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肠道益生菌联合奥曲肽对肝硬化合并胃食管静脉曲张初次出血患者血流动力学及预后的影响 *

董胜肖¹ 靳海峰¹ 刘惠敏² 刘文格¹ 姚欣¹

(1 中国人民解放军白求恩国际和平医院消化科 河北 石家庄 050000;

2 中国人民解放军白求恩国际和平医院呼吸科 河北 石家庄 050000)

摘要 目的:研究肠道益生菌联合奥曲肽对肝硬化合并胃食管静脉曲张初次出血患者血流动力学及预后的影响。**方法:**选取 2016 年 5 月 -2017 年 4 月我院收治的肝硬化合并胃食管静脉曲张初次出血患者 96 例,以随机数字表法分成研究组(n=48)和对照组(n=48)。对照组予以奥曲肽治疗,研究组则采用肠道益生菌联合奥曲肽治疗,疗程均为 28 天。分别比较两组临床治疗总有效率、再出血率、病死率、临床症状改善时间、止血时间以及住院时间,观察并比较治疗前后血流动力学、血清内皮素(ET)、一氧化氮(NO)、内毒素脂多糖(LPS)水平。**结果:**研究组临床治疗总有效率为 93.75%(45/48),高于对照组的 79.17%(38/48)($P<0.05$)。治疗后两组患者心输出量(CO)、心脏指数(CI)、门静脉血流量(PVF)、食管曲张静脉变化(EVD)均较治疗前降低,且研究组低于对照组($P<0.05$)。治疗后两组患者血清 ET、NO、LPS 水平均较治疗前降低,且研究组低于对照组($P<0.05$)。与对照组比较,研究组再出血率、临床症状改善时间、止血时间以及住院时间均降低($P<0.05$),而两组病死率比较差异无统计学意义($P>0.05$)。**结论:**肠道益生菌联合奥曲肽治疗肝硬化合并胃食管静脉曲张初次出血患者的临床疗效明显,能够改善患者血流动力学和促进肠道菌群的平衡,预后较佳。

关键词:肝硬化;胃食管静脉曲张;肠道益生菌;奥曲肽;血流动力学;预后

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Effect of Enteric Probiotics Combined with Octreotide on Hemodynamics and Prognosis in Patients with Cirrhosis Combined with Gastroesophageal Varicosity Primary Hemorrhage*

DONG Sheng-xiao¹, JIN Hai-feng¹, LIU Hui-mir², LIU Wen-ge¹, YAO Xin¹

(1 Department of Gastroenterology, Bethune International Peace Hospital of PLA, Shijiazhuang, Hebei, 050000, China;

2 Department of Respiration, Bethune International Peace Hospital of PLA, Shijiazhuang, Hebei, 050000, China)

ABSTRACT Objective: To study the effect of enteric probiotics combined with octreotide on hemodynamics and prognosis in patients with liver cirrhosis combined with gastroesophageal varicosity primary hemorrhage. **Methods:** 96 cases of liver cirrhosis combined with gastroesophageal varicosity primary hemorrhage who were treated in our hospital from May 2016 to April 2017 were selected. The patients were divided into the study group (n=48) and the control group (n=48) by random digital table method. The control group was treated with octreotide, and the study group was treated with enteric probiotics combined with octreotide, the course of treatment was 28 d. The total effective rate, rebleeding rate, fatality rate, clinical symptom improvement time, hemostasis time and hospitalization time were compared between the two groups, hemodynamics, serum endothelin(ET), nitric oxide(NO) and endotoxin lipopolysaccharide (LPS) levels were observed and compared before and after treatment. **Results:** The total effective rate of clinical treatment in the study group was 93.75% (45/48), which was higher than 79.17% (38/48) of the control group($P<0.05$). Cardiac output(CO), cardiac index (CI), portal venous blood flow(PVF) and esophageal varices (EVD) in the two groups after treatment were all lower than those before treatment, and the study group was lower than that in the control group ($P<0.05$). The levels of serum ET, NO and LPS in the two groups after treatment were lower than those before the treatment, and the study group was lower than the control group ($P<0.05$). Compared with the control group, the rebleeding rate, the time of improvement of clinical symptoms, the time of hemostasis and the time of hospitalization in the study group were all decreased($P<0.05$), but there was no statistically significant difference in fatality rate between the two groups by statistical analysis ($P>0.05$). **Conclusion:** Enteric probiotics combined with octreotide in the treatment of liver cirrhosis combined with gastroesophageal varicosity primary hemorrhage is effective. It can improve the hemodynamics and promote the balance of intestinal flora, and has better prognosis.

Key words: Liver cirrhosis; Gastroesophageal varicosity; Enteric probiotics; Octreotide; Hemodynamics; Prognosis

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作者简介:董胜肖(1979-),男,本科,主治医师,从事消化内科方面的研究,E-mail:mklgnc@163.com

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前言

肝硬化是临床上严重的肝脏疾病,患者因一种或多种病因反复、长期作用导致肝脏弥漫性损害,至疾病中后期患者可发生多种严重的并发症,死亡率较高^[1-3]。胃食管静脉曲张是肝硬化疾病患者常见的并发症,患者可表现为持续高热、黑便等临床症状,病情严重者可发生消化道大出血,病情凶险,严重威胁患者的生命健康^[4,5]。目前,临床上对于肝硬化合并胃食管静脉曲张消化道出血患者的主要治疗原则是迅速止血、补充血容量、积极防治并发症等^[6,7]。奥曲肽是人工合成的生长抑素衍生物,是治疗消化道出血的常用药物^[8,9]。但是肝硬化合并胃食管静脉曲张患者所致的消化道出血伴有血流动力学的改变和肝功能的降低,仅应用奥曲肽治疗效果不甚满意^[10]。肠道益生菌具有抑制病原微生物、增强免疫应答、预防癌症等多种效用,近年来有研究报道,肠道益生菌用于慢性肝病治疗取得了较好的疗效^[11,12]。鉴于此,本研究通过探讨肠道益生菌联合奥曲肽对肝硬化合并胃食管静脉曲张初次出血患者血流动力学及预后的影响,以期为临床治疗提供药物选择依据,现作以下阐述。

1 资料与方法

1.1 一般资料

选取我院于2016年5月-2017年4月收治的肝硬化合并胃食管静脉曲张初次出血患者96例。纳入标准:(1)所有患者均经内镜检查确诊为胃食管静脉曲张破裂引发的上消化道出血;(2)所有患者均符合《病毒性肝炎防治方案》^[13]中所制定的相关标准;(3)临床病历资料完整者。排除标准:(1)合并心、脑、肺、肾等脏器功能严重障碍者;(2)伴有肝癌疾病者;(3)入院前15天内接受过影响胃肠动力的药物治疗者;(4)妊娠期或哺乳期妇女;(5)对本研究相关药物过敏者。以随机数字表法分成研究组(n=48)和对照组(n=48),其中研究组男27例,女21例,年龄21-79岁,平均(53.26±7.32)岁;肝硬化类型:病毒性肝炎肝硬化33例,酒精性肝硬化7例,隐源性肝硬化8例;Child-Pugh分级:A级13例,B级28例,C级7例。对照组男29例,女19例,年龄23-76岁,平均(54.19±7.33)岁;肝硬化类型:病毒性肝炎肝硬化31例,酒精性肝硬化8例,隐源性肝硬化9例;Child-Pugh分级:A级12例,B级30例,C级6例。比较两组一般资料差异无统计学意义(P>0.05),均衡可比。两组患者均签

署了知情同意书,我院伦理委员会已批准本研究。

1.2 方法

两组患者入院后均予以保肝、输血、降门脉高压等常规治疗,在此基础上对照组予以奥曲肽(辽宁诺维诺制药股份有限公司,国药准字:H20090116,规格:0.1 mg)治疗,以25 μg/h的控制剂量持续静滴,治疗总剂量为100 μg,1次/天,治疗28天。研究组则在对照组的基础上采用肠道益生菌治疗,即口服肠道益生菌2粒/次,3次/天。治疗28天。

1.3 观察指标

分别比较两组临床治疗总有效率,其中临床疗效判定标准如下^[14],显效:治疗后患者胃食管底部无出血;有效:治疗后患者胃食管底部无出血,但存在呕血或便血等症状;无效:治疗后患者胃食管底部有出血,且存在呕血或便血情况。总有效率=(显效人数+有效人数)/总人数×100%。采用彩色多普勒超声诊断仪测定治疗前后血流动力学指标水平,包括心输出量(cardiac output, CO)、心脏指数(cardiac index, CI)、门静脉血流量(portal vein blood flow, PVF)、食管静脉曲张变化(esophagus varicose diversification, EVD),探头频率为3.5-4.0 MHz。分别于治疗前后采集两组患者清晨空腹静脉血5 mL,以3000 r/min离心10 min,取上层血清保存于-80℃冰箱中待检。其中血清内皮素(endothelin, ET)采用放射免疫法进行测定,一氧化氮(nitric oxide, NO)采用酶联免疫吸附法(试剂盒均购自上海酶联科技有限公司)进行检测,内毒素脂多糖(lipopolysaccharide, LPS)采用改良鲎试验法进行测定,试剂盒购自厦门鲎试剂试验厂。观察两组患者临床症状改善时间、止血时间以及住院时间,采用电话查询或者门诊复查等方式随访12个月内的再出血率、病死率。

1.4 统计学方法

本研究数据均采用SPSS20.0软件进行检测分析,PVF、EVD、ET水平等计量资料以($\bar{x} \pm s$)表示,实施t检验,总有效率、再出血率、病死率等计数资料以[n(%)]表示,实施 χ^2 检验,检验水准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组临床治疗总有效率比较

研究组临床治疗总有效率为93.75%(45/48),高于对照组的79.17%(38/48)(P<0.05)。见表1。

表1 两组临床治疗总有效率比较[n(%)]

Table 1 Comparison of total effective rates of clinical treatment in the two groups[n(%)]

Groups	n	Excellence	Effective	Invalid	Total effective rate
Study group	48	25(52.08)	20(41.67)	3(6.25)	45(93.75)
Control group	48	23(47.92)	15(31.25)	10(20.83)	38(79.17)
χ^2	-				4.360
P	-				0.037

2.2 治疗前后两组血流动力学指标水平对比

治疗前两组患者CO、CI、PVF、EVD水平对比差异无统计学意义(P>0.05);治疗后两组患者CO、CI、PVF、EVD均较治疗前降低,且研究组低于对照组(P<0.05)。见表2。

2.3 治疗前后两组ET、NO、LPS水平比较

治疗前两组患者血清ET、NO、LPS水平对比差异均无统计学意义(P>0.05);治疗后两组患者血清ET、NO、LPS水平均较治疗前降低,且研究组低于对照组(P<0.05)。见表3。

表 2 治疗前后两组血流动力学指标水平对比($\bar{x} \pm s$)

Table 2 Comparison of hemodynamics indexes in the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	CO(L/min)		CI(L/min·m ²)		PVF(L/min)		EVD(mm)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	48	6.89± 0.34	5.09± 0.28*	4.77± 0.32	3.12± 0.24*	1.40± 0.21	0.79± 0.12*	5.71± 1.48	3.20± 0.56*
Control group	48	6.85± 0.36	5.98± 0.31*	4.81± 0.30	3.93± 0.28*	1.41± 0.22	1.08± 0.18*	5.66± 1.50	4.90± 1.31*
t	-	0.560	14.761	0.632	15.217	0.228	9.287	0.164	8.267
P	-	0.577	0.000	0.529	0.000	0.820	0.000	0.870	0.000

Note: Compared with before treatment, *P<0.05.

表 3 治疗前后两组 ET、NO、LPS 水平比较($\bar{x} \pm s$)

Table 3 Comparison of the levels of ET, NO and LPS before and after treatment in the two groups($\bar{x} \pm s$)

Groups	n	ET(ng/L)		NO(μmol/L)		LPS(EU/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	48	85.18± 13.92	50.77± 12.12*	74.42± 11.18	36.31± 8.20*	0.21± 0.06	0.07± 0.01*
Control group	48	85.22± 14.01	66.25± 12.61*	75.02± 11.20	51.05± 8.11*	0.22± 0.05	0.14± 0.03*
t	-	0.365	6.132	0.263	8.855	0.015	15.336
P	-	0.716	0.000	0.793	0.000	0.987	0.000

Note: Compared with before treatment, *P<0.05.

2.4 两组术后情况比较

与对照组比较,研究组再出血率、临床症状改善时间、止血

时间以及住院时间均降低(P<0.05),而两组病死率经统计分析差异无统计学意义(P>0.05)。见表 4。

表 4 两组术后情况比较

Table 4 Comparison of postoperative condition in the two groups

Groups	n	Rebleeding rate(%)	Fatality rate(%)	Time of improvement of clinical symptoms(d)	Time of hemostasis(d)	Time of hospitalization(d)
Study group	48	6(12.50)	4(8.33)	25.02± 5.38	13.57± 4.87	6.75± 1.34
Control group	48	15(31.25)	5(10.42)	46.02± 6.29	22.54± 5.48	10.08± 2.21
x ² /t	-	4.937	0.123	17.578	8.477	8.927
P	-	0.026	0.726	0.000	0.000	0.000

3 讨论

肝硬化属于消化内科最为常见的一种疾病,且近年来随着人们生活水平的不断提高以及饮食习惯的逐渐改变,该病的发病率逐年递增,严重威胁着人们的生命健康安全^[15-17]。肝硬化患者门静脉压较高,容易发生体液循环紊乱,同时肠道内的菌群出现变化,使得致病菌数量增加,进一步引发各种并发症^[18]。对于肝硬化患者需进行及时有效的治疗,并注意饮食以及作息时间,一旦病情恶化,极易引发胃食管静脉曲张出血^[19,20]。且在初次出血后导致习惯性出血,进一步增加了临床治疗的难度。目前临床上对于肝硬化合并胃食管静脉曲张初次出血的治疗方法较多,主要包括气囊压迫法、内镜治疗、手术治疗等,由于各医院设备条件不同,保守治疗仍然是目前治疗的重要方法^[21-23]。奥曲肽是一种人工合成的生长抑素类似物,它具有天然生长抑素的多种生理功能,可以抑制生长激素,分泌促甲状腺激素、胰酶、胃酸、胰岛素等,能够有效降低门静脉压力、减少内脏血流量,是目前治疗消化道出血的常用药物^[24,25]。

本研究结果发现,研究组临床治疗总有效率较高,奥曲肽可有效抑制胃肠蠕动,从而降低静脉系统中的压力,同时具有修复组织的作用,而肠道益生菌可有效促进双歧杆菌、粪肠球菌以及嗜酸乳杆菌的平衡,有效防止消化道黏膜受损,并对菌群毒素的产生起到一定的抑制作用。两者联合应用可显著提高临床治疗效果。此外,治疗后两组患者 CO、CI、PVF、EVD 均较治疗前降低,且研究组低于对照组(P<0.05),肠道益生菌与奥曲肽联用可有效降低外周血管阻力、门脉高压以及内脏高动力循环有关,奥曲肽静脉滴注融入血液后,可有效抑制胃肠蠕动,从而降低静脉系统压力,同时还可对组织的修复起到一定的作用,改善患者的血流动力学^[26,27]。并且肠道益生菌可恢复肠道内菌群平衡,继而避免消化道黏膜受损,减少出血^[28,29]。另外,肠道益生菌与奥曲肽联用可显著降低血清 ET、NO、LPS 水平,可能是因为肠道益生菌可结合胃肠黏膜细胞受体,从而加快了增殖速度,并通过黏附于胃肠黏膜上皮细胞与病菌竞争营养,进而抑制病菌的定植以及入侵,进一步改善了肠道菌群的平衡,同时可以阻止肠道菌群异位至体循环系统中,从而减少肠源性

LPS血症的发生及其产生的级联反应状态,血清ET、NO水平也相应降低^[30]。本研究结果显示,与对照组比较,研究组再出血率、临床症状改善时间、止血时间以及住院时间均降低($P<0.05$),这表明了肠道益生菌与奥曲肽联用治疗肝硬化合并胃食管静脉曲张初次出血的预后较佳,而两组病死率比较差异无统计学意义,这可能是由于本研究样本量较小,结果存在一定的偏倚,后续研究将增大样本量以获得更为准确的数据。

综上所述,肠道益生菌联合奥曲肽治疗肝硬化合并胃食管静脉曲张初次出血患者较单用奥曲肽治疗,疗效更为显著,可改善患者血流动力学,降低血清ET、NO、LPS水平,提高患者预后。

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