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自体干细胞移植治疗失代偿期肝硬化的疗效及对肝脏储备功能、血清 LPS、HGF 水平的影响 *

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摘要 目的:探讨自体干细胞移植治疗失代偿期肝硬化的疗效及对肝脏储备功能、血清内毒素(LPS)、肝细胞生长因子(HGF)水平的影响。**方法:**选择 2015 年 9 月至 2017 年 9 月我院接诊的 86 例失代偿期肝硬化患者作为本研究对象,通过随机数表法将其分为观察组和对照组,每组 43 例。对照组给予失代偿期肝硬化常规综合治疗,观察组在对照组基础上进行自体干细胞移植治疗。比较两组治疗前、治疗 12 周后实验室指标、终末期肝病模型系统评分(MELD)、血清 LPS、HGF 水平的变化以及不良反应的发生情况。**结果:**治疗后,两组丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)、总胆红素(TBil)水平均明显低于治疗前,白蛋白(ALB)较治疗前显著升高 ($P<0.05$), 观察组 ALT、AST、TBil 均明显低于对照组,ALB 水平明显高于对照组 [(45.60±4.12)U/L vs. (56.84±6.20)U/L, (57.45±5.01)U/L vs. (68.99±6.84)U/L, (36.53±3.45)g/L vs. (30.42±2.89)g/L, (50.23±4.83)μmol/L vs. (62.30±6.76)μmol/L] ($P<0.05$); 治疗后,两组 MELD 评分较治疗前显著降低($P<0.05$),观察组 MELD 评分明显低于对照组[(21.89±2.74)分 vs.(27.84±3.51)分] ($P<0.05$); 治疗后,两组血清 LPS 较治疗前显著降低,HGF 较治疗前显著升高($P<0.05$),观察组血清 LPS 明显低于对照组,HGF 明显比对照组高[(0.43±0.05)ng/mL vs.(0.60±0.09)ng/mL, (389.56±27.40)pg/mL vs.(301.23±22.30)pg/mL] ($P<0.05$)。对照组和观察组治疗期间不良反应总发生率分别为 8.89%(4/43)、13.95%(6/43),差异无统计学意义($P>0.05$)。**结论:**自体干细胞移植治疗失代偿期患者可明显改善肝功能、肝脏储备功能及血清 LPS、HGF 的表达,且安全性高。

关键词:自体干细胞移植;失代偿期肝硬化;肝脏储备功能;内毒素;肝细胞生长因子

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Curative Efficacy of Autologous Stem Cell Transplantation in the Treatment of Decompensated Cirrhosis and Its Effects on the Liver Reserve Function, Serum LPS and HGF Levels*

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ABSTRACT Objective: To study curative efficacy of autologous stem cell transplantation in the treatment of decompensated cirrhosis and its effects on the liver reserve function, serum endotoxin(LPS) and hepatocyte growth factor(HGF) levels. **Methods:** 86 patients of decompensated cirrhosis who received therapy from September 2015 to September 2017 in our hospital were selected as research objects, according to random number table, they were divided into the observation group and the control group, 43 cases in each group. The control group was given conventional comprehensive treatment for decompensated cirrhosis, and the observation group was treated with autologous stem cell transplantation on the basis of the control group. The changes of laboratory indexes, end-stage liver disease model system score (MELD), serum LPS and HGF levels before treatment and 12 weeks after treatment and adverse reactions were compared between the two groups. **Results:** After treatment, the alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TBil) levels of two groups were significantly lower than those before treatment, and albumin (ALB) was significantly rise than before treatment ($P<0.05$), the ALT, AST and TBil levels in the observation group were significantly lower than those in the control group, and ALB levels was significantly higher than those in the control group [(45.60±4.12)U/L vs. (56.84±6.20)U/L, (57.45±5.01)U/L vs. (68.99±6.84)U/L, (36.53±3.45)g/L vs. (30.42±2.89)g/L, (50.23±4.83)μmol/L vs. (62.30±6.76)μmol/L] ($P<0.05$); after treatment, the MELD scores of the two groups were significantly lower than those before treatment ($P<0.05$), the MELD score in the observation

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group was significantly lower than those in the control group $[(21.89 \pm 2.74) \text{ scores vs. } (27.84 \pm 3.51) \text{ scores}] (P < 0.05)$; after treatment, the serum LPS in the two groups was significantly lower than those before the treatment, and the HGF was significantly higher than that before the treatment ($P < 0.05$), and the serum LPS in the observation group was significantly lower than those in the control group, and the HGF was significantly higher than those in the control group $[(0.43 \pm 0.05) \text{ ng/mL vs. } (0.60 \pm 0.09) \text{ ng/mL}, (389.56 \pm 27.40) \text{ pg/mL vs. } (301.23 \pm 22.30) \text{ pg/mL}] (P < 0.05)$. The incidence of adverse reactions in the control group and the observation group was 8.89% (4/43) and 13.95% (6/43) respectively, and the difference was not statistically significant ($P > 0.05$). **Conclusion:** Autologous stem cell transplantation in the treatment of decompensated patients can effectively improve the liver function, liver reserve function and the expression of serum LPS and HGF, and the safety is high.

Key words: Autologous stem cell transplantation; Decompensated cirrhosis; Liver reserve function; Endotoxin; Hepatocyte growth factor

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前言

肝硬化是由一种或多种病因对肝脏长期性产生刺激作用所致的一种弥漫性损伤, 主要特点为慢性弥漫性结缔组织增生, 在疾病早期肝功能尚可得到代偿, 但当肝硬化进展到一定程度后, 可超出肝功能的代偿能力, 出现失代偿期肝硬化^[1,2]。该病的发生、发展受到较多细胞因子的调节, 国内外均有学者发现血清内毒素(LPS)、肝细胞生长因子(HGF)肝组织损伤之间存在着密切关系, 对其的检测有助于判断病情及预后^[3,4]。

目前, 失代偿期肝硬化的药物治疗以抑制病毒复制、减少肝纤维化和炎症状态等为主, 原位肝移植是治疗该病最为可靠的方案, 但也有一定缺陷, 例如供体不足、费用高等, 也限制了该方式在临床上的应用^[5,6]。近年来, 有较多基础研究显示外周血干细胞(PBSC)具有繁殖能力强、速度快等优势, 可在损伤的肝脏中发生增殖、分化成为肝细胞, 缓解肝功能损伤等^[7,8]。本研究旨在分析外周血自体干细胞移植治疗失代偿期肝硬化患者的优势, 并观察其对肝脏储备功能、血清 LPS、HGF 水平的影响, 结果报道如下。

1 资料与方法

1.1 一般资料

选择我院 2015 年 9 月至 2017 年 9 月接诊的失代偿期肝硬化患者 86 例。纳入标准^[9]: ①符合《病毒性肝炎防治指南》、《慢性乙型肝炎防治指南》、《丙型肝炎防治指南》、《酒精性肝病及非酒精性脂肪肝病诊疗指南》中肝硬化的诊断标准, 且肝功能 Child-Pugh 分级 B、C 级(失代偿期); ②年龄 ≥ 18 岁; ③对本研究知情同意书。排除标准^[10]: ①伴活动性消化出血; ②伴自发性腹膜炎等感染; ③合并难以控制的高血压, 严重心、肺功能障碍等, 难以完成治疗; ④合并恶性肿瘤或可疑恶性肿瘤; ⑤凝血功能严重障碍; ⑥对研究方式有禁忌症。通过随机数表法将所有患者分为观察组和对照组, 每组 43 例。两组一般资料差异比较差异无统计学意义($P > 0.05$), 具有可比性。

1.2 治疗方法

对照组给予常规措施, 包括保持充足休息, 多进食高蛋白、高热量、维生素丰富易消化的失误, 并给予多烯磷脂酰胆碱、谷胱甘肽等进行护肝治疗, 合并腹水患者限制水、钠的摄取并给

予利尿药物, 对低蛋白血症患者定期酌情补充白蛋白或血浆等;

观察组在对照组基础上进行自体干细胞移植治疗, 给予粒细胞集落因子(规格 12 mL:300 μg , 厂家:协和发酵麒麟株式会社, 国药准字 S200100631)300 $\mu\text{g}/\text{d}$, 皮下注射, 注射期间严格对外周血白细胞数量的变化进行监测, 当结果至 $(2.5 \sim 3.0 \times 10^8/\text{mL})$ 时, 则进行干细胞分离, 仪器选择美国 Baxter 公司生产的 CS3000 PLUS 型血细胞分离机, 一次性分离剂量 70~102 mL, 选择细胞镜下 $1.02 \times 10^5/\text{kg} \sim 2.79 \times 10^6/\text{kg}$ 计数的细胞作为移植干细胞, 常温储存, 4h 内进行肝内移植。

1.3 观察指标

1.3.1 实验室指标 于治疗前、治疗 12 周后, 采集 5 mL 清晨空腹静脉血, 上机离心 10 min, 提取上层血清液, 储存至冷冻箱内待检, 使用合肥天 - 生物技术研究所提供的肝功能试剂盒, 检测丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)、白蛋白(ALB)、总胆红素(TBil)的变化。

1.3.2 肝脏储备功能 参照文献^[9]的终末期肝病模型系统评分(MELD)评价, 分值越高则表示患者肝脏储备功能越差、预后风险越高。

1.3.3 血清 LPS、HGF 检测均使用美国 ADL 公司提供的酶联免疫吸附法(ELISA)试剂盒。

1.4 统计学分析

以 SPSS18.0 软件包处理实验数据, 计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示, 组间比较采用 t 检验, 计数资料组间比较采用 χ^2 检验, 以 $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后肝脏功能指标的比较

治疗后, 观察组 ALT、AST、TBil 水平均明显低于对照组, ALB 水平明显高于对照组($P < 0.05$), 见表 1。

2.2 两组治疗前后肝脏储备功能的比较

两组治疗后 MELD 评分较治疗前显著降低 ($P < 0.05$), 观察组 MELD 评分比对照组低($P < 0.05$), 见表 2。

2.3 两组治疗前后血清 LPS、HGF 水平的比较

两组治疗后血清 LPS、HGF 水平较治疗前比较差异均具有统计学意义($P < 0.05$), 观察组血清 LPS 水平明显低于对照组, HGF 水平明显高于对照组($P < 0.05$), 见表 3。

表 1 两组治疗前后肝脏功能的比较($\bar{x} \pm s$)

Table 1 Comparison of the liver function between two groups before and after treatment($\bar{x} \pm s$, scores)

Groups		ALT(U/L)	AST(U/L)	ALB(g/L)	TBil(μ mol/L)
Observation group (n=43)	Before treatment	94.23 $\pm$ 12.03	99.85 $\pm$ 13.47	24.85 $\pm$ 2.50	89.75 $\pm$ 12.39
	After treatment	45.60 $\pm$ 4.12**	57.45 $\pm$ 5.01**	36.53 $\pm$ 3.45**	50.23 $\pm$ 4.83**
Control group(n=43)	Before treatment	93.79 $\pm$ 12.35	100.48 $\pm$ 13.12	25.03 $\pm$ 2.39	90.34 $\pm$ 12.08
	After treatment	56.84 $\pm$ 6.20*	68.99 $\pm$ 6.84*	30.42 $\pm$ 2.89*	62.30 $\pm$ 6.76*

Note: compared with before treatment, * $P < 0.05$; compared with the control group, ** $P < 0.05$.

表 2 两组治疗前后肝脏储备功能的比较($\bar{x} \pm s$, 分)

Table 2 Comparison of the liver reserve function between two groups before and after treatment($\bar{x} \pm s$, scores)

Groups		MELD scores
Observation group(n=43)	Before treatment	33.84 $\pm$ 4.20
	After treatment	21.89 $\pm$ 2.74**
Control group(n=43)	Before treatment	34.04 $\pm$ 4.04
	After treatment	27.84 $\pm$ 3.51*

Note: compared with before treatment, * $P < 0.05$; compared with the control group, ** $P < 0.05$.

表 3 两组治疗前后血清 LPS、HGF 水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the serum LPS and HGF between two groups before and after treatment($\bar{x} \pm s$)

Groups		LPS(ng/mL)	HGF(pg/mL)
Observation group(n=43)	Before treatment	0.94 $\pm$ 0.12	178.45 $\pm$ 18.40
	After treatment	0.43 $\pm$ 0.05**	389.56 $\pm$ 27.40**
Control group(n=43)	Before treatment	0.95 $\pm$ 0.20	176.93 $\pm$ 19.79
	After treatment	0.60 $\pm$ 0.09*	301.23 $\pm$ 22.30*

Note: compared with the before treatment, * $P < 0.05$; compared with the control group, ** $P < 0.05$.

3 讨论

失代偿期肝硬化是慢性肝病的一种终末阶段,此类患者的 5 年生存率仅有 14%^[11]。目前,该病的治疗目前是最大限度的缓解肝细胞炎症程度、延缓失代偿进展、延长存活时间,原位肝移植是该病治疗的最有效手段,但临床应用具有一定局限性^[12,13]。随着临床医学技术的不断发展,干细胞问世也为肝脏疾病患者的治疗提供了新思路^[14,15]。既往的研究中,国内外多选择使用骨髓穿刺的方式,进行骨髓基质细胞移植,但该方式在采集过程中需麻醉,对患者全身要求高、干细胞获取数量有限容易混入外周血,且患者较痛苦难以耐受^[16,17]。1997 年,有研究首次报道人外周血 CD34+ 和血管内皮生长因子受体 2 细胞可在体外发生增殖转化成为血管内皮细胞,由于此类细胞具有内皮样细胞功能,并将其定义为血管内皮祖细胞(EPC)^[18]。动物实验显示通过自体 EPC 移植至急性肝损伤大鼠可明显改善血管侧支循环和血流灌注^[19]。Shudo Y 等^[20]报道经过动员的 PBSC 和正常骨髓组织中的干数量相当,均为淋巴样的单核母细胞,且具有采集更加方面的优势。

MELD 评分在评价肝脏储备功能、肝脏手术风险及预后中均具有较大的优越性,是一种客观、准确的评分系统^[21,22]。本研究中,使用自体干细胞治疗 12 周后,患者 MELD 评分降低程

度更明显,且实验室指标改善程度也更佳,提示自体干细胞移植较常规的药物治可更佳有效的改善失代偿期肝功能,原因可能是由于自体干细胞可在特定环境下分化成为肝干细胞和干细胞,参与着肝功能的修复和重建。Sass FA 等^[23]报道也提出相似结论。此外,在自体干细胞移植期间,无严重不良反应发生,考虑和使用自体干细胞不存在免疫排斥相关,安全性高有关。

肠道细菌所生成的 LPS 可经过肝脏细胞灭活减毒,但在失代偿期肝硬化患者中,消化道通透性增加,继而增加肠道内毒素的生成和吸收,导致肝脏细胞对 LPS 的灭活能力减弱,多合并肠源性的内毒素血症,直接加重肝组织损伤^[24,25]。HGF 是在急性肝损伤患者中所存在的一种蛋白因子,具有促进肝细胞 DNA 合成、肝细胞增值等作用,且可提高肝细胞的抗损伤能力,起到保护肝细胞的效果^[26,27]。有研究显示肝损伤程度越重的患者血清 HGF 的表达越低^[28,29]。本研究中,使用自体干细胞移植的患者血清 LPS 明显降低、HGF 明显升高,通过分析是由于在移植干细胞,肝脏功能得到恢复,继而肝性细胞对 LPS 的灭活能力增加,而随着肝功能的恢复,血清 HGF 也随之明显升高^[30]。但失代偿期肝硬化患者的治疗是一个长期的过程,本研究仅观察了治疗后 12 周患者的病情变化,该治疗方式的远期疗效和预后仍需持续探讨。

综上所述,自体干细胞移植治疗失代偿期患者可明显改善

肝功能、肝脏储备功能及血清 LPS、HGF 的表达,且安全性高。

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