Long-term therapeutic effect of liver transplantation in patients with hepatic myelopathy☆

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Abstract

BACKGROUND: Hepatic myelopathy results from liver disease, which lacks of effective cure method. Liver transplantation has attempted to cure this disease; however, the long-term therapeutic effect is rarely reported.

OBJECTIVE: To explore the long-term therapeutic effect of liver transplantation in patients with hepatic myelopathy.

METHODS: The clinical data of 2 patients with hepatic myelopathy, who underwent orthotopic liver transplantation, in August 2002 and November 2004, at the 309 Hospital of Chinese PLA, were analyzed retrospectively. The time of follow-up was 18 and 43 months, respectively. The muscle strength of double lower limbs in 2 patients was assessed prior to and after operation.

RESULTS AND CONCLUSION: Two patients recovered well at 4 weeks after transplantation, the clinical symptom and physical signs of patients were improved obviously, the blood routine examination and other biochemical index were normal, and the function of transplanted kidney was normal. Two patients discharged at 6 weeks after transplantation. Patient 1 could stand for a long time at months 6 after transplantation, walked slowly with the supporter after 12 months and without the supporter at 43 months. The muscular strength of two lower limbs was grade 4. And the liver function was normal. Patients 2 could move his lower limbs in bed at months 6 after transplantation, walked with the supporter at 18 months. The muscular strength of two lower limbs was grade 3. The liver function was normal. It demonstrated that liver transplantation is beneficial to control hepatic myelopathy and recover muscular strength of two lower limbs. It is a newly developed, effective curing method for treating hepatic myelopathy. However, the numbers were small with short time observation, thus, the long-term therapeutic effect still need to be explored.

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Received:2009-10-25
Accepted:2009-12-18
(20091123006/GW)

Du GS, Lu H, Shi BY, Song JY, Jin HL, Cai M, Qian YY, Zhu ZD. Long-term therapeutic effect of liver transplantation in patients with hepatic myelopathy Zhongguo Zuzhi Gongcheng Yanjiu yu Linchuang Kangfu. 2010;14(18): 3397-3400.

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INTRODUCTION

The hepatic myelopathy is a complication of brain-spinal lesion, characterized by spastic paraplegia of two lower limbs, and commonly appeared at advanced stage of liver diseases. Currently, there is no effective therapeutic method for this complication, and few reports addressing the treatment of liver transplantation on hepatic myelopathy. Two patients, with liver cirrhosis and hepatic myelopathy, who underwent orthotopic liver transplantation, in August 2002 and November 2004, at the 309 Hospital of Chinese PLA, were analyzed retrospectively. The follow-up time was 18 and 43 months respectively. The liver function and the spastic paraplegia of two lower limbs with the hepatic myelopathy were improved significantly.

CASE INFORMATION

Patient 1

A male, aged 38 years (Inpatient No. 212458). Disconnected hematemesis, melena, abdominal distension and tiredness for 7 years, the patient was diagnosed as “liver cirrhosis, upper gastrointestinal bleeding”. Since the senses disturbance was often occurred after bleeding, the “hepatic myelopathy” was diagnosed. The splenectomy had been undergone as “upper gastrointestinal bleeding” again in emergency prior to 7 years, and the patient had the two lower limbs tired, dyspraxia and walking difficulty, which were worse gradually, had to be stayed in bed as no-standing for above 20 days since 2 months ago.

Physical examination: hepatic face, light icterus, liver palm and spider angioma could be seen, and no the varicose vein in abdominal wall or the sign of ascites was found. Nervous system examination: muscular strength of two lower limbs was 0−1 grade and hypermyotonia, hyperreflexia in double knee and heel jerk, two ankles and hip clonus were appeared. The abdominal reflex was weakened. Deep and light senses were normal. Double Babinski’s signs were positive. Blood routine examination showed: white blood cell 1.6×10^9/L, red blood cell 2.17×10^{12}/L, hemoglobin 62 g/L, blood platelets count 138×10^9/L; blood biochemical examination: Na^+ 146 mmol/L, K^+ 4.2 mmol/L, Cl^+ 104.1 mmol/L, fasting blood glucose 5.03 mmol/L, alanine aminotransferase 703.5 nkat/L, aspartate aminotransferase 901.8 nkat/L, total bilirubin 37.9 μmol/L, direct bilirubin 29.1 μmol/L, total serum protein 60.1 g/L, albumin 38.8 g/L, blood urea nitrogen 3.27 mmol/L, creatinine 77.4 μmol/L. Coagulation function: prothrombin time 20.8 seconds, prothrombin activity 35.5%, activated partial thromboplastin time 33.9 seconds, lactic acid 2.73 mmol/L, blood ammimine 95 μmol/L. Ultrosonic and CT examination: Liver was atrophy, the spot echo maldistribution of parenchyma of liver was occurred. The nodular echo could be seen in the liver. The inner diameter of portal vein was 1.4 cm. There was dropsy in the abdominal cavity. The left-right lobes of the liver were not in proportion, the liver gap was widened. The liver became smaller, the liver’s density was not even, the liver capsula was nodular, and the spleen was not found. The admission diagnosis: liver cirrhosis (decompensate stage), and hepatitis B, as well as hepatic myelopathy.

Patient 2

A male, aged 53 years (Inpatient No. 226857). He was diagnosed as "hepatitis B and liver cirrohosis" in the local hospital before 2 years. The patient was treated due to progressive dyspraxia of two lower lambs before 10 months and diagnosed hepatic myelopathy in Beijing Xuanwu Hospital and the 302th Hospital of Chinese PLA, respectively. The therapeutic effect was worse, and then the patient could not stand, until had to stay in bed for 9 months. Inpatient physical examination showed: hepatic face, light icterus, liver palm and spider angioma, and no varicose vein in abdominal wall and sign of ascites. Nervous system examination: muscular strength of two lower limbs was 0–1 grade and hypermyotonia, hyperreflexia in duoble knees and heel jerks, and two ankles and hip clonus were positive. The abdominal reflex was weakened. Deep and light sense was not abnormal. Double Babinski's sign was positive. Blood routine examination showed: white blood cell 2.0×10^9/L, red blood cell 3.39×10^{12}/L, hemoglobin 62 g/L, blood platelets count 26×10^9/L; blood biochemical examination: Na^+ 153 mmol/L, K^+ 4.0 mmol/L, Cl^+ 112.8.1 mmol/L, alanine aminotransferase 586.8 nkat/L, aspartate aminotransferase 1 035.2 nkat/L, total bilirubin 44.4 μmol/L, direct bilirubin 27.9 μmol/L, total serum protein 58.1 g/L, albumin 34.2 g/L, blood urea nitrogen 2.57 mmol/L, creatinine 68.4 μmol/L. Coagulation function: prothrombin time 23.1 seconds, prothrombin activity 26.5%, blood amimine 108 μmol/L. Ultrosonic and CT examination: Liver was atrophy. The solid rough spot echo distribution was not even. The inner diameter of portal vein was 1.9 cm, the liver gap was widened, the volume of liver was smaller, and the liver density was even. The liver capsula was nodular, with greater spleen. The admission diagnosis: liver cirrhosis (decompensate stage), viral hepatitis B, and hepatic myelopathy.

Liver transplantation and perioperative treatment

After active preoperative preparation, the allograft liver transplantation was undergone on August 16, 2002 and November 19, 2004 respectively. During operation, the livers of patient could be seen smaller and harder than normal one. The nodular change could be found on the surface of liver. The mean volume of ascites was about 1 500 mL. The course of operations went successfully, with mean time of 7 hours. After operation, the patients were returned into ICU and monitored. Routine immunosuppressive agents: Tacrolimus + mycophenolate + corticosteroids +Zenapax and neurous nutritional agents: Vitamins B1, vitamin 12 and so on were used.

RESULTS

Two patients were both returned into the transplantation ward after monitoring in ICU for 6 days and treated with immunosuppressive agents and nervous nutritional agents continually. At 4 weeks after operation, patients were recovered better. The blood routine examination and blood biochemical examination were returned normality. Two patients discharged after 6 weeks.

Recovery condition of lower limbs: Patient 1 could stand for a long time at months 6 after transplantation, walked slowly with the supporter after 12 months and without the supporter at 43 months. The muscular strength of two lower limbs was grade 4. And the liver function was normal.

Patient 2 could move his lower limbs in bed at months 6 after transplantation, walked with the supporter at 18 months. The muscular strength of two lower limbs was grade 3. The liver function was normal.

DISCUSSION

Pathogenesis of hepatic myelopathy

Hepatic myelopathy is a rare neurological complication as the spinal cord lesion in the later period of liver cirrhosis, clinical manifestation of which is spastic paraplegia, enhancement muscular power of two lower limbs, tendon hyperreflexia and positive pyramidal sign. This syndrome was reported firstly by Leigh and Card in 1949. In 1960, Zieve[1] in detail described the nervous pathological change of hepatic myelopathy by autopsy, and proposed that hepatic myelopathy is a demyelinated changes of pyramidal in the spinal cord.

The pathogenesis of hepatic myelopathy is correlative with severe hepatic cirrhosis (decompensate stage), the portosystemic split-flow, hepatic encephalopathy and blood ammine increase. It is the pathogenesis basis of demyelinated changes of pyramidal in spinal cord that is insufficiency of liver detoxication, which causes blood ammine increase, harmful substances and metabolism producers of protein without detoxication entering systemic circulation by the portosystemic split-flow. Hyperammonemia has a harmful effect on nervous system. The liver disease can cause metabolism disturbance of Vitamin B.

The two patients had the above characteristics: ① severe hepatic cirrhosis (decompensate stage); ② one patient had undergone splenectomy before 7 years, which caused the portosystemic split-flow severely; ③ hepatic encephalopathy was caused after upper gastrointestinal bleeding repeatedly; ④ broad form between portsystemic circulation; and ⑤ hyperammonemia.

Clinical manifestation of hepatic myelopathy

Hepatic myelopathy occurred in the later stage of all kinds of the liver cirrhosis. It is the main pathogenesis that the central nervous system was injured by harmful substances as the portsystemic split-flow[2]. The clinical manifestation includes two aspects: the former is the manifestation of liver cirrhosis (especially decompensate stage); the latter is the manifestation of neurous system as character of spastic paraplegia, which includes lower limbs tiredness, muscle stiff, walking difficulty, two knees adduction, two feet drooping and spastic gait. The muscular strength of two lower limbs was descended obviously. But the muscular tension was raised, the tendon reflex showed sthenia, knee or heel jerk and pathological reflex appeared positive. The reflexes of the abdominal reflex and the cremasteric were weakened or disappeared in the severe patient. The above symptoms are worse progressively and are not remitted normally, so as caused spastic paraplegia or limbsparalysis. The amyotrophy could be not seen normally. The deep or superficial sensation is normal, but the pallesthesia position sense is abnormal in a few patients, or with peripheral nervous lesion. But the sphincter function is not disturbed. The syndrome was divided into three stages as the clinical

manifestation: firstly, nervous presymptomatic stage, which mainly displayed as liver damage. Split-flow formed due to collateral circulation or post-shunt. Secondly, repeatedly encephalopathy stage: the main clinical manifestation is transient or repeated sense disturbance and mental symptom, such as emotional abnormality (euphoria, excitation and so on), behavior disturbance (unconsciousness hyperactivity and so on), intelligence abnormality (hypomnesia and disorientation), mental disturbance (paraphasia, confusion and mania), parasympathetic nerve symptoms (abnormal perspiration, tachycardia, skin redness and cold feeling in hand/foot), and the other neurous symptoms (dysarthria, asterixis, gutta serena and so on). Thirdly, spastic paraplegia stage: spastic paraplegia appeared, which the complete or uncomplete limbs paraplegia was. A few patients have pseudobulbarpalsy as the pyramidal tract lesion. It is worth noticing the imbalance in the spinal and brain symptom. The brain symptom was repeated and transient. The spinal symptom appeared slowly and progressively worse, exhibits extend spastic paraplegia in early stage and flexion spastic paraplegia in later stage.

Diagnosis and treatment of hepatic myelopathy

Hepatic myelopathy is rare, but the diagnosis is not difficult. ① the history of chronic hepatopathy or liver cirrhosis; ② repeated paroxysmal hepatic encephalopathy; ③ broad portosystemic collateral circulation and/or the history of portacaval shunt, splenectomy, lienectomy of stamach fundus-esophagus vein; ④ spastic paraplegia, without obvious hypomyotonia, amyotrophy and paraesthesia; ⑤ hyperammine; ⑥ cerebrospinal fluid normal and/or protein rise slightly; ⑦ except for multiple sclerosis, Wilson disease, spinal space occupying lesion, amyotrophic lateral sclerosis and so on.

There is not an effective method for treating hepatic myelopathy. The medical treatment includes restriction of protein intake, control of enteric bacteria growth, improvement of liver function, employment of decendens amminine agents and nerve cell nutrient agent[3]. The operation had been reported by the abroad scholar, which were colic free operation or ileal-rectal anastomosis for decreasing poisons intake. This operation could reduce blood amminine in a short period and improve the neurous symptom, but the satisfied effect could not be got, thus, the prognosis was poor[4-5]. Treatment of the liver disease can improve the symptom in the mild spastic paraplegia. However, hepatic myelopathy is the syndrome of irreversible and progressive spastic paraplegia, which normally appeared worse progressively. About 90% of patients would lose their walking function. As the progress of spastic paraplegia was slow, the hepatic myelopathy could not threaten patients' life directly. The prognosis of hepatic myelopathy mainly depends on the degree of liver cirrhosis. A majority of patients would die of complications, including hepatic coma, upper gastrointestinal bleeding, hepatorenal syndrome, infective shock, canceration, pulmonary infarction, respiratory palsy, cerebral hemorrhage, or gastric perforation as gastric ulcer at 2–3 years after hepatic myelopathy.

Effect of liver transplantation on the recovery of hepatic myelopathy

For many years, doctors have been striving to find an effective therapeutic method for hepatic myelopathy. As the liver function of these patients has normally been in the end period, the treatments could only postpone the progress. There is not a decisive method for this syndrome. The liver transplantation is a new therapeutic method from the pathogen. The liver transplantation not only can solve decompensation of liver function, but also clean the toxic substances effectively, which can recover the homeostasis of body. This is an effective therapeutic method, which could not be replaced by the other therapeutic methods. As we know, if the nervous system was injured, the recovery period would be long and difficult. The improved degree was positively correlated with the interval between hepatic myelopathy and the liver transplantation[6]. Here, the two patients both could stand at 6 months after liver transplantation and walked with the aid of the supporter after 12 months. Currently, one patient could walk slowly without the supporter at 43 months after transplantation. The results show that liver transplantation has received an obvious therapeutic effect on treating hepatic myelopathy. However, the cases involved in this study were few, and the time observation was short, thus, the long-term effect still needs to be assessed progressively.

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肝性脊髓病肝移植后的远期疗效☆

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摘要

背景：肝性脊髓病是肝病晚期引起的脑脊髓损害，目前尚缺乏有效的治疗方法。肝移植可作为从病因上治疗该疾患的一种尝试，但有关肝移植治疗肝性脊髓病的远期疗效罕有报道。

目的：进一步探讨肝移植对肝性脊髓病的远期疗效。

方法：回顾性分析 2002-08/2004-09 于解放军第三〇九医院行原位肝移植的 2 例肝性脊髓病患者临床资料。随访 18，43 个月，对肝移植后 2 例患者下肢肌力的恢复进行严密观察。

结果与结论：两例患者肝移植后 4 周全身情况恢复良好，患者的临床症状、体征均获得明显改善，血常规及各项生化指标全部正常，移植肝功能正常。于移植后 6 周出院。患者 1 于移植后 6 个月可下床长时间站立，12 个月手扶参照物缓慢行走，移植后 43 个月手无扶物可缓慢行走，下肢肌力 4 级；肝功能正常。患者 2：移植后 6 个月双下肢可在床上移动，18 个月手扶参照物可缓慢移动，下肢肌力 3 级；肝功能正常。说明肝脏移植可有效控制肝性脊髓病的发展并明显有利于双下肢肌力的恢复；肝移植对肝性脊髓病是一种新的、有效的治疗方法。但总结的肝移植治疗肝脊髓病例数较少，观察时间短，其疗效有待于进一步多方面评估。

关键词：肝性脊髓病；肝移植；远期疗效；肌力；肝功能

doi:10.3969/j.issn.1673-8225.2010.18.041

中图分类号: R318　文献标识码: A

文章编号: 1673-8225(2010)18-03397-04

杜国盛，陆宏，石炳毅，宋继勇，金海龙，蔡明，钱叶勇，朱志东.肝性脊髓病肝移植后的远期疗效[J].中国组织工程研究与临床康复，2010，14(18):3397-3400.

[http://www.crter.org　http://cn.zglckf.com]

(Edited by /Zhao LJ/Wang L)

医学英文句型正误辨析：本刊英文部

中文	修前	修后
大量的	A large number of apoptotic neurons (50%-60%) were observed following 1 mmol/L SIN-1 treatment.	SIN-1 (1 mmol/L) dramatically induced apoptosis (50%-60%).
直接动词	Chloride channel blockers display certain protective effects against neuronal injury induced by NO	Chloride channel blockers can protect against neuronal injury induced by NO.
	Moreover, studies have demonstrated the protective role of DIDS in staurosporin-induced mouse cortical or N-methyl-D-aspartate-induced rat hippocampal neuronal injury	DIDS also protects in a staurosporine-induced mouse cortical injury or N-methyl-D-aspartate-induced rat hippocampal neuronal injury
本文模拟脑缺血性脑损伤的发生机制，利用 3-吗啉斯德酮胺(SIN-1)作为 NO 供体诱导体外大鼠海马神经元凋亡，观察氯通道的活动是否参与神经元的凋亡过程，探讨缺血缺氧敏感性神经元的凋亡与氯离子通道活动间的关系。	This study induced rat hippocampal neuronal apoptosis in vitro by 3-morpholinosydnonimine (SIN-1) as nitric oxide (NO) donor according to the mechanism of ischemic brain injury to investigate the role of chloride channel activities in neuronal apoptosis as well as the relationship between ischemic/hypoxic sensitive neuronal apoptosis and chloride channel activities.	This study induced rat hippocampal neuronal apoptosis in vitro by 3-morpholinosydnonimine (SIN-1), a nitric oxide (NO) donor that induces ischemic brain injury, to investigate the role of chloride channel activities in neuronal apoptosis as well as the relationship between ischemic/hypoxic neuronal apoptosis and chloride channel activities.
荧光的	Nucleus of normal neurons was ovate and sent out blue fluorescence under fluorescence microscope; apoptotic neurons displayed shrinking or round cell bodies, chromatin aggregation or breakage or apoptotic bodies, sending out strong blue fluorescence	The nucleus of normal neurons was ovate and fluorescent; apoptotic neurons displayed shrinking or round cell bodies, chromatin aggregation or breakage or apoptotic bodies, with stronger blue fluorescence
剂量依赖效应	The results demonstrate that SITS and DIDS protect neurons, reduce apoptosis and improve survival rate in a dose-dependent manner.	SITS and DIDS dose-dependently protected neurons, reduced apoptosis, and improved survival rates.