Clinics and Research in Hepatology and Gastroenterology (2017) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Therapeutic efficacy and safety of umbilical cord mesenchymal stem cell transplantation for liver cirrhosis in Chinese population: A meta-analysis

Weiwei Sang[a], **Benji Lv**[b], **Ke Li**[c], **Yan Lu**[a,*]

[a] *Department of Gastroenterology, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, Dongchang West Road, No.67, 252000 Liaocheng, Shandong Province, China*
[b] *Department of Blood Transfusion, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, 252000 Liaocheng, Shandong Province, China*
[c] *Department of Central Laboratory, Liaocheng People's Hospital, Liaocheng Clinical School of Taishan Medical University, Dongchang West Road, No.67, 252000 Liaocheng, Shandong Province, China*

KEYWORDS
Umbilical cord mesenchymal stem cells;
Traditional supportive therapy;
Liver cirrhosis;
Meta-analysis

Summary
Background and objective: Mesenchymal stem cells transfusion has been considered as a promising option for liver cirrhosis (LC). The aim of this study was to systematically evaluate the efficacy and safety of umbilical cord mesenchymal stem cells (UMSC) combined with traditional supportive therapy (TST) for the treatment of patients with LC.
Methods: Data was extracted from clinical trials published on Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database. The evaluated outcome measurements included liver function, coagulation function, liver fibrosis indexes, clinical symptoms, quality of life (QOL) and adverse events.
Results: A total of 14 trials including 717 LC patients met our selection criteria were involved. The liver function of LC patients was significantly improved after combined therapy (UMSC plus TST), indicated by decreased total bilirubin, alanine aminotransferase and prothrombin time, and increased serum albumin, cholinesterase and prothrombin activity. The QOL of patients was also improved after UMSC therapy. Compared with TST alone, the combined therapy showed better treatment effect based on measurements of hyaluronic acid (OR = −143.20, CI = −181.58 to −104.82, $P < 0.00001$), laminin (OR = −50.65, CI = −53.70 to −47.61, $P < 0.00001$), type III procollagen (OR = −8.68, CI = −9.00 to −8.36, $P < 0.00001$), type IV collagen (OR = −105.79, CI = −132.44 to −79.14, $P < 0.00001$) and plasma prolidase (OR = −876.54, CI = −911.89 to −840.56, $P < 0.00001$). Moreover, the patients' clinical symptoms including fatigue (4th, $P = 0.003$; 8th, $P = 0.01$), appetite (4th, $P < 0.0001$; 8th,

* Corresponding author.
E-mail address: luyanxiaohua@163.com (Y. Lu).

https://doi.org/10.1016/j.clinre.2017.11.003

Please cite this article in press as: Sang W, et al. Therapeutic efficacy and safety of umbilical cord mesenchymal stem cell transplantation for liver cirrhosis in Chinese population: A meta-analysis. Clin Res Hepatol Gastroenterol (2017), https://doi.org/10.1016/j.clinre.2017.11.003

$P = 0.06$), ascites (4th, $P = 0.03$; 8th, $P = 0.17$), and abdominal distension (4th, $P = 0.0008$; 8th, $P = 0.64$) were also improved in patients treated by combined therapy without adverse events observed.

Conclusion: UMSC and TST combined therapy for LC patients improved their liver function, clinical symptoms and QOL without severe adverse events, therefore is safe and effective in LC therapy.

Introduction

Liver cirrhosis (LC) is a common complication of progressive liver disease with irreversible diffuse liver damage, which usually caused by alcohol or viral hepatitis [1,2]. Reduced liver regeneration and dysfunction in LC may cause portal hypertension, end-stage liver disease and other complications, such as hepatic encephalopathy and secondary infection [3,4]. LC morbidity and mortality has been increased remarkably in the past years, while most LC patients were not able to be diagnosed at early stage and had shown irreversible liver damage [1,5]. The currently available curative treatment for compensated LC is liver transplantation. [6] However, its implementation usually confronts with obstruction of donor shortage, and maybe accompanied with complications, immunological rejection, high medical costs and ethical restraints [3,6].

In order to develop new strategies to stimulate liver regeneration in LC, researchers have conducted considerable studies. Mesenchymal stem cells (MSC) are derived from mesoderm with self-renewal and multi-differentiation capacity [7—11]. They are able to differentiate into hepatocyte-like cells under appropriate in vivo and in vitro conditions, and were found with capability in promoting hepatocytes regeneration. MSC transplantation showed beneficial effects in LC preclinical studies, therefore MSC was considered with great potentiality in LC treatment [6—9]. Bone marrow mesenchymal stem cells (BMSC) are mainly used in current clinical application [9,11,12], which is usually thwarted by the invasiveness of bone marrow aspiration and age-dependent quantity and quality variation of BMSC [11,13].

Human umbilical cord is another source of MSC, which shows advantages over BMSC with wider range of collection sources, easier collection approach and fewer ethical constraints [14,15]. It has been reported in several clinical trials that UMSC transfusion was able to alleviate liver fibrosis with enhanced liver functions, while not causing severe side effects [14,16,17]. Compare to traditional supportive therapy (TST), the combination of UMSC transfusion and TST has been reported more effective in LC treatment in multiple researches with various respective focuses. To systematically assessing the therapeutic efficacy of this combined therapy for LC, we conducted a systematical review and meta-analysis of the published clinical trials, with the objective to provide valuable reference for its clinical application in the future.

Materials and methods

Data sources and selection criteria

This meta-analysis was conducted in accordance with the PRISMA guidelines. The main source of the searched literatures included Web of Science, PubMed, EMBASE, Cochrane Library, Wanfang and CNKI database. The search was performed in February 2017 and updated in April 2017, with key terms ''umbilical cord mesenchymal stem cells'' AND (''liver cirrhosis'' OR ''hepatocirrhosis'').

The manually searched literatures are reviewed, and those met the following inclusion criteria were involved in this study:

- case controlled clinical trials;
- more than 30 LC patients were included;
- patients had no hepatocellular carcinoma (HCC) or other malignant tumor, and without pregnancy or lactation;
- patients received either UMSC and TST combined therapy, or treated by TST alone.

Data extraction and quality assessment

According to the recommendations of Cochrane Collaboration and PRISMA statement, two authors (Weiwei Sang and Benji Lv) performed the literature research and data extraction independently. The following information of selected articles were summarized when available: first author's name, time of publication and enrollment, study location, LC stages, number of enrolled patients, age, cause of LC, therapeutic regimen, administration route, dosage of UMSC and parameter types. Discrepancies were resolved upon authors' discussion. The included studies' methodological quality was assessed according to Cochrane Handbook [18].

Outcome definition

The main interested outcomes in this research include treatment efficacy, clinical symptoms, quality of life (QOL) and adverse events. Treatment efficacy was assessed in terms of the levels of total bilirubin (TBIL), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (CHE), prothrombin time (PT), prothrombin activity (PTA), and liver fibrosis indexes

Please cite this article in press as: Sang W, et al. Therapeutic efficacy and safety of umbilical cord mesenchymal stem cell transplantation for liver cirrhosis in Chinese population: A meta-analysis. Clin Res Hepatol Gastroenterol (2017), https://doi.org/10.1016/j.clinre.2017.11.003