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Peripheral Blood Stem Cell Transplantation Improves Liver Functional Reserve

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Background: Currently available treatment options for decompensated hepatitis B-induced liver cirrhosis are limited and largely ineffective. Recently, stem cell transplantation has emerged as a promising treatment for cirrhosis. The aim of this study was to determine whether autologous peripheral blood stem cell transplantation can improve liver functional reserve in patients with hepatitis B-induced cirrhosis.

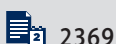
Material/Methods: In this study, 51 patients with hepatitis B-induced liver cirrhosis were assigned to the treatment group ($n=23$) or the control group ($n=28$). The treatment group underwent autologous peripheral blood stem cell transplantation in addition to comprehensive medical treatment, and the control group received comprehensive medical treatment alone. Liver functional reserve was monitored for 48 weeks after autologous peripheral blood stem cell transplantation.

Results: After transplantation, most patients showed improvements in symptoms such as fatigue, anorexia, and abdominal distension. The retention rate of indocyanine green at 15 minutes, a common indicator of liver functional reserve, declined from 41.99 ± 4.68 at baseline to 37.79 ± 3.75 by 48 weeks after transplantation, showing significant improvement.

Conclusions: Autologous peripheral blood stem cell transplantation can improve several markers of liver health and liver functional reserve and is a promising prospect for clinical application.

MeSH Keywords: **Adult Stem Cells • Liver Abscess • Liver Cirrhosis**

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Background

Currently available treatment options for decompensated hepatitis B-induced liver cirrhosis are limited and largely ineffective. Although liver transplantation is the standard treatment for this condition, its clinical application is restricted due to donor shortages and high medical costs [1]. As an alternative to liver transplantation, stem cell transplantation has emerged as a promising treatment for cirrhosis. This option has been gaining support in the clinic because autologous stem cells are readily available, acquired at low cost, and pose a mild risk of rejection. To date, bone marrow mesenchymal stem cells, hematopoietic stem cells, and umbilical cord blood stem cells have been used for transplantation. Many studies have focused on the regulation of stem cell differentiation, mechanisms of fibrosis, and stem cell homing to the impaired liver. However, few large-scale, controlled studies of patient outcomes have been conducted [2,3]. Some studies have reported that stem cell transplantation may improve synthetic function in patients with cirrhosis [4,5], but no study has examined the impact of stem cell transplantation on liver functional reserve in cirrhotic patients.

A commonly used drug-based quantitative liver function test employing indocyanine green (ICG) determines the functional reserve of hepatic parenchymal cells by measuring the amount of ICG that is not metabolized in the liver but directly excreted into the intestine. ICG clearance rates depend primarily on the number of viable liver cells, blood flow rates, and functional biliary excretion. The retention rate of ICG at 15 minutes (ICG R15) is used as the measure of liver functional reserve [6,7]. In this study, we used autologous peripheral blood stem cell transplantation to treat patients with hepatitis B-induced decompensated cirrhosis. By measuring changes in liver functional reserve, we assessed whether this technique can improve clinical outcomes in patients with cirrhosis.

Material and Methods

Patient Information and study design

Fifty-one patients with hepatitis B-induced decompensated liver cirrhosis were enrolled in this study. Patients were hospitalized in the Department of Liver Disease of Ningbo No. 2 Hospital from July 2011 to April 2012. The study population included individuals from 18 to 65 years old. Diagnoses were established according to the Guidelines for the Prevention and Treatment of Viral Hepatitis (2000) [8], Guidelines for the Diagnosis and Treatment of Liver Failure (2006) [9], and Guidelines for the Prevention and Treatment of Chronic Hepatitis B [10]. The patients were classified as Child-Turcotte-Pugh (CTP) B and C grades, with HBV-DNA copies less than 1.0×10^3 . No patients

carried liver tumors, as shown by imaging, and no patients reported the use of plasma, albumin, or other blood products a month before enrollment. Patients were excluded from the study if they had end-stage liver cirrhosis with severe complications, unstable vital signs, severe infections at other sites, or heart, lung, or kidney failure.

Patients were divided into a stem cell transplantation group ($n=23$, 14 males) and a control group ($n=28$, 17 males). The control group received conventional medical treatment including anti-HBV nucleoside analogue, liver protection, jaundice treatment, and diuretic administration. Patients in the stem cell transplantation group received conventional medical treatment and autologous peripheral blood stem cell transplantation. Bone marrow stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF; Kirin, Japan), peripheral blood was collected, and stem cells were purified (COM.TEC blood cell separator, Fresenius Kabi AG, Germany). The ethics committee of Ningbo No. 2 Hospital approved the study and informed consent was obtained from all patients.

Liver functional reserve assay

Fasted patients were given a bolus injection of 0.5 mg/kg ICG (Shenyang Jishi Pharmaceutical Co., Ltd, China.) A photosensitive nose probe from a DDG-3300K analyzer (Nihon Kohden Corporation, Japan) was attached to the nose of the patients. ICG R15 concentration was determined with a pulsed dye concentration image analyzer.

Stem cell harvest and transplantation

Patients received subcutaneous injection of G-CSF (5-10 $\mu\text{g}/\text{kg}$, QD) for 4 days before transplantation. Except for those with obesity or severe weight loss, patients were given 400 $\mu\text{g}/\text{d}$ of G-CSF. Stem cells were collected the day after the final injection. Venous blood was drawn from the left median cubital vein, and the blood was separated using centrifugation and a blood cell separator to isolate stem cells. The CD34⁺ cell count was determined using flow cytometry. Purified stem cells ($2-4 \times 10^7$) were administered to the hepatic artery via transfemoral catheterization within 2 hours of purification. Promoting hepatocyte growth factor was administered to both patient groups by intravenous drip, 120 mg QD. The first dose was given 1 day after transplantation and dosing was continued for 2 weeks.

Outcome measures

Both groups were monitored for 48 weeks for side effects, stem cell transplantation, ascites improvement, and tumor incidence. Changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined according to the performance rate method. The reactions were performed

Table 1. Baseline characteristics before transplantation.

| Group | No. of cases | Age (mean ±SD) | Sex (male) | Weight (kg) | Ascites (No. of cases) | CTP |
|-----------------------|--------------|----------------|------------|-------------|------------------------|-----------|
| Transplantation group | 23 | 51.52±10.30 | 14 | 58.22±11.95 | 17 | 8.43±1.04 |
| Control group | 28 | 50.82±7.98 | 17 | 61.25±14.81 | 18 | 8.07±1.36 |
| <i>P</i> | | 0.78 | 0.99 | 0.422 | 0.467 | 0.284 |

at 37°C and ALT and AST were detected at 340 nm. The equation $K \times$ (lowering speed of test tube/min), where $K=6105$ was used. Total bilirubin (Tbil) was measured using the vanadate oxidation method. Reactions were performed at 37°C and absorbances at 450 nm were determined before and after the reaction. Albumin (Alb) levels were measured with bromocresol green colorimetry. Bromocresol green colorimetry reacted with albumin to form a conjugate. Reactions were performed at 37°C and products were measured at 600 nm. ALT, AST, Tbil, and Alb were detected using a Beckman automatic biochemical analyzer (Beckman Coulter Inc., U.S.A). Prothrombin (PTA) activity was measured using the freezing method. Samples were kept at 37°C for 3 minutes. The reagents (PT reagent, tissue factor reagent, and buffer solution, stabilizer, preservative), 0.2 ml, were added to the sample, then the time to conglomeration was measured (Sysmex CA 1500, Sysmex Corporation, Japan). Values were recorded at baseline (week 0) and 4, 12, 24, 36, and 48 weeks after transplantation. ICG R15 was determined at baseline and 12, 24, 36, and 48 weeks after transplantation.

Statistical analyses

EPI DATA software was used for data entry and verification, and the SPSS 13.0 software package was used for data processing. Comparisons between groups were conducted using the Mann-Whitney U test. The Wilcoxon test was used to compare data before and after reinfusion. Repeated measurement data were analyzed using repeated measures analysis of variance. Time point data were compared using the t test. *P*-values less than 0.05 were considered statistically significant.

Results

General information

The transplantation group consisted of 14 males and 9 females, and the control group included 17 males and 11 females. The average age was 51.52±10.30 years in the transplantation group and 50.82±7.98 years in the control group. The number of patients with ascites at baseline (week 0) was 17 in the transplantation group and 18 in the control group. There were no statistical differences in CTP scores before transplantation between the two groups (Table 1). In the transplantation group

at 48 weeks, ascites resolved in nine patients and the amount of ascites decreased in eight patients. In the control group at 48 weeks, ascites resolved in seven patients, decreased in eight patients, and showed no changes in three patients. In the transplantation group, the CTP score at 48 weeks was 8.04±1.15, which was significantly different from the score at baseline (*P*=0.036) but not from the scores at weeks 12, 24, and 36. In the control group, the CTP score at 48 weeks was 7.93±1.05, which did not differ significantly from the score at baseline (*P*=0.547). Except for self-limiting temperature rises that developed 2 days after transplantation in 2 patients, no other adverse reactions were noted. Ultrasound did not reveal any liver tumor development after transplantation.

Comparisons of ALT, AST, Tbil, Alb, and PTA levels and ICG R15 before and after transplantation

Before transplantation, the concentrations of all biochemical markers (ALT, AST, Tbil, Alb, PTA, and ICG R15) were similar between the groups (Tables 2–6, Supplementary Table 1). The concentrations of ALT, AST, and Tbil did not change due to transplantation, and the control and transplantation groups remained similar (*P*>0.05) (Tables 2, 3, Supplementary Table 1). In contrast, Alb, PTA, and ICG R15 concentrations did improve in the transplantation group at 24, 36, and 48 weeks relative to baseline and the 12-week time point.

As summarized in Table 4, there were no significant differences in Alb levels within the control group at different time points, whereas the Alb levels increased over time within the transplantation group. In the transplantation group, the Alb level at baseline did not differ from week 12, but the Alb level at 24 weeks was significantly higher than at baseline. Similarly, the Alb levels at 36 and 48 weeks were significantly higher than those recorded at both baseline and 12 weeks. The Alb levels in the transplantation group at weeks 0 and 12 were not different from those in the control group. However, the Alb levels in the transplantation group at 24, 36 and 48 weeks were significantly different from the same time points in the control group.

Table 5 summarizes PTA measurements. There were no differences in PTA levels within the control group, and PTA increased over time in the transplantation group. Specifically,

Table 2. TBIL measurements (μmol/L).

| Group | Time | | | | | F | P |
|-----------------------|-------------|-------------|-------------|-------------|-------------|-------|-------|
| | Week 0 | Week 12 | Week 24 | Week 36 | Week 48 | | |
| Transplantation group | 56.88±42.18 | 57.39±36.83 | 57.48±33.48 | 55.87±33.77 | 55.18±37.32 | 0.07* | 0.97* |
| Control group | 56.99±28.72 | 54.40±26.16 | 55.35±37.36 | 56.31±26.82 | 54.13±30.25 | | |
| t | 0.01 | 0.33 | 0.21 | 0.06 | 0.11 | 0.05# | 0.98# |
| P | 0.99 | 0.75 | 0.83 | 0.95 | 0.91 | | |

* F and P values of main effect; # F and P values of the interaction effect; t values compare time points.

Table 3. ALT measurements (IU/L).

| Group | Time | | | | | F | P |
|-----------------------|-------------|-------------|-------------|-------------|-------------|-------|-------|
| | Week 0 | Week 12 | Week 24 | Week 36 | Week 48 | | |
| Transplantation group | 36.78±19.78 | 38.39±22.31 | 37.52±24.26 | 38.09±22.26 | 35.78±16.94 | 0.03* | 0.99* |
| Control group | 38.29±24.48 | 38.29±15.60 | 38.29±13.98 | 39.07±13.46 | 39.68±28.34 | | |
| t | 0.24 | 0.02 | 0.14 | 0.20 | 0.58 | 0.10# | 0.95# |
| P | 0.81 | 0.98 | 0.89 | 0.85 | 0.56 | | |

* F and P values of main effect; # F and P values of interaction effect.

Table 4. Alb measurements (g/L).

| Time | Transplantation group (mean ±SD) | Control group (mean ±SD) |
|---------|----------------------------------|--------------------------|
| Week 0 | 29.68±4.12 | 28.4±4.89 |
| Week 12 | 31.74±5.5 | 28.91±4.8 |
| Week 24 | 33.29±5.5 ^{a,e} | 28.46±3.88 |
| Week 36 | 34.22±4.32 ^{b,c,f} | 30.25±3.87 |
| Week 48 | 34.67±4.69 ^{b,d,f} | 30.88±4.51 |

^a P<0.05; ^b P<0.01 vs. week 0; ^c P<0.05; ^d P<0.01 vs. week 12; ^e P<0.05; ^f P<0.01 at different time points between the two groups.

Table 5. PTA measurements (%).

| Time | Transplantation group (mean ±SD) | Control group (mean ±SD) |
|---------|----------------------------------|--------------------------|
| Week 0 | 0.5±0.07 | 0.47±0.08 |
| Week 12 | 0.53±0.09 | 0.48±0.08 |
| Week 24 | 0.56±0.09 ^{a,f} | 0.48±0.07 |
| Week 36 | 0.57±0.07 ^{b,c,e} | 0.52±0.07 |
| Week 48 | 0.58±0.08 ^{b,d,e} | 0.53±0.08 |

^a P<0.05; ^b P<0.01 vs. week 0; ^c P<0.05; ^d P<0.01 vs. week 12; ^e P<0.05; ^f P<0.01 at different time points between the two groups.

PTA at weeks 0 and 12 were similar. The PTA level recorded at 24 weeks was significantly higher than baseline. Similarly, PTA measurements at 36 and 48 weeks were significantly higher

compared to weeks 0 or 12. PTA levels in the transplantation group at weeks 0 and 12 were not significantly different from those of the control group. However, PTA levels in the

Table 6. ICG R15 measurements (%).

| Time | Transplantation group (mean ±SD) | Control group (mean ±SD) |
|---------|----------------------------------|--------------------------|
| Week 0 | 41.99±4.68 | 42.11±5.57 |
| Week 12 | 41.13±6.00 | 41.4±5.41 |
| Week 24 | 38.87±4.01 ^{a,c} | 41.89±4.36 |
| Week 36 | 38.69±3.81 ^{a,c} | 41.11±4.45 |
| Week 48 | 37.79±3.75 ^{b,d} | 40.77±4.18 |

^a $P < 0.05$; ^b $P < 0.01$ vs. week 0; ^c $P < 0.05$; ^d $P < 0.01$ at different time points between the two groups.

Supplementary Table 1. AST measurements (IU/L).

| Group | Time | | | | | F | P |
|-----------------------|-------------|-------------|-------------|-------------|-------------|-------|-------|
| | Week 0 | Week 12 | Week 24 | Week 36 | Week 48 | | |
| Transplantation group | 66.00±39.48 | 66.43±53.49 | 66.70±74.06 | 66.57±43.96 | 67.26±24.44 | 0.01* | 1.00* |
| Control group | 66.75±29.26 | 67.54±26.54 | 67.75±28.60 | 67.89±27.74 | 66.57±26.68 | | |
| <i>t</i> | 0.08 | 0.10 | 0.07 | 0.12 | 0.10 | 0.01# | 0.99# |
| <i>P</i> | 0.94 | 0.92 | 0.95 | 0.90 | 0.92 | | |

* F and P values of main effect; # F and P values of interaction effect.

transplantation group at 24, 36, and 48 weeks were significantly different from levels in the control group.

Table 6 summarizes the ICG R15 measurements. Similar to the Alb and PTA measurements, there were no differences in ICG R15 levels within the control group at different time points. ICG R15 decreased over time in the transplantation group, showing significant decreases between weeks 0 and 48. ICG R15 in the transplantation group at week 0 and 12 were not significantly different from those of the control group; however, ICG R15 measurements in the transplantation group at 24, 36 and 48 weeks were significantly different from those of the control group.

Discussion

In this study, we examined the effects of peripheral blood-derived stem cell transplantation on liver function in patients with hepatitis B-induced cirrhosis. Our results showed that stem cell transplantation improved liver functional reserve, suggesting that this technique may be used to increase liver function in the clinic.

In recent years, rapid progress has been made in the use of stem cells to treat various diseases, including those of the liver [11]. Stem cell transplantation is commonly used in cirrhosis,

and recent research has partially revealed the mechanisms by which stem cells improve cirrhosis. Following transplantation, stem cells increase serum albumin levels and promote high expression of matrix metalloproteinases. Both effects combine to facilitate extracellular matrix degradation, upregulate apoptotic factors, inhibit stellate cells via paracrine activity, induce hepatic stellate cell apoptosis, suppress type I collagen gene expression in the liver, and reduce the concentration of serum hydroxyproline. Previous studies have shown that stem cell transplantation also reduces fibrin deposition in the liver, alleviates liver fibrosis, and improves liver function [3,12,13]. In addition, Theise and Oh et al. [14,15] showed that stem cells can home to the damaged liver.

Liver functional reserve is a measurement of the functional capacity of liver cells, reflecting the number of living liver cells and liver blood flow. Liver functional reserve decreases as complications and severity of cirrhosis increases [16]. Liver functional reserve is a particularly meaningful indicator for surgical liver resection [17], as it is directly associated with treatment outcomes and is a useful predictor of patient survival, the need for liver transplantation, and liver function before surgery.

A commonly used assay for determining liver functional reserve is the ICG clearance test. In healthy subjects, serum ICG R15 ranges from 0% to 10%. In contrast, ICG R15 is often 15% to 20% in patients with chronic hepatitis and 35% in those with cirrhosis. A higher ICG R15 value suggests decreased liver

functional reserve. Elevated ICG R15 is also independently correlated with the development of liver failure after liver resection [18]. Some studies suggest that ICG R15 levels are more accurate than CTP scores in the assessment of liver functional reserve [19]. Increased ICG R15 levels are also positively correlated with portal vein pressure and liver fibrosis. Therefore, ICG R15 measurements are important for the assessment of liver function [20]. Studies have shown that ICG clearance tests are simple, convenient, and sensitive indicators of the presence of hepatic dysfunction in patients with liver resection or liver transplantation, as well as in critically ill patients [6].

In the present study, Alb levels increased by 2 g/L on average 12 weeks after transplantation and exhibited significant improvement at 24 weeks compared with the control group. This result is consistent with the findings of other similar studies on stem cell transplantation in the treatment of cirrhosis [2]. Liver functional reserve showed significant improvement starting from 24 weeks, suggesting that autologous peripheral blood stem cells may enhance both Alb levels and liver functional reserve. However, the improvement in liver functional reserve did not occur until late in treatment. This finding may be explained by the presence of underlying liver cirrhosis, which leads to prolonged degradation of the extracellular matrix. The slow response of the liver functional reserve measurements to stem cell transplantation suggests that the improvement in

liver functional reserve is not only a direct result of stem cells, but also may be closely related to various immunoregulatory events that occur after stem cell transplantation.

Conclusions

We speculate that the improvement in liver functional reserve after stem cell transplantation may be closely associated with the differentiation of stem cells into liver cells, the fusion of stem cells with damaged liver cells, the regeneration of endogenous liver cells by paracrine activity, stem cell immunomodulation, and anti-fibrotic pathways [21,22]. However, it remains unknown which mechanism plays a major role in improving liver function after stem cell transplantation.

Taken together, our results show that stem cell transplantation can restore liver functional reserve. Further studies over extended periods are needed to determine whether the benefits are persistent in the long-term.

Declaration of conflicts of interest

The author(s) declare no potential conflicts of interest related to the manuscript, including financial, consultant, institutional, or other relationships.

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