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Original Article

Intravenous Administration is the Best Route of Mesenchymal Stem Cells Migration in Improving Liver Function Enzyme of Acute Liver Failure

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Abstract

Background: Mesenchymal stem cells (MSCs) migrate and transmigrate to acute liver failure (ALF) area due to vascular endothelial growth factor (VEGF) stimulation as an attractant molecule then actively giving the paracrine signaling and or differentiating into primary hepatocytes, however the best route of MSCs transplanted to liver injury area remains unclear.

Aim: In this study we compare intravenous (IV) and intraperitoneal (IP) route of MSCs administration by analyzing serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT) and bilirubin level as improvement markers of liver function and VEGF as attractant-proliferation molecule on days 2 and 5.

Materials and methods: Eighteen male Sprague-Dawley rats weighting 200 g were used in this study. They were divided in three study groups: vehicle control, IP and IV groups. The IV group was treated by MSCs at dose 1×10^6 by lateral tail vein injection and IP group received 1×10^6 MSCs via IP injection. The level of SGPT, SGOT and bilirubin were measured by an automatic analyzer, the VEGF level using enzyme-linked immunosorbent assay (ELISA), while the CD73 expression was evaluated using immunohistochemistry.

Results: This study showed that IV injection of MSCs was more efficient for increasing liver function than IP treatment group that confirmed by the observed significant decrease in SGPT, SGOT and bilirubin level on days 2 and 5 ($p<0.001$). This effect was most likely mediated by the significant increase of VEGF level ($p<0.05$) on days 2 and 5.

Conclusion: Our result conclude that an IV administration of MSCs was more efficacious than the IP administration for liver injury regeneration.

Keywords

acute liver failure, intravenous, intraperitoneal, mesenchymal stem cells, vascular endothelial growth factor

INTRODUCTION

Acute liver failure (ALF) is a life-threatening disease, characterized by massive hepatic necrosis of multiple lobes or acini and the infiltration of inflammatory cells, without pre-existing liver disease.[1] The excessive inflammation and massive hepatocyte necrosis associated with ALF result in the sudden loss of liver function and multiple organ failure, which can lead to a high mortality rate.[2] A previous study reported that liver tissue has the enormous regenerative potential to restore hepatocytes, even after most hepatocytes are completely lost[3], through the activation of liver progenitor cell (LPC)-mediated regeneration, which can be derived from endogenous progenitor cells or bone marrow-derived circulating cells, particularly mesenchymal stem cells (MSCs).[4] These findings suggested that MSCs play a role as an alternative cell source for the replacement of primary hepatocytes, in addition to immunoregulatory functions. Therefore, MSC transplantation could represent a promising strategy for liver regeneration during ALF.[5] However, the best route for the delivery of MSCs to liver injuries remains unclear.

MSCs are adult stem cells that are widely defined as plastic-adherent stromal cells, with multipotent differentiation capacity. MSCs naturally express various surface marker proteins, including CD73, CD90, CD105, CD44, and CD29, and lack the expression of other surface marker proteins, including CD45, CD34, CD14, CD11b, CD79a, CD19, and human leukocyte antigen (HLA) class II. Under standard in-vitro differentiation conditions, MSCs are able to differentiate into chondrocytes, osteocytes, adipocytes[6], and hepatocytes[7]. MSCs also have immunosuppressive properties, inhibiting the release of pro-inflammatory cytokines from several inflammatory cells, resulting in the transition into the proliferative phase.[8] Improved liver function is characterized by decreased levels of biochemical markers, such as bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT).[9]

Several studies have demonstrated that the intravenous (IV) delivery of MSCs may accelerate their homing to injury sites, including ALF areas, due to their immune-cell-like properties, which are also referred to as leukocyte-like.[10,11] Under certain stimulation conditions, such as in the presence of stromal-derived factor (SDF-1), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), MSCs may migrate and then transmigrate over the endothelial barrier to reach the target area.[12] Other studies have indicated that VEGF appears to be particularly important in enhancing and directing MSC motility because CD44, an MSC marker protein, can also act as a co-receptor for VEGFR-2.[13] Although IV injection is the most common technique used for the administration of MSCs for ALF treatments[14], this method has several limitations, particularly the pulmonary "first-pass" effects that can cause the entrapment of cells in the lungs[15]. Another study showed the opposite results, demonstrating that intraperitoneal (IP) administration was preferable to IV administration for the delivery of MSCs to the injury site. The IP technique provides a nutrient-rich and hemodynamically stable environment for isolated cells, including MSCs.[16] These conflicting results indicate that the optimal route for MSCs administration to ensure their migration to the liver injury area remains unclear. The aim of this study was to determine the best route for the administration of MSCs for ALF treatments by analyzing serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and bilirubin levels, as serum markers of liver recovery, and VEGF levels, to represent homing molecules, both before and after the IP and IV administration of MSCs.

MATERIALS AND METHODS

MSC isolation

An umbilical cord was obtained from a healthy, 19-day pregnant rat (Sprague-Dawley), under deep anesthesia. After the blood vessel was removed, the umbilical cord was cut into pieces and transferred to a T25 culture flask, containing complete growth medium, which consists of Dulbecco's modified Eagle medium (DMEM, Sigma-Aldrich, Louis St, MO), containing 10% fetal bovine serum (FBS, Gibco™ Invitrogen, NY, USA) and 100 IU/ml penicillin/streptomycin. The cells were incubated in a humidified atmosphere, containing 5% CO2, at 37°C. The medium was changed every 3 days. When cells reached 80% confluence, the MSCs were passaged. Cells in their fourth passage were used for the following experiments.

ALF animal model

Eighteen male Sprague-Dawley (SD) rats, weighing 200 g, were housed in individually ventilated cages, with constant temperature (22 ± 2°C), 60% relative humidity, and a 12:12-hour light-dark cycle. Starting at 5 weeks old, rats were fed with standard food. To establish an animal model of ALF, all rats were induced by the IP injection of 0.1 mL/kg carbon tetrachloride (CCl4, Sigma- Aldrich, Louis St, MO), dissolved in olive oil (1:1), 2 times per week, for 2 weeks.

Flow cytometric immunophenotyping of MSCs

To confirm the identity of MSCs, these cells were analyzed by flow at the fourth passage. Cell suspensions were incubated with fluorescein isothiocyanate (FITC)-conjugated, Allophycocyanin (APC)-conjugated, peridinin chlorophyll protein (PerCP)-Cy5.5-conjugated, and phycoerythrin (PE)-conjugated monoclonal antibodies, including antibodies against CD90, CD73, CD105, and Lin, for 30 min, at 4°C, in the dark. The analysis was performed using a BD

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PharmingenTM flow cytometer (BD Bioscience, Franklin Lakes, NJ, USA).

In vitro differentiation

We further performed an osteogenic differentiation assay at the fourth passage, to characterize the isolated cells. The MSCs were cultured in osteogenic induction medium, containing 50 µM/L ascorbate-2-phosphate, 10 mM/L β glycerophosphate, 10-7 mol/L/0.1 µM dexamethasone (Sigma-Aldrich, Louis St, MO), and 10% FBS (Gibco™ Invitrogen, NY, USA) in DMEM (Sigma-Aldrich, Louis St, MO), at 37°C and 5% CO_2. To evaluate calcium deposition, the cells were fixed and stained with 0.2% Alizarin Red (Sigma-Aldrich Corp., St. Louis, MO, USA) (21 days).

MSC administration

Experimental rats were randomly assigned into two groups. The first group (n = 6) received 1×10^6 MSCs in 1 ml NaCl by lateral tail vein injection (IV). The second group (n = 6) received 1×10^6 MSC in 1 ml NaCl by IP injection (IP).

Liver functional enzyme assay

SGOT, SGPT, and bilirubin were measured to determine liver function on days 0 (pre-treatment), 2, and 5. Blood samples were collected from the peri-orbital vein under anesthesia, using xylazine + ketamine (5 mg/kg + 100 mg/kg intramuscularly) (Alfasan, Netherlands). Serum levels of SGOT, SGPT, and bilirubin were measured using an automatic analyzer (BT 3000 PLUS, Italy).

Enzyme-linked immunosorbent assay (ELISA)

The serum levels of VEGF in both groups were measured using ELISA, according to the manufacturer's protocols (Fine Test, Wuhan, China). Serum levels were measured on days 0 (pre-treatment), 2, and 5, according to standard curves constructed for each assay. The colorimetric absorbance was recorded at a wavelength of 450 nm.

MSC phenotyping in liver tissue

The expression of MSCs in liver tissue was evaluated using immunohistochemistry techniques to detect MSC-positive markers. The liver tissue of each animal was fixed in 10% formaldehyde, embedded with paraffin, sectioned, and deparaffinized. We incubated the cells with a primary antibody against CD73, an MSC marker protein, according to a previously described protocol, and then observed the stained tissue under a microscope.

Data Analysis

The data are presented as the mean ± standard deviation (SD). All calculations were performed using IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA). Significant differences between groups were assessed by two-way analysis of variance (ANOVA) and Tukey's post hoc test. P values: $*p< 0.05$, $**p < 0.001$.

RESULTS

Characteristics of MSCs

MSCs expressing specific markers were evaluated in Figure 1. The specific marker profiles for MSCs are CD73+, CD105+, CD90+, and Lin-, as described by the International Society of Cellular Therapy (ISCT). The results showed that UC-MSCs were 99.9% CD90+, 95.9% CD105+, 99.2% CD73+, and 2.0% Lin- **(Fig. 1)**.

MSC morphology and osteogenic differentiation

The capacity of MSCs for plastic attachment was determined under standard culture conditions, in DMEM, supplemented with 10% FBS, 1% antibiotic, and 0.25%

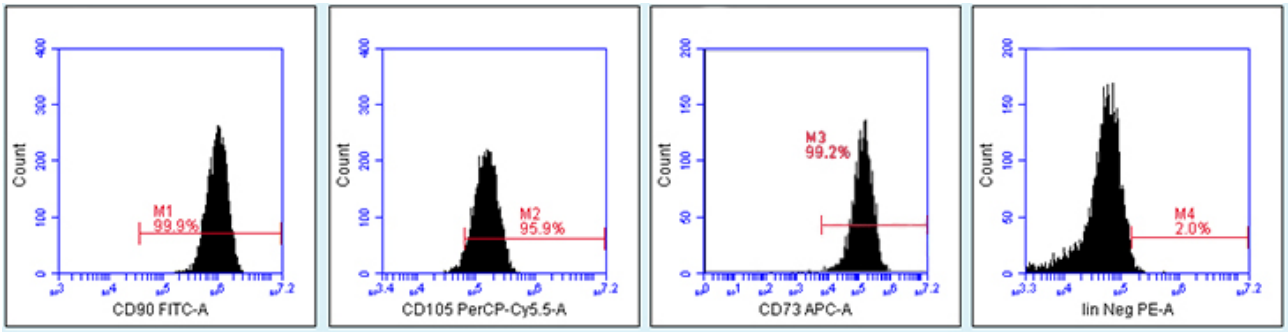
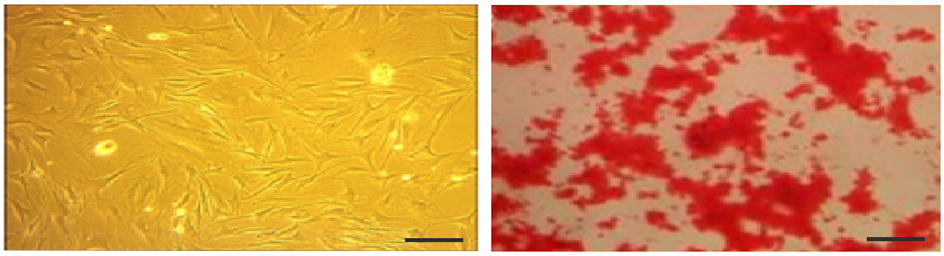


Figure 1. Flow cytometry characterization of UC-MSCs expressed CD90 (99.9%), CD105 (95.9%), CD73 (99.2%) and Lin (2.0%).

fungizone. Cells exhibited spindle shapes and polygonal characteristics **(Fig. 2a)**. Moreover, multilineage differentiation was achieved by culturing MSCs in osteogenic medium for 27 days **(Fig. 2b)**.

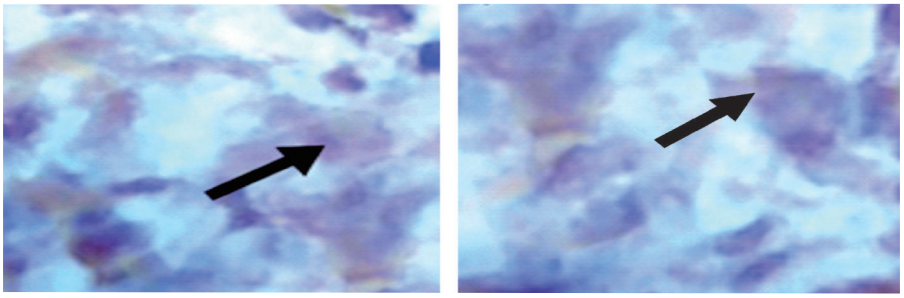


2a 2b

Figure 2. (a) In vitro culture of UC-MSC candidate showed spindle form of fibroblast-like cells, ×10 magnification, **(b)** and the osteogenic differentiation test with osteogenic medium appears red color in MSC population (Alizarin Red Staining).

MSC phenotyping in liver tissue

The presence of MSCs in liver tissue was evaluated by the MSCs-positive marker CD73 using immunohistochemistry techniques and appeared as a brown color in cells as below **(Fig. 3)**.



3a 3b

Figure 3. The expression of CD73 in liver tissue appeared as a brown color following (a) IV and (b) IP admninstration of MSCs, identified by an arrow.

Liver function enzymes

We measured the levels of SGPT, SGOT, and bilirubin on days 2 and 5, using an automatic analyzer. The levels of SGPT, SGOT, and bilirubin decreased significantly on days 2 ($P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively) and 5 ($P < 0.001$) following the injection of MSCs for all treatments of ALF rat models **(Fig. 4)**. On both days 2 and 5, the IV treatment showed the lowest levels of SGPT (87.80 µ/L and 52.40 µ/L, respectively) and SGOT (155.20 µ/L and 105.80 µ/L, respectively). The IV group was significantly more effective than the vehicle group ($P < 0.001$) with regards to the SGPT and SGOT levels. In addition, the IV group had a greater effect than the IP group on the SGPT level on day 5 and on the SGOT level on both days 2 and 5 ($P < 0.05$). No significant difference was observed among all treatments for bilirubin levels on days 2 and 5.

VEGF levels

We examined VEGF levels using ELISA. VEGF concentrations significantly increased ($p < 0.001$) on days 2 and 5 compared with pre-treatment levels, and a significant difference ($p < 0.001$) was observed in VEGF concentrations between rats administered with MSCs via the IV and IP routes **(Fig. 5).** The results showed that rats that received IV treatments had the highest VEGF levels on days 2 (110.11 pg/mL) and 5 (101.31 pg/mL). The VEGF levels were increased more effectively in the IV group than in the IP group ($P < 0.001$), on both days 2 and 5.

DISCUSSION

ALF is a devastating syndrome that results in the sudden loss of hepatic cells and/or cellular function, leading to organ failure and death.[17] The necrosis of liver cells during ALF is dramatic and progressive, and the time between the development of initial symptoms and death can be very short.[18] Thus, new treatment approaches that focus on liver regeneration would provide great clinical value.[19] To delineate the homing mechanisms of MSCs during the regener-

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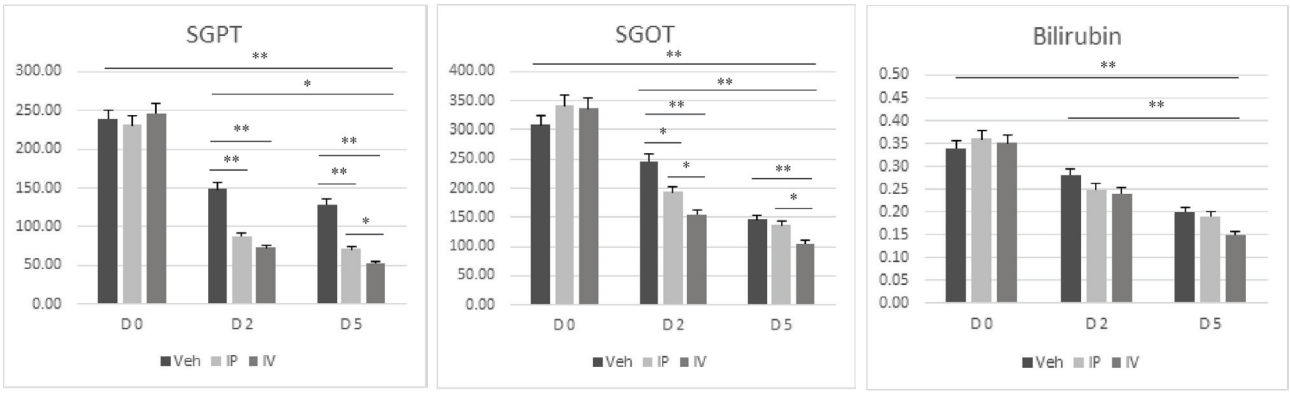

Figure 4. MSCs treatment decrease the level of (a) SGPT (b) SGOT and (c) bilirubin in all treatments. On day 2, the IV treatment showed the lowest level SGPT and SGOT (87.80 and 155.20 u/L) as well as on day 5 (52.40 and 105.80 u/L). * $p<0.05$, ** $p<0.001$.

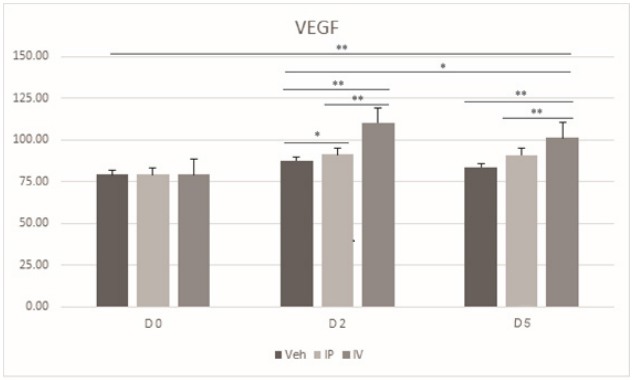

Figure 5. ELISA assay showed IV treatments have the highest VEGF level on days 2 and 5 (110.11 and 101.31 pg/mL), * $p<0.05$, ** $p<0.001$.

ation of liver injuries, animal models with CCL4-induced liver injuries have been used to imitate human ALF disease.[2,20] CCL4 was used in our study to induce ALF in a rat model, as described by previous protocols.[9] In this study, we injected MSCs into ALF rat models, through the IP and IV routes.

We found that the level of SGPT and SGOT on days 2 and 5 significantly decreased compared with those on day 0 (pre-treatment) for both treatment groups. We also found significant differences in the SGPT and SGOT levels between rats treated with IV and IP injections, and IV injections appeared to be more efficacious than IP injections, based on the expression of CD73, an MSC marker, in the liver tissue **(Fig. 3)**. This result was in line with the observed significant increase in VEGF levels on days 2 and 5. Our findings suggested that IV injections of MSCs are more efficient for ALF regenerative processes than the IP route and that the migration of MSCs to the liver injury correlated with VEGF levels. MSCs have the ability to control inflammation by suppressing activated inflammatory cells and accelerating the transition of inflammation to the proliferation phase.[21]

We hypothesize that MSCs administration by IV injection have the ability to migrate to injured areas more quickly than those administered through then IP route, due to the leukocyte-like properties of MSCs.[10,11] Injured cells release hypoxia-inducible factor (HIF)-1a, which acts as a stabilizer and activator molecule for the release of chemoattractant signals, such as SDF-1, hepatocyte growth factor (HGF), and VEGF.[22] MSCs respond to these chemoattractant signals by expressing CD44, which acts as an adhesion molecule for cell-cell and cell-substrate interactions, in addition to VLA-4, CXCR-4, and cMet.[23] Specifically, in MSCs, CD44 acts as a co-receptor for VEGFR-2[13] and activates the CD44-Src-integrin signaling axis[24]. These signals may initiate the homing of MSCs to injured areas by triggering CD44-VEGF and VLA-4-VCAM-1 binding in capillary endothelial cells, facilitating the transmigration to injured areas **(Fig. 6)**. MSCs in the injured area suppress the activation of resident inflammation cells, particularly activated macrophages, through the release of prostaglandin E2 (PGE2), TSG 6, interleukin (IL)-10, transforming growth factor (TGF)-β, and IL-1ra.[21,25] The regulation of the inflammatory process may result in the initiation of the regeneration phase, which is characterized by the increased expression of several proliferation molecules, such as VEGF and platelet-derived growth factor (PDGF).[26] VEGF levels correlated with the acceleration of liver function re-

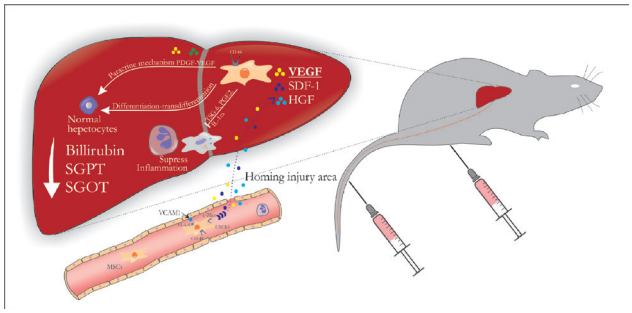

Figure 6. Schematic for MSCs homing in intravenous administration in rats.

pair, as characterized by the significant decreases in SGPT and SGOT levels.

The transplantation of MSCs through IV injections may also inhibit hepatocyte death and increase hepatocyte survival in the ALF rat model.[27] Another study showed increasing VEGF levels following the IV administration of MSCs to injured tissues, followed by improved angiogenesis, including vascular necrosis.[28] Our study showed that the administration of MSCs through IV injection was more efficacious than those administered through the IP route in ALF model rats. We hypothesize that MSCs respond to a homing mechanism that attracts them to injured areas, which corresponds with an increase in VEGF levels. However, in our studies, we did not analyze the concentrations of SDF-1, CXCR-4 or HGF, which may act as additional chemoattractant molecules during the homing process; thus, the detailed mechanism associated with the homing of MSCs to injured areas remains unclear.

CONCLUSION

In this study, we concluded that the IV administration of MSCs was more efficacious than the IP administration of MSCs for ALF treatment. This study provided new insight into the benefits of the IV administration of MSCs and encourages the clinical application of IV-injected MSCs for injured tissues, particularly ALF.

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Conflict of Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of this article.

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Внутривенное введение является лучшим путём для миграции мезенхимальных стволовых клеток для улучшения функции печени при острой печёночной недостаточности

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Абстракт

Введение: Мезенхимальные стволовые клетки мигрируют и трансмигрируют в область печёночной недостаточности, чтобы стимулировать сосудистый эндотелиальный фактор роста, каким является фактор аттрактантных молекул, а затем активно передают паракринную сигнализацию и / или дифференцируются в первичные гепатоциты. Однако лучший путь для трансплантации мезенхимальных стволовых клеток, трансплантированных для миграции в область печёночной недостаточности, остаётся невыясненным.

Цель: В этом исследовании мы сравниваем внутривенный и внутрибрюшинный пути введения мезенхимальных стволовых клеток с помощью анализа сывороточной глутаминовой пировиноградной трансаминазы, сывороточной глутамино-оксалоуксусной трансаминазы и билирубина в качестве маркеров улучшения функции печени и сосудистого эндотелиального фактора роста в качестве аттрактантной молекулы пролиферации в дни 2 и 5.

Материалы и методы: В этом исследовании использовали 18 самцов крыс Sprague-Dawley. Они были разделены на три группы: контрольную, внутрибрюшинного введения и внутривенного введения. Первой группе вводили 1 × 106 мезенхимальных стволовых клеток путём внутривенной инъекции в хвостовую вену, а второй группе вводили 1 × 106 мезенхимальных стволовых клеток путём внутрибрюшинной инъекции. Уровни сывороточной глутаминовой пировиноградной трансаминазы, сывороточной глутамино-оксалоуксусной трансаминазы и билирубина были измерены с использованием автоматического анализатора, в то время как уровень сосудистого эндотелиального фактора роста был исследован с помощью иммуноферментного анализа.

Результаты: Это исследование показало, что внутривенный путь был более эффективным, чем внутрибрюшинный, с улучшением функции печени, сопровождаемым значительным снижением сывороточной глутаминовой пировиноградной трансаминазы, сывороточной глутамино-оксалоуксусной трансаминазы и билирубина в дни 2 и 5 ($p < 0{,}001$). Этот эффект, скорее всего, был обусловлен значительным увеличением уровня сосудистого эндотелиального фактора роста ($p < 0{,}05$) в дни 2 и 5.

Выводы: Наши результаты показывают, что внутривенная инъекция является лучшим путём для восстановления функции печени.

Ключевые слова:

острая печёночная недостаточность, внутривенный, внутрибрюшинный, мезенхимальные стволовые клетки, сосудистый эндотелиальный фактор роста