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Stem cell transplantation for the treatment of liver diseases: A systematic review and meta-analysis

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ABSTRACT

Background/Aims: The therapeutic efficacy of stem cell transplantation in liver diseases has not yet been determined. The objective of this study was to conduct a meta-analysis to evaluate changes in liver function and clinical outcome following stem cell transplantation in patients with liver disease.

Materials and Methods: A literature review of NCBI, Cochrane Library, and MEDLINE was performed. Eligible studies reported liver function indices and prothrombin time (PT) before and after transplantation. The weighted mean difference (WMD) was defined by the distinction before and after stem cell transplantation. Either a fixed-effects model or random-effects model was used to analyze the data.

Results: A total of 17 publications involving 21 original studies were included. We found that the levels of serum albumin significantly increased at 4, 8, 12, 24, and 48 weeks after stem cell transplantation compared with that at baseline. Serum alanine aminotransferase levels notably decreased at 1, 3, 4, 12, 24, and 48 weeks after stem cell transplantation. Aspartate aminotransferase levels significantly decreased at 4, 8, 12, and 48 weeks after transplantation. Total bilirubin levels significantly decreased at 4, 12, 24, and 48 weeks after transplantation. PT decreased at 4, 12, 24, and 48 weeks after transplantation. The MELD score significantly decreased at 24 weeks after transplantation. Stem cell infusion through the hepatic artery had better biochemical outcomes than an injection through the portal vein.

Conclusion: Our meta-analysis verified that there are clinical and biochemical improvements in patients who suffered from liver diseases after stem cell transplantation, suggesting that stem cell transplantation may be a viable clinical solution for treating such patients.

Keywords: Stem cells, transplantation, liver function, liver diseases, meta-analysis

Review

INTRODUCTION

Worldwide, the occurrence of liver diseases is common, with liver failure correlated to a high mortality rate of 40%–80% (1). Liver transplantation is deemed to be the standard treatment for end-stage liver diseases, characterized by decompensated hepatic cirrhosis and liver failure (2). However, the limitations of liver transplantation include a relative shortage of organ donors, operation complications, transplant rejection, and high cost (3). By the end of 2006, more than 17000 patients were on the liver transplant waiting list in the United States (4). Annually, over the past 6 years, approximately 2000 patients have died due to the lack of organ availability (5). The use of a bioartificial liver has been reported as a substitute treatment for liver diseases (6). However, its efficiency is restricted by the lack of sources of liver cells, subnormal in vitro activity, and difficulties in constructing a three-dimensional biological reactor as an artificial liver (7).

Stem cell therapy, particularly by adult hematopoietic stem cells (HSCs) and bone marrow mesenchymal stem cells (BMSCs), represents a potential clinical alternative (8). Unlike other cell types, HSCs promote recovery from hepatic injury under a strong positive selection pressure when the normal mechanisms of regenera-

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tion are either blocked or inadequate. HSCs may not be the key contributors to hepatocyte populations in normal situations, but they are supposed to make a significant contribution to regeneration after a severe injury (9). As shown by Lagasse et al. (10), HSCs have the potential to reinstate normal function in a murine model of genetic tyrosinemia. Huang et al. (11) conducted a feasibly study on 80 patients suffering from end-stage liver diseases using HSCs that were infused into the hepatic artery and portal vein and reported an improvement in the major indices of hepatic function, including prothrombin time (PT) and serum albumin (ALB), bilirubin, and alanine aminotransferase (ALT) levels. BMSCs have been shown to play a significant role in cellular therapy and tissue engineering (12). They manifest potential therapeutic effects against fibrogenesis by decreasing collagen deposition and inducing hepatocyte differentiation. The advantages of BMSCs include easy separation and cultivation, high expansion potential, stable phenotype, substantial immunocompatibility, and mild side effects after transplantation (13).

Previous studies employed very small numbers of patients with varying follow-up time points after transplantation. No randomized controlled trials demonstrating the clinical benefit of stem cell transplantation are available. Therefore, we decided to conduct a systematic review and meta-analysis to evaluate the short- and long-term efficacy of stem cell transplantation. The main objectives of the current meta-analysis include the assessment of liver function indices and clinical outcomes during the follow-up of patients with end-stage liver failure and decompensated liver diseases.

Review

MATERIALS AND METHODS

Literature search

A literature review of NCBI, Cochrane Library, EMBASE, and MEDLINE was independently performed by two authors. This was done from the inception of the databases to November 2015 using the following keywords: (stem cell or bone marrow hematopoietic stem cell) and (transplantation) and (liver cirrhosis or liver disease or liver failure). The titles and abstracts of selected articles were examined. Full-text articles were read in detail. The bibliographic references of selected papers were scrutinized for additional studies.

Inclusion and exclusion criteria

An article was considered relevant to our study if it reported at least liver function indices and PT in patients with liver disease before and after stem cell transplantation. Animal studies were not included. Studies evaluating the feasibility or safety of stem cell transplantation in patients with liver disease available only in the abstract form were excluded. Studies involving graphic data alone were also excluded. In case of multiple publications involving the same study, only the most recent study was selected. Ongoing studies and reviews were also excluded.

Data extraction

Data extraction was independently performed by two reviewers. In addition to the study by author and year, we collected information pertaining to the country in which the study was conducted, patient number, gender and age, disease type, stem cell transplantation route, stem cell type, follow-up time points, mean and standard deviations of pre- and post-transplantation biochemical values and MELD scores, as well as clinical symptoms pre- and post-transplantation.

Statistical methods

The differences before and after stem cell transplantation were defined as WMD (standard mean difference) due to the large difference in the means of liver indices among the studies. Statistical heterogeneity was evaluated using the I^2 statistic, with I^2>50% representing statistically significant heterogeneity. In the absence of significant heterogeneity (p>0.05), data were analyzed using a fixed-effects model (Mantel–Haenszel procedure). If there was significant heterogeneity, a random-effects model (DerSimonian–Laird approach) was employed. The visual inspection of funnel plots in which the WMDs were plotted against their standard errors were used to evaluate the publication bias. Egger's test of funnel plot asymmetry was also performed at the p<0.05 level of significance. If there was publication bias, the trim and fill method was used to calculate the adjusted WMD. Subgroup analyses were conducted to explore heterogeneity across studies, and the differences between subgroups were tested by meta-regression analysis. All analyses were performed with STATA version 11.0 (StataCorp LP; College Station, Texas, USA).

RESULTS

Study selection

The primary literature search engendered 1618 articles, of which 1399 were excluded after screening the title and abstracts based on the inclusion criteria. A total of 219 studies were selected for full-text retrieval. Of these retrieved studies, 202 were excluded because of animal experiments, reviews, or insufficiently detailed data. Overall, we identified and included 17 publications involving 20 studies that met the inclusion criteria (11,14-29). There were five papers that involved two studies. Huang et al. (11) studied two different transplantation routes: hepatic artery and portal vein. Salama et al. (25) studied two kinds of diseases: end-stage autoimmune liver disease and end-stage hepatitis C. El-Ansary et al. (26) reported two transplantation routes: intrasplenic and peripheral. Zekri et al. (29) conducted two kinds of treatments: one session (G-I) and two sessions 4 months apart (G-II) of autologous HSC transplantation.

The 17 publications reporting 20 studies were published between 2003 and 2015 and involved a total of 507 patients with hepatic disease. Study characteristics and patient demographics of the included studies are listed in Table 1. Of these stud-

Table 1. Description of selected studies

Study (year)	Origin of study	No. of patients	Male/ Females	Age	Disease	Transplantation route	Stem cell type	Follow-up time points (week)
Huang et al. (11)	China	44	NA	NA	Decompensated end-stage liver disease	Hepatic artery	HSCs (CD34+)	12, 24, 48
Li et al. (13)	China	40	37/3	51.6±9.2	Decompensated hepatitis B cirrhosis	Hepatic artery	BMSCs	4
Bai et al. (16)	China	32	20/12	46.4±11.6	Decompensated liver cirrhosis	Hepatic artery	BMSCs	1, 4, 12, 24, 48
Liao et al. (17)	China	6	NA	NA	Decompensated hepatitis B cirrhosis	Hepatic artery	BMSCs	12
Peng et al. (18)	China	53	50/3	42.2±10.8	Decompensated hepatitis B cirrhosis	Hepatic artery	BMSCs	1, 2, 3, 4, 12, 24, 36, 48
Khan et al. (19)	India	25	25/0	50.6±8.5	Decompensated liver cirrhosis	Hepatic artery	Fetal liver-derived stem cell	8, 16, 24
Pai et al. (20)	UK	9	6/3	53.0±3.6	Decompensated alcoholic liver cirrhosis	Hepatic artery	HSCS (CD34+)	1, 4, 6, 8, 12
Khan et al. (21)	India	4	NA	NA	Decompensated liver Cirrhosis	Hepatic artery	BMSCs (CD34+)	24
Lyra et al. (14)	Brazil	10	8/2	52 (24–70)	Advanced chronic liver disease	Hepatic artery	BMSCs	4, 16
Huang et al. (11)	China	36	NA	NA	Decompensated end-stage liver disease	Portal vein	HSCs (CD34+)	12, 24, 48
Nikeghbalian et al. (22)	Iran	6	3/3	35.7±4.1	Decompensated liver cirrhosis	Portal vein	BMSCs	12, 24, 96
Salama et al. (23)	Egypt	90	NA	50.3±6.1	Decompensated end-stage liver cirrhosis	Portal vein	HSCS (CD34+, CD133+)	4, 8, 12, 24
Mohamadnejad et al. (24)	Iran	4	1/3	47.3±9.8	Decompensated liver cirrhosis	Peripheral vein	BMSCs	24, 48
Zekri et al. (29)	Egypt	30	25/5	49.6±4.6	Hepatitis C cirrhosis	Peripheral vein	HSCs	2, 4, 8, 12, 24, 36, 48
Zekri et al. (29)	Egypt	30	26/4	51.0±4.2	Hepatitis C cirrhosis	Peripheral vein	HSCs	2, 4, 8, 12, 24, 36, 48
Salama et al. (25)	Egypt	12	NA	48.5±10.5	Decompensated end-stage autoimmune liver cirrhosis	Hepatic artery or Portal vein	HSCs (CD34+)	1, 3, 8, 12, 24, 36, 48
Ansary et al. (26)	Egypt	6	NA	48.5±11.1	Decompensated Hepatitis C cirrhosis	Splenic artery	BMSCs	24
Ansary et al. (26)	Egypt	6	NA	50.8±6.9	Decompensated Hepatitis C cirrhosis	Peripheral blood	BMSCs	24
Wang et al. (27)	China	10	9/1	49.1±8.6	UDCA- PBC	NA	BMSCs	12, 24
Lorenzini et al. (28)	Italy	18	17/1	53.4±8.8	Decompensated liver cirrhosis	NA	BMSCs	1, 4

NA: not applicable; BMSCs: bone marrow mesenchymal stem cells; HSCs: hematopoietic stem cells
UDCA-PBC, ursodeoxycholic acid-resistant primary biliary cirrhosis; Huang et al. (11)-transplanted by the hepatic artery route, Huanget al. (2014-B)-portal vein route; Salama et al. (23)-patients with decompensated hepatitis cirrhosis, Salama et al. (25)-patients with decompensated end-stage autoimmune liver diseases; El-Ansary et al. (26)-transplanted by the splenic artery route, El-Ansary et al. (26)-transplanted by the peripheral vein route; Zekri et al. (29)-received one-session treatment, Zekri et al. (29)-received two sessions 4 months apart.

ies, nine used the hepatic artery route, three the portal vein route, three the peripheral vein route, one the splenic artery route, one by peripheral blood, and two were undocumented or unknown. Twelve used BMSCs as the transplantation source, eight used HSCs, and one used fetal liver stem cells. Follow-up time points were reported by more than three publications, including seven follow-up time points for serum ALB levels: 1, 3, 4, 8, 12, 24, and 48 weeks after transplantation. There were also seven follow-up time points for serum ALT levels: 1, 3, 4, 8, 12, 24, and 48 weeks after transplantation. There were five follow-up time points for aspartate aminotransferase (AST) levels: 1, 4, 8, 12, and 24 weeks after transplantation. There were eight follow-up time points for total bilirubin (TBIL) levels: 1, 3, 4, 8, 12, 16, 24, and 48 weeks after transplantation. There were four follow-up time points for PT: 4, 12, 24, and 48 weeks after transplantation. There was only one follow-up time point for MELD score: 24 weeks after transplantation. There were three follow-up time points for alleviative ascites: 8, 12 and 24 weeks.

Table 2. Pooled SMDs of ALB, ALT, AST, and TBIL levels and PT

Index	Time point	No. of studies	SMD (95% CI)	z	P	Heterogeneity I^2 (%)	p
ALB	1	6	0.09 (−0.19, 0.37)	0.62	0.537	73.9	0.002
	3	3	0.67 (0.55, 1.88)	1.08	0.282	92.8	0.000
	4	9	0.71 (0.41, 1.00)	4.63	0.000	95.8	0.000
	8	7	0.51 (0.28, 0.75)	4.26	0.000	93.1	0.000
	12	12	0.73 (0.47, 1.00)	5.43	0.000	88.5	0.000
	24	15	0.73 (0.48, 0.98)	5.70	0.000	90.8	0.000
	48	8	1.56 (1.04, 2.08)	5.92	0.000	94.6	0.000
ALT	1	7	−11.31 (−15.97, −6.65)	4.75	0.000	11.0	0.345
	3	3	−23.92 (−36.97, −10.88)	3.59	0.001	41.3	0.182
	4	7	−19.37 (−33.58, −5.16)	2.67	0.008	91.8	0.000
	8	4	−6.53 (−13.33, 0.27)	1.88	0.060	33.6	0.211
	12	10	−11.81 (−17.35, −6.27)	4.18	0.000	48.3	0.043
	24	8	−17.20 (−26.61, −7.80)	3.58	0.000	64.9	0.006
	48	6	−20.07 (−25.02, −15.13)	7.69	0.000	40.6	0.151
AST	1	3	−26.41 (−38.97, −13.86)	4.13	0.000	27.6	0.251
	4	4	−24.29 (−29.49, −19.09)	2.33	0.020	85.9	0.000
	8	3	−15.47 (−21.11, −9.84)	5.38	0.000	44.4	0.165
	12	5	−19.13 (−24.27, −13.98)	7.29	0.000	0.00	0.701
	24	4	−25.23 (−31.96, −18.51)	7.35	0.000	92.1	0.000
TBIL	1	8	−0.50 (−1.16, 0.17)	1.46	0.143	74.8	0.000
	3	3	−0.18 (−1.78, 1.41)	0.22	0.828	84.5	0.002
	4	9	−1.19 (−2.21, −0.17)	2.28	0.023	94.2	0.000
	8	7	−0.39(−0.81, 0.02)	1.88	0.060	74.0	0.001
	12	12	−1.72 (−2.07, −0.27)	2.54	0.011	87.8	0.000
	16	3	−1.35 (−3.11, 0.40)	1.51	0.130	84.6	0.002
	24	15	−1.13 (−1.80. −0.46)	3.29	0.001	91.1	0.000
	48	9	−3.94 (−5.90, −1.97)	3.93	0.000	94.3	0.003
PT	4	3	−4.36 (−7.48, −1.25)	2.74	0.006	93.9	0.000
	12	5	−1.91 (−3.31, −0.51)	2.67	0.008	85.8	0.000
	24	5	−2.32 (−3.74, −0.91)	3.23	0.001	85.1	0.000
	48	6	−2.03 (−3.02, −1.04)	4.01	0.000	74.7	0.001

SMD: standardized mean difference; ALB: albumin; ALT: alanine aminotransferase; AST: aminotransferase; TBIL: total bilirubin; PT: prothrombin time; CI: confidence interval

ALB analysis

The ALB levels significantly increased at 4, 8, 12, 24, and 48 weeks after transplantation (Table 2). The pooled WMDs are as follows: at 4 weeks after transplantation, 0.71 (95% CI: 0.41, 1.00; p=0.000); at 8 weeks, 0.51 (95% CI: 0.28, 0.75; p=0.000); at 12 weeks, 0.73 (95% CI: 0.47, 1.00; p=0.000); and at 24 weeks, 1.56 (95% CI: 1.04, 2.08; p=0.000). The results at 1 and 3 weeks after infusion showed no significant differences compared with those after pre-infusion, as shown in Table 2.

ALT analysis

The ALT levels significantly decreased at 1, 3, 4, 12, 24, and 48 weeks after transplantation (Table 2). The pooled WMDs are as follows: at 1 week after transplantation, −11.31 (95% CI: −15.97, −6.65; p=0.000); at 3 weeks, −23.92 (95% CI: −36.97, −10.88; p=0.001); at 4 weeks, −19.37 (95% CI: −33.58, −5.16; p=0.008); at 12 weeks, −11.81 (95% CI: −17.35, −6.27; p=0.000); at 24 weeks, −17.20 (95% CI: −26.61, −7.80; p=0.000); and at 48 weeks, −20.07 (95% CI: −25.02, −15.13; p=0.000). The ALT levels

8 weeks after transplantation were not significantly increased compared with those before transplantation.

AST analysis

The AST levels significantly decreased at 1, 4, 8, 12, and 48 weeks after transplantation (Table 2). The pooled WMDs are as follows: at 1 week after transplantation, −26.41 (95% CI: −38.97, −13.86; p=0.000); at 4 weeks, −24.29 (95% CI: −29.49, −19.09, p=0.020); at 8 weeks, −15.47 (95% CI: −21.11, −9.84; p=0.000); at 12 weeks, −19.13 (95% CI: −24.27, −13.98; p=0.000); and at 24 weeks, −25.23 (95% CI: −31.96, −18.51; p=0.000).

TBIL analysis

The TBIL levels at 4, 12, 24, and 48 weeks after transplantation notably declined compared with baseline levels. The results are shown in Table 2. The pooled WMDs are as follows: at 4 weeks after transplantation, −1.19 (95% CI: −2.21, −0.17; p=0.023); at 12 weeks, −1.72 (95% CI: −2.07, −0.27; p=0.011); at 24 weeks, −1.13 (95% CI: −1.80, −0.46; p=0.001); and at 48 weeks, −3.94 (95% CI: −5.90, −1.97; p=0.000). The TBIL levels at 1, 3, 8 and 16 weeks after transplantation were not significantly increased compared with those at baseline.

PT analysis

The PTs after transplantation at four follow-up time points (weeks 4, 12, 24, and 48) were notably declined compared with those at baseline, as shown in Table 2. The pooled WMDs are as follows: at 4 weeks after transplantation, −4.36 (95% CI: −7.48, −1.25; p=0.006); at 12 weeks, 1.91 (95% CI: −3.31, −0.51; p=0.008); at 24 weeks, −2.32 (95% CI: −3.74, −0.9; p=0.001); and at 48 weeks, −2.03 (95% CI: −3.02, −1.04; p=0.000).

Improvement in MELD Score and ascites

The MELD score was used to assess the overall liver function, and the MELD score at 24 weeks after transplantation significantly decreased compared with that at baseline, and the pooled WMD at 24 weeks after transplantation was −5.74 (95% CI: −8.55, −2.93, p=0.000). Patients showed a decrease in ascites following stem cell transplantation, 56.5% (95% CI: 49.3%, 63.7%) at 12 weeks after transplantation and 63.2% (95% CI: 56%, 70.4%) at 24 weeks.

Subgroup analysis

Due to the high heterogeneity, we performed subgroup analyses on the effects of transplantation route and stem cell type on liver function at 24 weeks after the date of operation. First, we separated the studies in the eligible publications into five categories based on transplantation routes. There were five studies based on the use of the hepatic artery, three on the use of the portal vein, one based on the splenic artery, one based on peripheral blood, and three based on the peripheral vein, while two studies did not specify the transplantation route. The ALB levels in transplantations through the hepatic artery route were significantly increased compared with those transplanted by routes apart from the portal vein. The pooled WMDs for the hepatic artery and peripheral vein were 3.36 (95% CI: 1.66, 5.06) and 0.46 (95% CI: 34, 0.58), respectively (Figure 1a). For ALT levels, there was no significant difference among the different transplantation routes; the pooled WMDs for the hepatic artery and portal vein were −33.51 (95% CI: −60.62, −6.39) and −11.33 (95% CI: −25.00, 2.34), respectively (Figure 2a). The AST levels in transplantations through the hepatic artery were significantly lower than those in transplantations through the portal and peripheral veins, but there was no difference for transplantations through the portal and peripheral veins, as shown in Figure 3a. TBIL levels in transplantations through the hepatic artery were significantly lower than those in transplantations through the peripheral vein; the pooled WMDs were −3.67 (95% CI: −5.67, −1.66) and −0.43 (95% CI: −0.75, −0.11), respectively (p<0.05) (Figure 4a). PTs were not significantly different among the various routes (Figure 5a). Generally, the clinical outcome of transplantation through the hepatic artery was superior to that through the other routes. Further, we separated the trials into two categories according to stem cell type. The first category included six studies related to HSCs. The second category in-

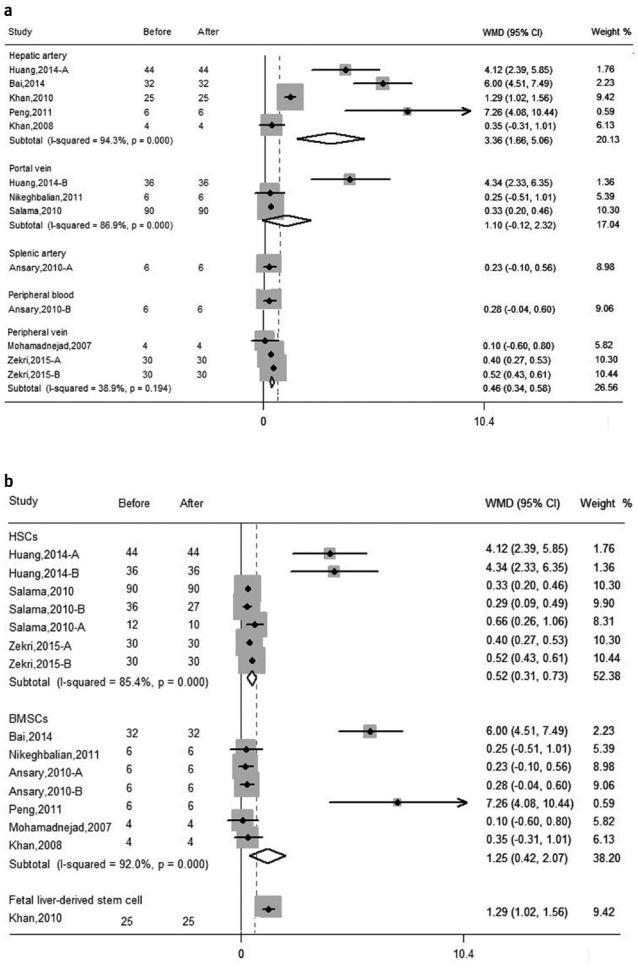

Figure 1. a, b. Upper (a) and lower (b) subgroup analyses of ALB levels at 24 weeks after transplantation with different stem cell types images show. Different stem cell types (a), transplantation by various routes (b). Before, the number of patients before transplantation; after, the number of patients after transplantation.

Review

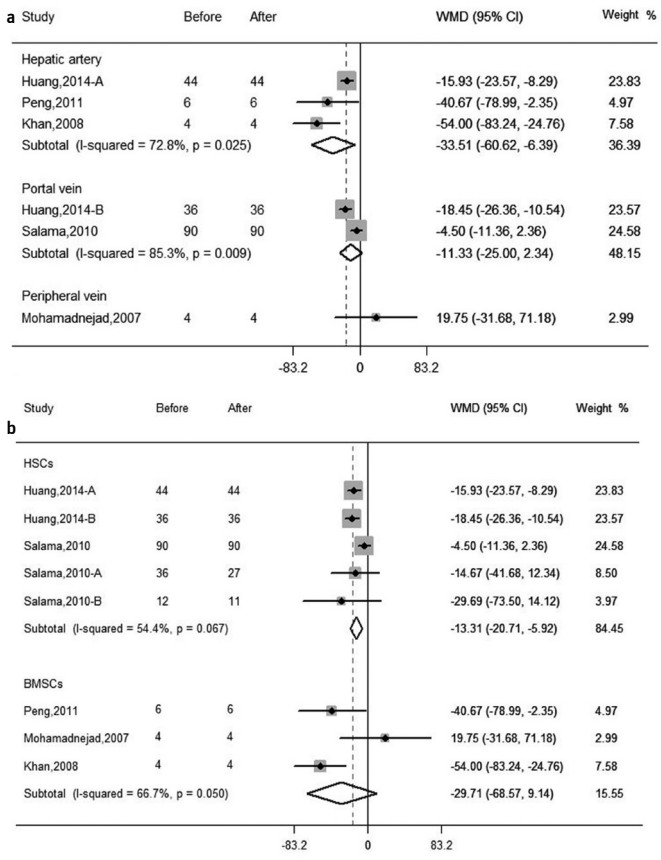

Figure 2. a, b. Upper (a) and lower (b) subgroup analyses of ALB levels at 24 weeks after transplantation with different stem cell types images show. Different stem cell types (a), transplantation by various routes (b). Before, the number of patients before transplantation; after, the number of patients after transplantation.

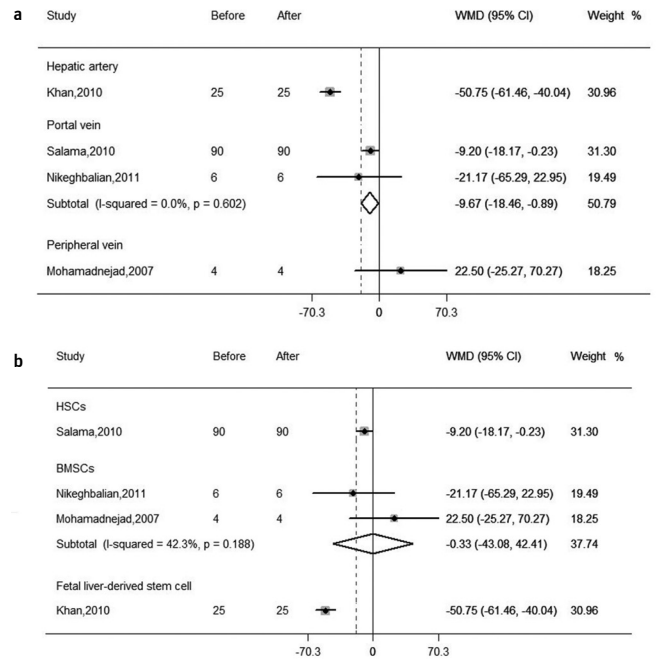

Figure 3. a, b. Upper (a) and lower (b) subgroup analyses of AST levels at 24 weeks after transplantation images show. Different stem cell types (a), transplantation by various routes (b). Before, the number of patients before transplantation; after, the number of patients after transplantation.

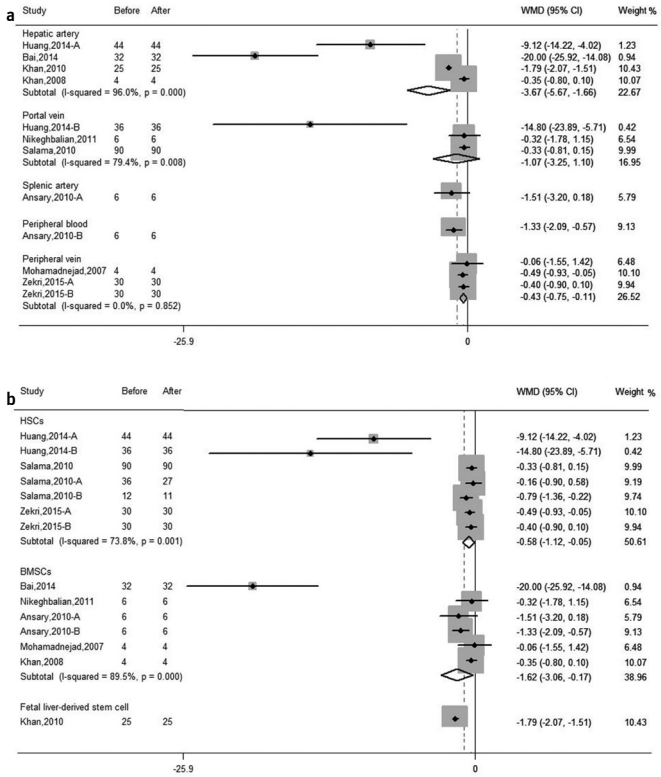

Figure 4. a, b. Upper (a) and lower (b) subgroup analyses of TBIL levels at 24 weeks after transplantation images show. Different stem cell types (a), transplantation by various routes (b). Before, the number of patients before transplantation; after, the number of patients after transplantation.

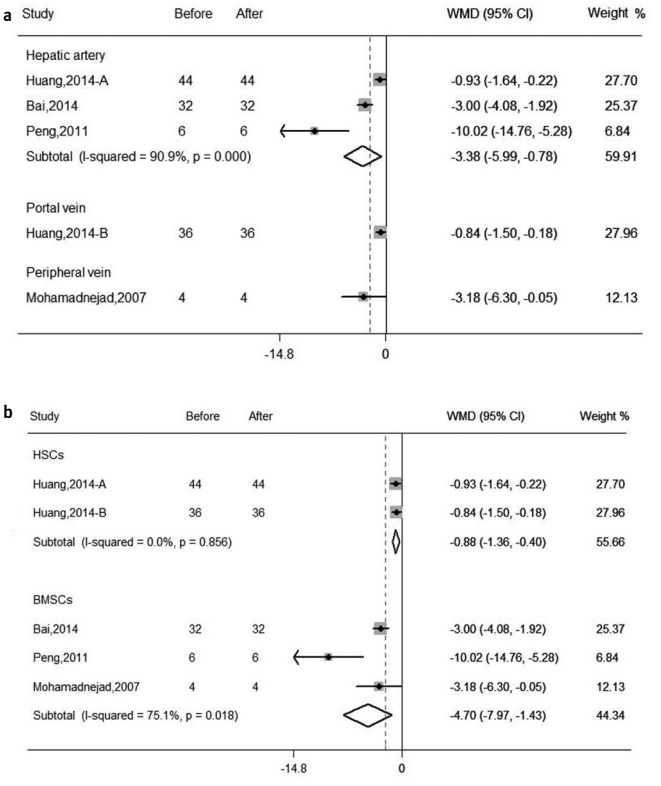

Figure 5. a, b. Upper (a) and lower (b) subgroup analyses of PT at 24 weeks after transplantation images show. Different stem cell types (a), transplantation by various routes (b). Before, the number of patients before transplantation; after, the number of patients after transplantation.

cluded eight studies involving BMSCs. In publications dealing with HSCs for ALB levels, the pooled WMD at 24 weeks after transplantation was 0.52 (95% CI: 0.31, 0.73); in publications involving BMSCs, the pooled WMD was 1.25 (95% CI: 0.42, 2.07); the ALB levels in transplantations with BMSCs were higher than those in transplantations with HSCs, although the difference was not significant as determined by meta-regression (p>0.05) (Figure. 1B). For the ALT levels, the pooled WMDs for HSCs and BMSCs were −13.31 (95% CI: −20.71, −5.92) and −29.71 (95% CI: −68.57, 9.14), respectively (p>0.05) (Figure 2b). For AST levels, the pooled WMD for BMSCs was −0.33 (95% CI: −43.08, 42.41); the AST levels in transplantations with fetal liver-derived stem cells was higher those in transplantations with HSCs. There was no difference between HSCs and BMSCs (Figure 3b). For TBIL levels, the pooled WMDs for HSCs and BMSCs were −0.58 (95% CI: −1.12, −0.05) and −1.62 (95% CI: −3.06, −0.17), respectively; the TBIL levels in transplantations with fetal liver-derived stem cells was higher than those in transplantations with HSCs. There was no also difference between HSCs and BMSCs (Figure 4b). However, there was a significant difference in PT; the pooled WMDs for HSCs and BMSCs were −0.88 (95% CI: −1.36, −0.40) and −4.70 (95% CI: −7.97, −1.43), respectively (Figure 5b).

Publications bias

Funnel plots indicated that three meta-analyses showed publication bias, including ALB levels at 12, 24, and 48 weeks after transplantation and TBIL levels at 4 weeks after transplantation. Trim and fill methods were used to adjust the pooled WMD for the three analyses with publication bias. The results showed that adjusted pooled WMD at 12 weeks after transplantation for ALB levels was 0.55 (95% CI: 0.23, 0.87); the difference was significant even after transplantation (p<0.05). The adjusted pooled WMD at 24 weeks after transplantation for ALB levels was 0.59 (95% CI: 0.30, 0.88; p<0.05). The adjusted pooled WMD at 48 weeks after transplantation for ALB levels was 0.75 (95% CI: 0.17, 1.34) (p<0.05). The adjusted pooled WMD for TBIL levels at 4 weeks after transplantation was −1.19 (95% CI: −2.21, −0.17, p<0.05). The adjusted pooled WMD for TBIL levels at 12 weeks after transplantation was −1.17 (95% CI: −2.08, −0.27; p<0.05).

DISCUSSION

The present meta-analysis aimed to evaluate the effect of stem cell transplantation on clinical outcomes and biochemical functions in patients with liver disease. Stem cell transplantation improved major indices of hepatic function, including PT and serum ALB, ALT, AST, and TBIL levels. Notably, improvements in most measures were still evident at 48 weeks after transplantation, suggesting that transplanted cells are successful in establishing themselves in the liver and in maintaining function in a sustainable manner. Meanwhile, the MELD score notably declined at 24 weeks after transplantation, and a large proportion of patients experienced alleviate ascites. The results showed short- and long- outcomes of improved liver function after stem cell transplantation in patients with decompensated liver diseases.

In particular, we found a significant increase in ALB levels, while other liver function parameters were significantly decreased. Likewise, in the report by Terai et al. (30), there were nine patients with cirrhosis who underwent autologous bone marrow cell infusion from the peripheral vein at 24 weeks after infusion and who had significant improvements in the average serum albumin levels. By the infusion of autologous bone marrow mononuclear stem cells through the hepatic artery into patients with liver failure caused by hepatitis B, Peng et al. (18) concluded that ALB and TBIL levels, PTs, and MELD scores of patients in the transplantation group markedly improved from 2–3 weeks after transplantation, which was consistent with our results with respect to short-term efficacy.

The results obtained in the present study demonstrated that after stem cell transplantation, patients exhibited a marked clinical recovery and significant decrease in the MELD score. The present study also showed that ascites reduced over time, recovered in 52% of patients at week 8, in 64% at week 12, and in 66% at week 24. Compared our results to those of Pai et al. (19) and Terai et al. (30).

Because the hepatopetal blood flow of the venous system is considerably larger than that of the hepatic artery, there may be different results between the two ways to infuse stem cells into the liver. The current meta-analysis showed that injection via the hepatic artery was better than that via the peripheral vein in improving liver function; however, there was no difference between the hepatic artery and portal vein in improving liver function except for AST levels. Sun et al. (31) showed that the transplantation of stem cells by either the hepatic artery (87 patients) or portal vein (64 patients) leads to a similar increase in ALT, ALB, TBIL, BUN, and creatinine levels; PTA; and urine volume, which was consistent with the results of the current study. Wang et al. (32) showed that infusion through the portal vein was better due to a relatively lower percentage of adverse effects. In all the 17 publications that met the inclusion criteria of our study, there were four studies that divided the patients into treated and untreated groups. However, in the different groups, there were different conditions, such as medicines for the untreated group, type of stem cells, and route of transplantation. It is hardly to make a comparison in such a situation. The four studies however came to the same conclusion that those in the treated group treated have a significant improvement in liver function and clinical signs than those in the untreated group.

Liver function significantly improved after the infusion of HSCs or BMSCs, and there were no significant differences between the two stem cell types. BMSCs and HSCs have been extensively studied as alternatives to hepatocyte transplantation for the treatment of liver diseases (8). Despite the wide application of HSCs and BMSCs in clinical practice, there are still many issues that need to be resolved, such as the fact that different sources of stem cells exist, besides those obtained from the

bone marrow (umbilical cord Wharton's Jelly, adipose tissue). Specially, Khan et al. (19) showed that after the transplantation of fetal hepatic stem cells, patients demonstrated marked clinical recovery and a significant decline in the MELD score over time. The Canals of Herring to the adult liver and ductal plates of the fetal liver are the richest source of human fetal liver-derived hepatic stem cells in humans (8,33-35). The self-renewal capacity of HSCs was demonstrated by phenotypic stability after expansion for more than 150 population doublings in a serum-free, defined medium and with a doubling time of 36 h (36). Recently, several studies have indicated the ability of rapid proliferation and regeneration of liver cells derived from human fetal liver compared with the adult liver (37-40). Earlier work has shown that treatment for acute liver failure by human fetal hepatocytes is feasible (41). In the present study, we found that liver function more greatly improved by the infusion of human fetal liver-derived hepatic stem cells than by the infusion of HSCs with respect to the levels of ALB, AST and TBIL. However, there was no difference between human fetal liver-derived hepatic stem cells and BMSCs.

The current study showed that at various periods (weeks 4–48), the stem cell transplantation group showed a significant decrease in ALB levels and increase in ALT, AST, and TBIL levels and PT. Therefore, this study suggests that stem cell transplantation showed variable improvement in hepatic failure and liver function over time. Short- and long-term improvement of liver function was found following stem cell transplantation, supporting the hypothesis that stem cells are primarily concerned with the repair and regeneration of hepatic tissue. The exact mechanism underlying the efficacy of stem cell therapy is unknown. Stem cells stimulate hepatic regeneration (42). The regeneration of the liver following injury mainly depends on the proliferation of mature parenchymal cells. For recovery, the capacity of parenchymal cells is limited; an external supply to replenish the reserves is inevitable (43). Stem cells directly differentiate into parenchymal hepatocytes to compensate for the loss in cell numbers. They secrete protective factors that prevent the progressive apoptosis of functional cells (44). Moreover, stem cells may directly differentiate into myofibroblasts and promote fibrogenic processes in an injured liver. In addition, stem cell transplantation strengthens cell transfusion with parenchymal cells for recovery from liver cirrhosis (45). The safety of cell fusion is suspicious due to possible tumor formation. Stem cells are associated with the formation of scar and portal myofibroblast-mediated angiogenesis in the fibrotic liver (46). A previous study showed fewer hepatocyte-like cells; however, myofibroblast-like cells were observed in significant numbers (47).

In our previous mouse models, we demonstrated that bone marrow mononuclear cells and bone marrow mesenchymal stem cells improved liver function by targeting liver tissues induced by carbon tetrachloride toxicity (48). Additionally, transplanted stem cells transdifferentiated into early-stage hepatocyte-like cells. The combined use of hepatocyte growth factor (HGF) administration and stem cell transplantation enhances therapeutic effects in an animal model (49). Studies on other types of stem cells await further confirmation. Medical therapies including antivirals, treating the complications, and supportive care combined with stem cell transplantation against liver failure need to be explored.

There are some limitations in this study. The publications included in this meta-analysis may not be comprehensive enough to cover all related references. In the current meta-analysis, it was impossible to regulate or stratify potential confounders. Important confounding factors include age (associated with the functional activity of stem cells) and the severity of clinical complications (50). Furthermore, we pooled different routes of stem cell injection and stem cell types in addition to different liver diseases reported in the publications, contributing to a high heterogeneity degree. Heterogeneity was observed among studies owing to the difficulty in matching patient characteristics in all studies. In addition, it was impossible to conduct all subgroup analyses according to the injection route and stem cell type. Thus, we only selected week 24 for the subgroup analysis. A meta-analysis has the inherent weakness of combining heterogeneous data sets. Although the random-effects model was used, it may not have completely eliminated the effect of heterogeneity. Still more information is needed for a complete analysis of the provided trials such as the number of cells used, their assessed quality, if the cells used were freshly isolated and/or cryopreserved, and how many cell infusion sessions are required, which was not considered much in this current study. Additionally, from our included studies, we found that there almost no information on therapeutic medications or supportive treatment.

In conclusion, our meta-analysis verified that there are clinical and biochemical improvements in patients who suffered from liver disease after stem cell transplantation. However, the specific route of stem cell injection and stem cell type need to be studied further to evaluate the clinical advantages of stem cell transplantation. It is important to track the fate of transfused stem cells *in vivo*. Additional research is needed to study hematopoietic stem cells and umbilical cord blood stem cells induced to differentiate into liver cells and the injection route of transplanted cells. If these challenges are addressed, the clinical application of stem cell-based therapy could be a reality in patients with liver diseases.

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