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The efficacy and safety of acupoint application for cirrhotic ascites: A protocol for systematic review and meta-analysis

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Acupoint Application,
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ABSTRACT

Cirrhotic ascites significantly impacts patients' quality of life and poses serious clinical challenges. Conventional treatments, such as diuresis and abdominocentesis, are costly and prone to recurrence. Acupoint application, a traditional Chinese medicine (TCM) external therapy, offers a safe, painless, and cost-effective alternative widely used in clinical practice. However, its efficacy and safety lack systematic evaluation. This study aims to comprehensively assess the effectiveness and safety of acupoint application for treating cirrhotic ascites through a meta-analysis of randomized controlled trials retrieved from databases including CNKI, VIP, WanFang, PubMed, Embase, and the Cochrane Library. The findings will provide evidence to guide clinical decision-making.

1. Introduction

Cirrhotic ascites is caused by degeneration, necrosis, and regeneration of hepatocytes, which contribute to the proliferation of fibrous tissue and contraction of scarring, resulting in the hardening of the liver texture to form cirrhosis, causing portal hypertension and impairment of liver function, leading to the generation of ascites. The mechanism of ascites formation is complex, mainly due to portal hypertension caused by cirrhosis, which leads to obstruction of portal blood flow; increased intravascular pressure and capillary hydrostatic pressure in the portal venous system, which leads to fluid leakage into the abdominal cavity[1]; Portal hypertension also enhances renin-angiotensin-aldosterone system (RAAS) activity by triggering splanchnic and systemic circulatory changes, leading to sodium and water retention[2, 3]; Ascites formation is also closely associated with increased vasoactive substances and hypoproteinemia[4], After the onset of cirrhosis, secretion and activity of atrial natriuretic peptide, prostaglandins and other vasoactive substances increase, stimulating extensive dilation of small splenic arteries and thus increasing venous inflow. After the impaired liver function, albumin synthesis is significantly reduced, leading to a decrease in plasma colloid osmotic pressure, which promotes the leakage of fluid from the plasma into the peritoneal cavity and the formation of ascites[5]. At the stage of cirrhotic ascites, patients will have symptoms such as abdominal distension, loss of appetite, weakness, low urine, etc., and are often accompanied by swelling of the lower limbs, dyspnea, chest tightness, etc. About 60% of patients develop

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ascites within 10 years after the diagnosis of cirrhosis, and the mortality rate is about 15% at 1 year and 44% to 85% at 5 years after the occurrence of cirrhotic ascites[6, 7]. There is no doubt that cirrhotic ascites seriously affect patients' quality of life and threaten their life safety, which is a major clinical challenge. The current main treatments for cirrhotic ascites include diuretics, salt restriction, albumin supplementation and invasive therapies such as abdominocentesis, transjugular intrahepatic portosystemic shunt (TIPS) and even liver transplantation[8, 9], but 10% of patients will develop diuretic resistance[10]. Long-term repeated abdominocentesis causes great pain to patients, while TIPS and liver transplantation are effective treatments for cirrhotic ascites but are difficult, risky, and expensive.

Acupoint application is a unique Chinese medicine external treatment method based on the theory of Chinese medicine meridian science by mixing specific Chinese medicine into a paste or boiling Chinese medicine soup into a paste and applying it to the acupuncture points on the surface of the body, usually for several hours, so that the acupuncture points are stimulated. The medicine is absorbed through the body's surface, which has achieved the purpose of treating diseases. Acupoint application is easy to learn, safe and painless, widely applicable and inexpensive, especially for the treatment of chronic diseases. In recent years, acupoint application has been widely used for cirrhotic ascites, but its efficacy and safety are still controversial. Therefore, we will study the efficacy and safety of acupressure in the treatment of cirrhotic ascites and objectively evaluate its efficacy and safety in order to provide evidence-based medical evidence for clinical practice and further clinical research.

2. Methods and Analysis

2.1. Study Registration

This study protocol was registered on the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/) on September 25, 2022 (registration number: CRD42022360397) and is authentically available.We will write the study protocol in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement guidelines[11].

2.2. Eligibility Criteria

2.2.1. Type of Studies

All the randomized controlled clinical trials (RCTs) that report using acupoint application for cirrhotic ascites will be included.

Inclusion:

1. Studies must be randomized controlled clinical trials;
2. Developed by treatment guidelines[10, 12] .The diagnosis of cirrhotic ascites needs to meet the following three conditions: 1) imaging examination indicates cirrhosis and peritoneal fluid; 2) positive mobile turbid sounds on physical examination; 3) exclusion of ascites due to cancer, cardiogenic, nephrogenic, tuberculosis and other causes；
3. Patients in the treatment group will be given acupoint application whether or not combined with treatments received in the control group, while patients in the control group will be given no acupoint application treatment;
4. Trials must have reported at least one outcome indicator of cirrhotic ascites;
5. Studies must be published in English or Chinese language.

Exclusion:

1. The diagnostic criteria of the original study did not meet the clinical diagnosis of cirrhotic ascites;
2. Studies without consistent diagnostic criteria or relevant outcome indicators;
3. Non-English or Chinese-language articles;
4. Duplicate reports, or the data cannot be extracted.

2.2.2. Type of Participants

Subjects had a clinical diagnosis of cirrhotic ascites and no other acute or chronic disease. Patients were not restricted by age, sex, or source.

2.2.3. Type of Intervention

Patients in the treatment group will all receive acupoint application treatment regardless of whether they receive conventional Western medical treatment (e.g. diuretics and albumin supplementation); There is no restriction on the acupuncture points, types of herbs and duration of acupoint application treatment in our study.

2.2.4. Type of Comparators

Patients in the control group will be given treatment, including simple routine western medicine treatment compared with the acupoint application treatment group.

2.2.5. Type of Outcome Measures

2.2.5.1. Main Outcomes

Ascites volume (obtained by ultrasound or other ancillary tests)

2.2.5.2. Additional Outcomes

1. Body weight; 2. Abdominal circumference; 3. Aspartate aminotransferase(AST); 4. Alanine aminotransferase(ALT); 5. Incidence of adverse events

2.3. Search Strategy

Computerized comprehensive searches of databases such as China Knowledge Network (CNKI), Chinese Science and Technology Journal Database (VIP), WanFang Database (WangFang), China Biomedical Literature Database (CBM), PubMed, SCI, Embase, and Cochrane Library were conducted for the period of establishment to September 2022. The search terms included: "cirrhotic ascites," "live cirrhosis with ascites," "portal hypertension, " "ascites," " acupoint application," "point application, "and "randomized controlled trial." The search strategy (Table 1) was tailored to the specific database.

2.4. Data Collection and Analysis

2.4.1. Selection of Studies

We will strictly follow the flowchart shown in Figure 1 to filter the final eligible literature. The specific process is as follows: ①We will import all the retrieved literature into the literature management software NoteExpress (3.2.0.7535) to check and eliminate duplicate literature according to the above 2.3 search strategy. ②Subsequently, we will review the titles, abstracts and keywords of the literature and screen out the literature that seriously does not meet the inclusion criteria and those that meet the exclusion criteria. ③The remaining literature was downloaded one by one and evaluated for the level of methodological quality evidence for each literature according to the Jadad scale[13]. Literature suspected of data falsification or serious data errors was excluded from obtaining the final included literature. Two researchers (Yulan Gao and Xiaoying Yao) screened the literature separately, and if differences of opinion arose, they were determined by discussion or consultation with a third researcher (Liuping Zhang).

2.4.2. Data Extraction and Management

Two researchers extracted information from the final included literature separately using an Excel sheet, which which had: the study title, first author, time of publication, sample size, basic information about the study population (gender, age), interventions, duration of treatment, and outcome indicators, and cross-checked, and in case of disagreement was determined by discussion or consultation with a third researcher (Liuping Zhang). If important information or data needed were missing from the article, they would be obtained by contacting the authors by phone or email.

2.4.3. Risk of Bias Assessment

We will assess the quality of the included literature by using the Cochrane Risk of Bias Assessment Tool and GRADE evidence grading method[14]. This includes method of random allocation; allocation protocol concealment; blinding of investigators and subjects; blinding of judges of randomized trial results; completeness of outcome data; selective description of trial results, and other sources of bias. The above situations in the literature were judged as "unknown risk of bias," "low risk of bias," and "high risk of bias.

2.4.4. Measures of Treatment Effect

Meta-analysis of the data was performed using Review Manager 5.4 software. Dichotomous data were subjected to Meta-analysis using relative risk (RR) to indicate effect indicators. As for the measurement data, the mean difference (WMD) was chosen if all data had the same unit of measure; the standard deviation (SMD) was used if the unit of the measure did not agree. Both data types had 95% confidence intervals (95% CI).

2.4.5. Assessment Of Heterogeneity

Heterogeneity analysis was performed on the study data, and its P value and I2 were calculated. If $P>0.1, I^2 \leq 50\%$, it means that there is no statistically significant heterogeneity among the included study

groups, then the fixed-effect model was selected for statistical analysis; if P<0.1, I^2>50%, it means that there is statistically significant heterogeneity, then the random-effect model was selected for statistical analysis.

2.4.6. The Publication Bias

If more than 10 papers were eventually included, funnel plots were drawn using Review Manager 5.4 software to assess publication bias among the studies. If the distribution was symmetrical on both sides of the funnel plot, it indicated no significant publication bias; if the funnel plot was asymmetrical on both sides, it indicated some publication bias.

2.4.7. Subgroup Analysis

Subgroup analyses will be performed according to the degree of the patient's condition and the control group intervention.

2.4.8. Sensitivity Analysis

A sensitivity analysis using STATA software will be performed to verify the robustness of the review conclusions.

2.5. Ethics and Dissemination

This study is not a human or animal test and does not involve personal information or personal data, so there is no need to undergo ethical review. The results of this Meta-analysis will be published in a peer-reviewed journal.

3. Discussion

Ascites is the most common complication of cirrhosis and a hallmark of the decompensated stage of cirrhosis. The formation mechanism of ascites in cirrhosis is complex and is related to portal hypertension, RAAS system activity, increased vasoactive substances and hypoproteinemia. Currently, treatment is mainly includes the use of diuretics, salt restriction, albumin supplementation and treatment by abdominocentesis, TIPS and even liver transplantation. However, long-term diuretic use and ascites discharge may bring side effects such as diuretic resistance, electrolyte disorders, gynecomastia, and hepatic encephalopathy, while the risks and costs of surgery are difficult for patients to bear.

This disease has been documented in ancient Chinese medical texts, and acupoint application has been one of the main tools in treating cirrhotic ascites in Chinese medicine. Acupoint application, as an external Chinese medicine treatment, has been proven to treat many chronic diseases[15-17]. On the one hand, many acupuncture points themselves have the effect of reducing ascites, which can be eliminated by stimulating specific acupuncture points[18]; On the other hand, the selection of diuretic Chinese medicine made into ointment, the drug can be absorbed by the body through the skin, to achieve the purpose of eliminating ascites[19]. Acupoint application is inexpensive, easy to use, non-invasive, and can be used according to the patient's different symptoms of different points and drugs. And has become an important treatment of cirrhotic ascites, especially for refractory ascites, with excellent efficacy. Acupoint application is rarely associated with adverse reactions, and the main adverse event of acupoint application was local skin reaction without systemic side effects.[20] However, there is a lack of systematic evaluation and discussion on the efficacy and safety of acupoint application in the treatment of cirrhotic ascites, so this study aims to evaluate the efficacy and safety of acupressure in the treatment of cirrhotic ascites and provide a basis for the clinical decision of physicians.

There are still limitations in this study; for example, the included studies were biased by choice of acupuncture points, the type of drug preparation resulting in efficacy, and studies or reports in other languages may be overlooked due to the search of English and Chinese literature, which we will try to avoid and improve in subsequent studies.

Abbreviations

CNKI = China National Knowledge Infrastructure, VIP = Chinese Scientific Journals Database,CBM = China BioMedical Literature, TIPS = transjugular intrahepatic portosystemic shunt, RAAS = renin-angiotensin-aldosterone system, PRISMA-P = preferred reporting items for systematical reviews and meta-analyses protocols, RCTs = randomized controlled clinical trials, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, RR = risk ratio, SMD = standardized mean difference, WMD = weighted mean difference, 95%CI = 95% confidence interval, OR = odds ratio.

Author Contributions

Conceptualization: Liuping Zhang, Xiaoying Yao,

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Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or

analyzed during the current study.

Conflict of Interest

declare no conflicts

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