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自体干细胞移植治疗胆汁性肝硬化的临床疗效及对患者肝脏弹力硬度、血清 TGF- β 1、SIL-2R 水平的影响 *

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摘要 目的:探讨自体干细胞移植治疗胆汁性肝硬化的临床疗效及对患者肝脏弹力硬度、血清转化生长因子- β 1(TGF- β 1)、可溶性白细胞 2 受体(SIL-2R)水平的影响。**方法:**选取 2015 年 1 月至 2017 年 8 月于我院就诊 90 例的胆汁性肝硬化患者作为本研究对象,采用随机数表法将其分为观察组和对照组,每组 45 例。对照组给予熊去氧胆酸胶囊、多烯磷脂酰胆碱胶囊、复方甘草酸苷片等常规治疗,连续治疗 24 周;观察组在对照组相同方法治疗 4 周后,进行自体干细胞移植治疗。比较两组的临床疗效、治疗前和治疗后 24 周的肝功能、肝脏弹力硬度值、血清 TGF- β 1、SIL-2R 水平的变化及不良反应的发生情况。**结果:**治疗后,观察组临床疗效总有效率为 86.67%(39/45),明显高于对照组[66.67%(30/45)]($P < 0.05$)。两组治疗后血清碱性磷酸酶(ALP)、谷氨酰转氨酶(GGT)、丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、总胆红素(TBil)较治疗前均显著降低($P < 0.05$),且观察组血清 ALP、GGT、ALT、AST、TBil 水平均明显低于对照组($P < 0.05$)。两组治疗后肝脏弹力硬度值较治疗前均明显降低($P < 0.05$),且观察组肝脏弹力硬度值明显低于对照组[(6.20 $\pm$ 1.05) kPa vs. (7.33 $\pm$ 1.27) kPa]($P < 0.05$)。两组治疗后血清 TGF- β 1、SIL-2R 水平较治疗前均明显降低($P < 0.05$),且观察组血清 TGF- β 1、SIL-2R 水平均明显低于对照组[(7.40 $\pm$ 1.21)ng/mL vs. (9.23 $\pm$ 1.49)ng/mL, (130.45 $\pm$ 11.03) ng/L vs. (162.93 $\pm$ 15.62)ng/L]($P < 0.05$)。两组不良反应总发生率分别为 11.11%(5/45)、15.56%(7/45),组间比较差异无统计学意义($P > 0.05$)。**结论:**自体干细胞移植治疗胆汁性肝硬化患者的临床效果显著,可有效改善患者肝功能、肝脏弹力硬度值,降低血清 TGF- β 1、SIL-2R 的表达,且安全性高。

关键词:胆汁性肝硬化;自体干细胞移植;肝脏弹力硬度值;转化生长因子- β 1;可溶性白细胞 2 受体

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Curative Efficacy of Autologous Stem Cell Transplantation in the Treatment of Biliary Cirrhosis and its Effects on the Serum TGF- β 1 and SIL-2R Levels*

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ABSTRACT Objective: To study the curative efficacy of autologous Stem cell transplantation in the treatment of biliary cirrhosis and its effects on the serum transforming growth factor β 1(TGF- β 1) and soluble interleukin 2 receptor(SIL-2R) levels. **Methods:** 90 cases of patients with primary biliary cirrhosis who were treated from January 2015 to August 2017 in our hospital were selected and divided into the observation group and the control group with 45 cases in each group according to random number table. The control group was given conventional treatment for 24 weeks, such as Ursodeoxycholic Acid Capsules, polyene ester choline capsule, Compound Glycyrrhizin Tablets and so on. The observation group was treated with the same method as the control group for 4 weeks, autologous stem cell transplantation was performed. The clinical efficacy, the changes of liver function, liver elasticity hardness, serum TGF- β 1 and SIL-2R levels before and at 24 weeks after treatment, and the incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was 86.67% (39/45), which was significantly higher than that of the control group[66.67%(30/45)]($P < 0.05$); the alkaline phosphatase (ALP), glutamyl transaminase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase(AST), and total bilirubin (TBil) levels of both groups were significantly lower than those before treatment($P < 0.05$), and the serum ALP, GGT, ALT, AST and TBil levels of observation group were significantly lower than those of the control group($P < 0.05$); the liver elastic hardness value of both groups were significantly lower than those before treatment($P < 0.05$), which was significantly lower in the observation group than that of the control group [(6.20 $\pm$ 1.05) kPa vs. (7.33 $\pm$ 1.27) kPa]($P < 0.05$); the serum TGF- β 1 and SIL-2R levels of both groups were significantly lower than those before treatment ($P < 0.05$), and the serum TGF- β 1 and

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SIL-2R levels of observation group were significantly lower than those of the control group [(7.40± 1.21) ng/ml vs. (9.23± 1.49) ng/ml, (130.45± 11.03) ng/L vs. (162.93± 15.62) ng/L]($P < 0.05$); the total incidence of adverse reactions in two groups were 11.11% (5/45) and 15.56% (7/45) respectively, and there was no significant difference between two groups($P > 0.05$). **Conclusion:** Autologous Stem cell transplantation is effective for biliary cirrhosis, which can effectively improve the liver function, liver elastic hardness, and reduce the expression of TGF- β 1 and SIL-2R in serum with high safety.

Key words: Biliary cirrhosis; Autologous Stem cell transplantation; Liver elastic hardness; Transforming growth factor β 1; Soluble interleukin 2 receptor

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前言

胆汁性肝硬化主要是由于胆道阻塞、胆汁淤积所致的肝硬化,患者病理表现主要为肝内细小胆管和汇管区发生渐进性炎症改变等,可出现瘙痒、乏力、黄疸等临床症状,部分患者可合并腹水,好发于中年女性,若未得到及时的治疗极易进展成为肝硬化、肝衰竭等,危及着生命^[1,2]。临床上主要采用熊去氧胆酸、多烯磷脂酰胆碱等治疗该病,可延长肝移植时间、改善预后,但也有部分患者对此类药物不应答率较高,疗效欠佳^[3]。

干细胞移植可从根本上改善肝功能、延长生存期,是肝硬化患者的理想治疗方案,但由于治疗费用昂贵、器官紧缺、异体移植后并发症较多的问题,在临床上的应用也受到限制。近年来随着学者发现通过自体外周血干细胞(PBSC)进行肝内移植治疗在改善肝硬化病情中也可取得一定疗效,但相似报道仍较少^[4,5]。胆汁性肝硬化的发生、发展过程受到多种细胞因子调节,病理过程十分复杂,研究表明血清转化生长因子- β 1(TGF- β 1)、可溶性白细胞 2 受体(SIL-2R)在介导胆汁性肝硬化患者免疫病理过程中发挥着重要作用^[6,7]。因此,本研究通过观察自体干细胞移植治疗胆汁性肝硬化对患者肝脏弹性硬度、血清转化生长因子- β 1(TGF- β 1)、可溶性白细胞 2 受体(SIL-2R)水平的影响,探讨自体干细胞用于胆汁性肝硬化的临床疗效。

1 资料与方法

1.1 一般资料

选取 2015 年 1 月至 2017 年 8 月于我院收治的 90 例的胆汁性肝硬化患者作为本研究对象。纳入标准:①原发性肝硬化诊断标准参照《原发性胆汁性肝硬化诊断和治疗共识(2015)》^[8]中相关内容,临床症状可表现为瘙痒、乏力,或合并黄疸、腹水;碱性磷酸酶(ALP)、谷氨酰转氨酶(GGT)表达明显升高,丙氨酸转氨酶(ALT)、天冬氨酸转氨酶(AST)、总胆红素(TBil)表达异常;血清线粒体抗体(AMA)结果或 AMA-M2 检测结果呈阳性;肝组织活检提示胆管出现破坏、减少;②疾病分期 II~III 期;③近 1 个月内未接受过熊去氧胆酸等类似药物治疗;④签署本研究知情同意书;排除标准:①继发于病毒、酒精性、药物性肝炎等所致的肝功能损伤;②通过影像学检查显示存在肝外胆管梗阻;③合并肝硬化相关终末期并发症,例如大量顽固性腹水、消化道出血、肝性脑病等;④心、脑、肾功能存在严重异常,以及造血疾病等;⑤对本研究所涉及药物过敏。本研究已获得我院伦理委员会批准实施,通过随机数表法将所有患者分为观察组($n=45$)和对照组($n=45$),两组一般资料比较差异无统计学意义($P > 0.05$),具有可比性,具体见表 1。

表 1 两组一般临床资料的对比($\bar{x} \pm s, n(\%)$)

Table 1 Comparison of the general information between two groups($\bar{x} \pm s, n(\%)$)

Groups	Sex(M/F)	Age(years)	Course of disease (years)	Stages	
				II	III
Observation group($n=45$)	7/38	51.49± 8.42	4.92± 0.89	20(44.44)	25(54.35)
Control group($n=45$)	5/40	50.87± 8.95	5.04± 0.81	22(48.89)	23(51.11)

1.2 治疗方法

对照组给予熊去氧胆酸胶囊(规格 250 mg, 厂家: Losan Pharma GmbH, 国药准字 H20150365)口服, 250 mg/次, 3 次/d; 多烯磷脂酰胆碱胶囊(规格 228 mg, 厂家: 北京赛诺菲制药有限公司, 国药准字 H20059010)口服, 456 mg/次, 3 次/d; 复方甘草酸苷片(规格 25 mg, 厂家: 中国卫材药业有限公司, 国药准字 J20130077)口服, 100 mg/次, 3 次/d; 合并腹水则给予利尿剂、有低蛋白血症者则相应补充清蛋白; 连续治疗 24 周。

观察组在和对照组相同方法治疗 4 周后, 进行自体干细胞移植治疗: 皮下注射重组人粒细胞集落刺激因子(规格 12 mL: 300 μ g, 厂家: 协和发酵麒麟株式会社, 国药准字 S200100631)进行 PBSC 动员, 密切监测外周血白细胞数量, 当数量达到

(2.5~3.0)× 10⁹/mL 后, 使用美国 Baxter 公司生产的血细胞分离机 CS3000 PLUS 型进行一次性分离干细胞 70~102 mL, 之后常温保存, 4 h 内行移植术; 经股动脉穿刺和造影, 将促干细胞生长素 150 μ g 和干细胞和混悬液由左肝动脉注入干细胞, 过程注意需缓慢, 时间 > 15 min; 拔管后加压包扎穿刺点预防血肿。

1.3 观察指标

1.3.1 肝功能 采集两组治疗前、治疗 24 小时后 5 mL 空腹静脉血, 以 3000 r/min 的速度离心 10 min, 提取上层血清液, 储存于零下 80℃ 的冷冻箱内待检, 使用磷酸苯二钠法检测 ALP, 以速率法检测 GGT、ALT、AST, 以钒酸盐法检测 TBil, 试剂盒均购于上海科华生物工程股份公司。

1.3.2 弹性硬度值 使用法国 Echosens 公司 FibroScan 瞬时弹

性成像检测仪检测,连续检测 10 次结果,取中位数为最终值。

1.3.3 血清 TGF- β 1、SIL-2R 水平 使用酶联免疫吸附法 (ELISA)检测,试剂盒购于美国 GENZYME 公司,使用德国西门子公司生产的 ADVID 型全自动生化分析仪检测。

1.3.4 不良反应的发生情况 主要包括服药后胃肠道反应、血磷升高情况,以及自体干细胞移植过程中白细胞降低、肝区疼痛、发热、穿刺部位疼痛、恶心呕吐等常见不良反应。

1.4 疗效评价标准

治疗后 24 周,参照文献^[9]评价临床疗效:完全反应:瘙痒、乏力、黄疸等临床症状得到大部分缓解,肝功能等生化指标 (ALP、GGT、ALT、AST、TBil)基本恢复至正常;部分反应:临床

症状、肝生化指标部分改善;无反应:上述内容无明显改善,甚至恶化。以完全反应 + 部分反应为总有效率。

1.5 统计学分析

以 SPSS18.0 软件包处理数据,计量资料均数 $\pm$ 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 两组临床疗效对比

治疗后,观察组临床总有效率为 86.67%,明显高于对照组 (66.67%, $P < 0.05$),见表 2。

表 2 两组临床疗效的对比[例(%)]

Table 2 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Complete reaction	Partial reaction	No reaction	Total effective rate
Observation group(n=45)	18(40.00)	21(46.67)	6(13.33)	39(86.67)*
Control group(n=45)	14(31.11)	16(35.56)	15(33.33)	30(66.67)

Note: Compared with the control group, * $P < 0.05$.

2.2 两组治疗前后肝功能对比

治疗前,两组各肝功能指标比较差异无统计学意义 ($P > 0.05$);与治疗前比较,两组治疗后需求 ALP、GGT、ALT、AST、

TBil 水平均明显降低($P < 0.05$),且观察组以上各指标均明显低于对照组($P < 0.05$),见表 3。

表 3 两组治疗前后肝功能对比($\bar{x} \pm s$)

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

Groups		ALP(U/L)	GGT(U/L)	ALT(U/L)	AST(U/L)	TBil(μ mol/L)
Observation group (n=45)	Before treatment	317.45 $\pm$ 35.69	217.43 $\pm$ 19.84	89.56 $\pm$ 11.20	50.74 $\pm$ 5.59	18.40 $\pm$ 2.12
	After treatment	155.85 $\pm$ 18.45* [#]	64.33 $\pm$ 9.84* [#]	45.60 $\pm$ 6.52* [#]	35.02 $\pm$ 3.41* [#]	8.94 $\pm$ 1.18* [#]
Control group (n=45)	Before treatment	315.93 $\pm$ 36.10	216.39 $\pm$ 20.59	90.04 $\pm$ 10.56	51.11 $\pm$ 5.20	18.94 $\pm$ 2.04
	After treatment	178.94 $\pm$ 24.21*	79.45 $\pm$ 13.84*	62.18 $\pm$ 8.20*	42.44 $\pm$ 4.19*	13.02 $\pm$ 1.59*

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

2.3 两组治疗前后肝脏弹力硬度值对比

治疗前,两组肝脏弹力硬度值比较差异无统计学意义 ($P > 0.05$)。与治疗前比较,两组治疗后肝脏弹力硬度值均显著降低

($P < 0.05$),且观察组肝脏弹力硬度值明显低于对照组 ($P < 0.05$),见表 4。

表 4 两组肝脏弹力硬度值对比($\bar{x} \pm s$, kPa)

Table 4 Comparison of the liver elastic hardness value between two groups before and after treatment($\bar{x} \pm s$, kPa)

Groups	Time	Liver elastic hardness value
Observation group(n=45)	Before treatment	9.12 $\pm$ 1.82
	After treatment	6.20 $\pm$ 1.05* [#]
Control group(n=45)	Before treatment	9.05 $\pm$ 1.89
	After treatment	7.33 $\pm$ 1.27*

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

2.4 两组治疗前后血清 TGF- β 1、SIL-2R 水平对比

治疗前,两组血清 TGF- β 1、SIL-2R 水平比较差异无统计学意义 ($P > 0.05$);两组治疗后血清 TGF- β 1、SIL-2R 水平均明显低于治疗前($P < 0.05$),且观察组血清 TGF- β 1、SIL-2R 均水平明显低于对照组($P < 0.05$),见表 5。

2.5 两组不良反应发生的比较

治疗过程中,对照组出现 3 例腹痛腹泻,2 例血磷轻度升高,观察组出现 2 例腹痛腹泻、1 例血磷轻度升高,在干细胞移植后未发生白细胞降低、肝区疼痛、发热等不良反应,有 1 例患者出现穿刺部位轻微疼痛、1 例轻微头晕、2 例恶心呕吐,无需特殊处理自行缓解,两组不良反应总发生率分别为 11.11% (5/45)、15.56%(7/45),组间比较无显著差异($P > 0.05$)。

表 5 两组治疗前后血清 TGF-β1、SIL-2R 水平对比($\bar{x} \pm s$)

Table 5 Comparison of the serum TGF-β1 and SIL-2R levels between two groups before and after treatment($\bar{x} \pm s$)

Groups		TGF-β1(ng/mL)	SIL-2R(ng/L)
Observation group(n=45)	Before treatment	15.84± 2.85	217.23± 19.84
	After treatment	7.40± 1.21* [#]	130.45± 11.03* [#]
Control group(n=45)	Before treatment	16.10± 2.70	219.18± 19.20
	After treatment	9.23± 1.49*	162.93± 15.62*

Note: Compared with before treatment, *P<0.05; compared with the control group, [#]P<0.05.

3 讨论

目前,国内外肝病专家和学会均推荐长期进行熊去氧胆酸治疗胆汁性肝硬化,大量研究表明其在改善胆汁淤积、胆汁淤积、延缓疾病进展中效果显著,且药物不良反应少安全性高,但也有部分患者难以获得较好的应答率,效果欠佳^[10,11]。

干细胞在体内外均具有较强的向肝系细胞分化作用,而通过抑制具有分化增殖能力的干细胞可令其在体内分化成为肝细胞,继而达到代偿肝功能的效果。在自体干细胞移植方面,国内外多使用骨髓穿刺获得骨髓基质细胞等进行治疗,主要是通过多点骨髓腔穿刺,抽取含有造血干细胞的骨髓血混合液,是一种经典的移植方法,但该方式过程需麻醉,骨髓血混合液需达到 80~120 mL,对患者全身要求高,且获取过程十分痛苦,多数患者难以接受^[12,13]。近年来研究显示 PBSC 和正常骨髓的干细胞数量相当,不失为一种新的细胞移植方法。Gulbas Z^[14]的报道中指出 PBSC 不仅可获得更加丰富的单核细胞和 CD34⁺ 干细胞,且相比于骨髓移植无需麻醉,操作更为简单。

本研究结果显示经过自体干细胞移植治疗的患者临床疗效、肝功能指标、肝脏弹力硬度值等结果上均优于常规治疗的患者,分析原因可能在于在干细胞进入肝损伤部位后,可在表面趋化因子的迁移作用下到达损伤的肝细胞位点,并大量释放肝细胞生长因子、表皮生长因子等,有利于减轻肝功能损伤。干细胞也可直接在胞外基质发挥作用,起到重塑和调节效果,逆转肝纤维化,继而改善弹力硬度,Gautier SV 等^[15]报道中也得出相似结论。本研究中,经过自体干细胞移植的患者并未出现较多严重不良反应,提示其安全性较高。

目前,胆汁性肝硬化的确切发病机制仍不明确,较多研究认为与自身免疫机制所介导的炎症反应密切相关。SIL-2R 是体内活化淋巴细胞膜 IL-2R 的 α 链成分,其释放入血后可使 IL-2R 失去活性,发挥免疫抑制作用。研究表明急慢性肝炎、肝硬化、肝癌患者血清 SIL-2R 浓度均明显升高,可提示患者免疫功能的紊乱、肝细胞的炎症、纤维化程度^[16,17]。TGF-β1 是体内重要的负性免疫调节因子,有报道指出 TGF-β1 信号通路的紊乱在诸多癌症、纤维化、自身免疫性疾病中均发挥着重要作用^[18]。Dong Z 等^[19]实验也证实胆汁性肝硬化患者血清 TGF-β1 水平明显升高,且和肝功能 Child 分期明显相关,是肝纤维发生机制中重要的细胞因子之一。本研究结果显示使用自体干细胞移植的患者血清 TGF-β1、SIL-2R 较常规治疗的患者明显降低,可能是由于免疫球细胞亚群在组织修复中发挥的生物学作用可有效调节免疫失衡,且干细胞在促进局部微环境、促进炎症因子代谢上效果显著,因此血清血清 TGF-β1、SIL-2R 的降低

程度更显著。Zhang C 等^[20]研究也指出干细胞可促进巨噬细胞的表型转化,改善自身免疫功能,继而对损伤的肝细胞起到修复作用。

但本研究仍存在一定不足,如随着患者年龄的不断增长,可同样伴随着脏器、免疫功能衰退等,而自体干细胞是否对各年龄段的患者均具有相似疗效方面仍无法明确,且本研究时间较短,自体干细胞治疗对胆汁性肝硬化患者的长期疗效上仍需深入研究。

综上所述,自体干细胞移植治疗胆汁性肝硬化患者的临床效果显著,可有效改善患者肝功能、肝脏弹力硬度值,降低血清 TGF-β1、SIL-2R 的表达,且安全性高。

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