experience that may be relevant to the trial should be clearly described in future studies. Copies of documents or details of training given to the staff involved in acupuncture study should be clearly described.

3. To give stratification according to the correct diagnosis of the patient's syndrome based on TCM theories.

Although according to the classic theory of TCM, hepatic fibrosis belongs to the syndrome of "Qi stagnation and Blood stasis" and "Deficient healthy energy", for different patients, the predominant syndrome may differ. As we know the effects of acupuncture on all the diseases would be predicted to improve with the correct diagnosis of the patient's syndrome based on TCM theories; also the outcomes may vary according to which syndromes are predominant. For the patients with hepatic fibrosis, during the acupuncture treatment, the angle/direction of insertion, the manipulation method (thrusting, lifting, and rotating techniques) and intensity of these manipulation methods are all based on the TCM syndrome diagnosis for the disease. When treating patients with hepatic fibrosis with acupuncture, the acupuncturists must take into account the unique nature of each presentation, the secondary signs and symptoms, and "constitutional" factors that underpin the health of each person, these subtle changes are considered as important means to enhance the effectiveness of treatment and reduce any unwanted adverse effects in treating hepatic fibrosis. Based above, a TCM syndrome diagnosis for the patients with hepatic fibrosis could be used as a form of stratification. This will lead to a correct conclusion on which TCM sub-types of hepatic fibrosis may be more responsive to acupuncture treatment than others, which would definitely be useful in designing future research.

4. To apply an appropriate placebo intervention

Double-blind RCT is widely recognized as the gold standard in clinical researches, however, the biggest challenges and the difficulties to the researchers in the fields of clinical acupuncture are the design of an ideal placebo-control method and the credibility and ethics behind sham acupuncture (Emanuel and Miller, 2001; Margolin et al., 1998; Sherman et al., 2002; Tang et al., 1999; Vincent and Lewith, 1995). An ideal acupuncture placebo that avoids the necessity of penetration of the skin and shows the same psychological impact has not yet been found. A study has shown that for non-drug interventions including acupuncture, it was difficult to establish a placebo or sham control that is both inert and indistinguishable (Dincer and Linde, 2003). Among the clinical trials of acupuncture in treating hepatic fibrosis, most of the researchers chose acupoint injection of CHM or other drugs, which made even more difficult to find a rational and safe placebo intervention. To apply an appropriate placebo intervention in the trials of treating hepatic fibrosis with acupuncture, safety may be the top one issue.

5. Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) must be taken into account when designing clinical trials of treating hepatic fibrosis with acupuncture

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STRICTA should be used as the gold standard not only in reporting the trials, but in designing the whole study. STRICTA provides researchers a way to structure their reports of interventions with a minimum set of items within a checklist (MacPherson et al., 2010). However, none of the published clinical trials of treating hepatic fibrosis with acupuncture is consistent to STRICTA. STRICTA facilitates transparency in published reports, enables a better understanding and interpretation of results, aids their critical appraisal, and provides details. In 2010, the revised STRICTA was published (MacPherson et al., 2010). The revised STRICTA includes 6 items and 17 sub-items, which set the reporting guidelines for the acupuncture rationale, the details of needling, the treatment regimen, other components of treatment, the practitioner background, and the control or comparator intervention (Schulz et al., 2010).

6. To give a sufficient dose of acupuncture treatment

The average period of acupuncture treatment for the patients with hepatic fibrosis in the published trials is 3 months, however, as the hepatic fibrosis is a chronic pathological process, 3 months may too short to lead to satisfactory curative effects. A more sufficient dose of acupuncture treatment is expected to be given in the future trials.

7. To describe more parameters for hepatic fibrosis.

The most commonly used indicators for hepatic fibrosis in the published animal experiments and clinical trials are aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, hyaluronic acid, laminin, procollagen III and ECM. More parameters for hepatic fibrosis should be used in the future.

8. To take patient expectation into account

The preferences and expectation of the patients with hepatic fibrosis can play a role in trials on acupuncture treatment. The influence of patient expectations on outcomes is related to both for within-group changes and between-group differences. High expectations might be associated with high response rates and improved outcomes in the placebo control group. This could result in a ceiling effect, making it more difficult to detect a significant difference between active and placebo interventions. A simple method by asking questions such as: "How effective do you consider the treatment in general?" to access the expectations of the patients at baseline should be applied.

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