Abstract

Background: Liuweiwuling (LWWL) tablet, a kind of plant-derived traditional Chinese medicine preparation, has been widely applied as a promising adjunctive drug for hepatitis B virus-related cirrhosis (HBVC). However, its exact clinical efficacy and safety is still not well investigated. In this study, we aimed to summarize the efficacy of LWWL tablet on biochemical and virological parameters, and quality of life (QoL) in patients with HBVC through the meta-analysis.

Methods: All available randomized controlled trials and high-quality prospective cohort studies that investigated the efficacy and safety of LWWL for patients with HBVC were searched from the following electronic databases: PubMed, Medline, Cochrane Library, Google Scholar, Web of Science, Excerpt Medica Database, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, China Scientific Journal Database, and Wanfang Database. Papers in Chinese or English published from January 2000 to August 2020 will be included without any restrictions.

Study selection and data extraction will be performed independently by 2 authors. The clinical outcomes including biochemical (liver function and fibrosis indexes) and virological parameters, QoL, immune function and adverse events, were systematically evaluated. Review Manager 5.3 and Stata 14.0 were used for data synthesis, sensitivity analysis, meta regression, subgroup analysis, and risk of bias assessment.

Results: The results of this study will be published in a peer-reviewed journal, and provide a helpful evidence for clinicians to formulate the best postoperative adjuvant treatment strategy for HBVC patients.

Conclusion: Our study will draw an objective conclusion of the efficacy of LWWL on biochemical and virological parameters, and QoL in patients with HBVC.

INPLASY registration number: INPLASY202080010.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, HBV= hepatitis B virus, HBVC = hepatitis b cirrhosis, INPLASY = international platform of registered systematic review and meta-analysis protocols, LC = liver cirrhosis, LWWL = Liuweiwuling, NAs = nucleotide analoge, QoL = quality of life, RCTs = randomized controlled trials.

Keywords: efficacy, hepatitis B virus-related cirrhosis, Liuweiwuling tablet, meta-analysis

1. Introduction

1.1. Description of the background

Liver cirrhosis (LC, being the 14th most common cause of death worldwide) is an increasing cause of morbidity and mortality in more developed countries, which usually results from prolonged or repeated alcohol excess, viral hepatitis, and other etiologies.[1–5] There are over 350 million people with chronic hepatitis B worldwide, and hepatitis B virus (HBV) infection is one of the main causes of LC and hepatocellular carcinoma (HCC).[6,7] More than one million HBV carriers die of LC and HCC every year.[7] As reported by the World Health Organization, 45% of the population lives in high-prevalence chronic hepatitis B areas.[7,8] Among untreated chronic hepatitis B patients, 8% to 20% develop to cirrhosis in 5 years.[7,9,10] Meanwhile, untreated decompensated cirrhosis patients show a poor prognosis, with a 5-year survival rate ranging from 14% to 35%.[7,9,10]
1.2. Description of the intervention

Currently, clinical treatments for hepatitis B virus-related cirrhosis (HBVC) are orally administered nucleotide analogs (NA), such as entecavir, adefovir dipivoxil, tenofovir, lamivudine, and telbivudine. As NA suppress HBV replication only at the point of deoxyribonucleic acid (DNA) synthesis progression, most patients require long-term treatment. However, prolonged use of NA may lead to drug resistance and kidney injury, the most importantly, eradication or suppression of HBV does not reverse the fibrosis of liver and eliminate the risk of occurrence of HBWC. Therefore, exploring new alternative regimens for patients with HBVC are urgently required.

Traditional Chinese Medicine has been clinically used as a complementary treatment for various diseases including HBVC, and plays an important role in the health of Asian people. Many scholars pointed out that the combination of Chinese and Western medicine may be the potential trend for refractory disease treatment in the future. Liuweiwuling (LWWL) tablet is a famous plant-derived traditional Chinese medicine, which composed of 6 traditional Chinese herbs: Schisandrae chinensis fructus, Fructus Ligustri Lucidi, Forsythiae fructus, Curcumae rhizoma, Perennial sow thistle, and Ganodermata spore in a ratio of 3.5:2.5:1.5:1:1.5:1, respectively. Modern pharmacological studies have shown that Schisandra chinensis is effective in reducing enzymes and in protecting the liver from chronic liver injury; Ligustri lucidi fructus nourishes the liver and kidney; Forsythiae fructus and Perennial sow thistle have a positive effect on clearing heat and detoxifying for the liver; Curcumae rhizoma can desilt the extravasated blood and promote microcirculation; and Ganodermata spore can enhance immunity and promote tissue repair. Lei et al pointed out that LWWL tablet can protect hepatocytes from liver injury by decreasing the levels of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and the release of inflammatory cytokines, such as high mobility group box protein B1, tumor necrosis factor-α, and interleukin-1β, and promoting liver regeneration.

Several preclinical studies have demonstrated that LWWL tablet are effective against a variety of acute or chronic liver injuries that are caused by drugs, viruses, and alcohol. It is effective in preventing the progression of hepatitis fibrosis and cirrhosis, and when combined with antivirals, may produce improved clinical effects. Despite the intensive clinical studies, its clinical efficacy was still not well investigated. In this study, we are prepared to summarize the efficacy of LWWL on biochemical and virological parameters, and quality of life (QoL) in patients with HBVC through the meta-analysis, in order to provide a helpful evidence for clinicians to formulate the best postoperative adjuvant treatment strategy for HBVC patients.

2. Review question

Is LWWL tablet effective on biochemical and virological parameters, and QoL in patients with HBVC?

3. Objective

A systematic review and meta-analysis will be performed to systematically evaluate the efficacy of LWWL tablet on biochemical and virological parameters, and QoL in patients with HBVC.

4. Methods

The protocol of this meta-analysis will be reported according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. Our protocol has been registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY). The registration number was INPLASY202080010 (DOI number is 10.37766/inplasy2020.8.0010, https://inplasy.com/inplasy-2020-8-0010/). This meta-analysis is a secondary research which based on some previously published data. Therefore, the ethical approval or informed consent was not required.

4.1. Search strategy

To perform a comprehensive and focused search, experienced systematic review researchers will be invited to develop a search strategy. The plan searched terms are as follows: “hepatitis B virus” or “liver cirrhosis” or “hepatitis B cirrhosis” or “hepatitis B virus-related cirrhosis” or “HBV-cirrhosis” or “HBV-C” combined with “Liuweiwuling” or “Liuwei wuling tablet” or “Liuwei wuling tablet” or “LWWL” in Title/Abstract. An example of search strategy for PubMed database shown in Table 1 will be modified and used for the other databases.

4.2. Eligibility criteria

4.2.1. Types of studies. All available randomized controlled trials (RCTs) or quasi-RCTs, and high-quality prospective cohort studies that investigated the efficacy of LWWL tablet on biochemical and virological parameters, and QoL in patients with HBVC will be included in this systematic review.
4.2.2. Types of participants. Patients were diagnosed with hepatic cirrhosis that caused by HBV. No restrictions regarding age, gender, racial, region, education, and economic status in this analysis. Patients who had no HCC or other malignant tumor exclusion will be listed in a table. A Preferred Reporting Items for Systematic Review and Meta-Analysis-compliant flow chart (Fig. 1) will be used to describe the selection process of eligible literatures.

4.5.2. Data extraction and management. Two investigators (Li D and Zhu M) will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention.

The following data will be extracted from eligible literatures:

- Study characteristics and methodology: country of study, the first author, year of publication, study design, sample size, periods of data collection, total duration of study, follow-up duration, and so on.
- Participant characteristics: age, gender, ethnicity, inclusion and exclusion criteria, and so on.
- Interventions: therapeutic means, manufacturer of the drugs, dosage of LWWL tablet, administration route and cycles, duration of treatment, follow-up time, and so on.
- Outcome and other data:
  (1) Liver function indexes (total bilirubin, albumin, ALT, and AST);
  (2) Virological indicators (HBV DNA levels and HBeAg status);
  (3) Liver fibrosis indexes (hyaluronic acid, laminin, type III procollagen and type IV collagen levels);
  (4) Immune indicators: (CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios);
  (5) Model for end-stage liver disease and Child-Pugh score;
  (6) Other data (QoL, alpha-fetoprotein, adverse effects, etc).

Dealing with missing data: we will attempt to contact the authors to request the missing or incomplete data. If those relevant data are not acquired, they will be excluded from the analysis.

4.6. Assessment of risk of bias

Two review authors (Li D and Zhu M) will independently assess the methodological quality of the included trials by using the following criteria described in the Cochrane Handbook for Systematic Reviews of Interventions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.[29,30] Evidence quality will be classified as low risk, high risk, or unclear risk of bias. Effective Practice and Organisation of Care guidelines will be used to assess the risks of non-RCTs.[31] Any disagreements will be resolved via discussion with a third researcher (Zhou CH).

4.7. Data synthesis

Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX) statistical software will be used to pool the data and carry out the data analysis. Heterogeneity between studies will be assessed using the Cochran Q and Higgins I² statistic. P < .1 or I² > 50% will be considered as showing considerable heterogeneity, and the random effect model will be used.[32] Otherwise, a fixed effect model will be used for data analysis. Dichotomous data will be recorded as risk ratio with 95% confidence intervals. Continuous data will be presented as standardized mean difference with their confidence intervals. A 2-tailed P < .05 was considered statistically significant.
4.8. Subgroup and meta-regression analysis

Subgroup and meta-regression analysis based on cirrhosis stage, treatment period, dose of LWWL tablet, level of risk of bias, and other unpredictable factors will be performed to detect the source of heterogeneity.

4.9. Sensitivity analysis

Sensitivity analysis will be carried out to assess the reliability and robustness of the pooled results via eliminating trials with low quality. A summary table will report the results of the sensitivity analyses.

4.10. Other relevant information

4.10.1. Publication bias analysis. Funnel plot, Begg, and Egger regression test will be performed to analyze the existence of publication bias if 10 or more studies are included in this meta-analysis. If reporting bias is suspected, we will consult the study author to get more information. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted results were compared with the original pooled risk ratio.

4.10.2. Evidence evaluation. The Grading of Recommendations, Assessment, Development, and Evaluation system will be used for assessing the strength of the body of evidence. According to the grading system, the quality of evidence will be evaluated as high, moderate, low, and very low level.

4.11. Dissemination plans

We will disseminate the results of this systematic review by publishing the manuscript in a peer-reviewed journal.

5. Discussion

HBV infection is one of the most common chronic viral infections in the world, which causes 40% of men and 15% of women to die of LC or HCC. Timely and effective treatment of HBVC at...
the compensatory stage could prevent cirrhosis transformation to decompensated cirrhosis and HCC. At present, the recognized therapeutic strategies are antiviral therapy for etiology and direct antifibrotic therapy for extracellular matrix, metabolism, and hepatic stellate cell activation. However, antiviral therapy alone cannot inhibit the formation and deposition of extracellular matrix in liver fibrosis tissues, and single anti-fibrosis therapy cannot inhibit the replication of hepatitis virus and promote the repair of liver injury. Evidence-based medicine has shown that antiviral therapy plus traditional Chinese medicine has better long-term control effect on HBVC than antiviral treatment alone. LWLL tablet is a famous plant-derived traditional Chinese medicine preparation against hepatitis fibrosis and cirrhosis which produced by Shandong Shibo Jindu Pharmaceutical Co., Ltd. It have been approved by Chinese State Food and Drug Administration, and granted the manufacturing approve number accordingly (Z20060238).

6. Strengths and limitations

Several studies have shown that LWLL tablet has a reliable effect on improving the pathological state of cirrhosis and delaying the formation of liver fibrosis. Even though there was statistical analysis of published clinical trials, the exact effects of LWLL tablet on biochemical and virological parameters, and QoL in patients with HBVC were still not systematically investigated. This systematic review will conduct a systematic, comprehensive, and objective evaluation of LWLL-based treatment. The findings of this analysis will provide a helpful evidence for clinicians to formulate the best postoperative adjuvant treatment strategy for patients with advanced HBVC, and also provide scientific clues for researchers in this field. There may be a language bias with the limitation of English and Chinese studies.

Author contributions

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References

[1] Tsiochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383: 1749–61.
[2] Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol 2016;51:629–50.
[3] Romanelli RG, Stazi C. Recent advancements in diagnosis and therapy of liver cirrhosis. Curr Drug Targets 2016;17:1804–17.
[4] Smith A, Baumgartner K, Boutis C. Cirrhosis: diagnosis and management. Am Fam Physician 2019;100:759–70.
[5] Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12:145.
[6] Lun-Gen L. Antiviral therapy of liver cirrhosis related to hepatitis B virus infection. J Clin Transl Hepatol 2014;2:197–201.
[7] Sun A, Gao W, Xiao T. Autologous bone marrow stem cell transplantation via the hepatic artery for the treatment of hepatitis B virus-related cirrhosis: a PRISMA-compliant meta-analysis based on the Chinese population. Stem Cell Res Ther 2020;11:104.
[8] Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97–107.
[9] Wang FY, Li B, Li Y, et al. Entecavir for patients with hepatitis B decompensated cirrhosis in China: a meta-analysis. Sci Rep 2016;6:32722.
[10] European Association for the Study of the LiverEASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–85.
[11] Zhang T, Yang Y, Wang B, et al. Meta-analysis of influences of Beijiajian Pill combined with entecavir on serum liver fibrosis markers of compensatory period of hepatitis b cirrhosis: Protocol of systematic review and meta-analysis. Medicine 2019;98:e18458.
[12] Huang C, Shen D, Sun S, et al. Effect of Fufang Biejia Ruangan Tablet on lowering biochemical and virological parameters of hepatitis fibrosis in patients with chronic hepatitis B: Protocol for a systematic review and meta-analysis of randomized controlled trials and cohort studies. Medicine 2019;98:e13297.
[13] Hou J, Wang G, Wang F, et al. Guideline of prevention and treatment for chronic hepatitis B (2015 Update). J Clin Transl Hepatol 2017;5:297–318.
[14] Chen GF, Wang C, Lau G. Treatment of chronic hepatitis B infection-2017. Liver Int 2017;37(Suppl 1):39–66.
[15] Chen EQ, Tang H. Optimization therapy for the treatment of chronic hepatitis B. World J Gastroenterol 2014;20:3730–6.
[16] Chen EQ, Tang H. The current status of combination therapy of chronic hepatitis B. Eur Rev Med Pharmacol Sci 2013;17:2023–31.
[17] An J, Ni W, Qiao J. Therapeutic efficacy and quality of life investigation of traditional Chinese medicine-based therapy of chronic hepatitis B-related liver fibrosis. Chin J Hepatology 2014;22:30–2.
[18] Wang Z, Qi F, Cui Y, et al. An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. Biosci Trends 2018;12: 220–39.
[19] Liu J, Wang S, Zhang Y, et al. Traditional Chinese medicine and cancer: history, present situation, and development. Thorac Cancer 2015;6:561–9.
[20] Du K, Jaeschke H. Liuweiwuling tablets protect against acetaminophen hepatotoxicity: what is the protective mechanism? World J Gastroenterol 2016;22:3302–4.
[21] Lei YC, Li W, Luo P. Liuweiwuling tablets attenuate acetaminophen-induced acute liver injury and promote liver regeneration in mice. World J Gastroenterol 2015;21:8089–95.
[22] Liu H, Dong F, Li G, et al. Liuweiwuling tablets attenuate BDL-induced hepatic fibrosis via modulation of TGF-β/Smad and NF-kB signaling pathways. J Ethnopharmacol 2018;210:232–41.
[23] Liu H, Zhang Z, Hu H, et al. Protective effects of Liuweiwuling tablets on carbon tetrachloride-induced hepatic fibrosis in rats. BMC Complement Altern Med 2018;18:212.
[24] Wang JB, Cui HR, Wang RL, et al. A systems pharmacology-oriented discovery of a new therapeutic use of the TCM formula Liuweiwuling for liver failure. Sci Rep 2018;8:3645.
[25] Lei Y, Li W, Luo P. Association between protective effect of Liuwei Wuling tablets against acute liver injury and its inhibitory effect on cytoplasmic translocation of high-mobility group box-1 in hepatocytes in mice. Chin J Hepatology 2016;24:114–8.
[26] Li L. Clinical study of entecavir combined with Liuweiwuling tablets in the treatment of compensated hepatitis B cirrhosis. J Clin Med Lit 2017;4:5293–4.
[27] Liu JQ, Wang SY, Cao LH, et al. Clinical efficacy of entecavir combined with Liuweiwuling tablets in the treatment of compensated hepatitis B cirrhosis. Shandong Med J 2018;58:75–7.
[28] Samseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
[29] Huggins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s and for assessing risk of bias in randomized trials. BMJ 2011;343:d5928.
[30] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8:2–10.
[31] Grimshaw J, McAuley LM, Bero LA, et al. Systematic reviews of the effectiveness of quality improvement strategies and programmes. Qual Saf Health Care 2003;12:298–303.

[32] Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805–20.

[33] Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics 2018;74:785–94.

[34] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[35] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[36] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

[37] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

[38] Trépo C, Chan HLY, Lok A. Hepatitis B virus infection. Lancet 2014;384:2053–63.

[39] Liaw YF. Reversal of cirrhosis: an achievable goal of hepatitis B antiviral therapy. J Hepatol 2013;59:880–1.

[40] Kong Z, Liang N, Yang GL, et al. Xiao Chai Hu Tang, a herbal medicine, for chronic hepatitis B. Cochrane Database Syst Rev 2019;2019:CD013090.

[41] Wang T, Zhou X, Liu H, et al. Fuzheng Huayu capsule as an adjuvant treatment for HBV-related cirrhosis: a systematic review and meta-analysis. Phytother Res 2018;32:757–68.