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# 双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱对NAFLD患者肝功能、脂糖代谢及炎症因子的影响*

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**摘要 目的:**探讨双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱对非酒精性脂肪性肝病(NAFLD)患者肝功能、脂糖代谢及炎症因子的影响。**方法:**选取我院收治的123例NAFLD患者,根据乱数表法将患者分为对照组(n=61)和研究组(n=62),其中对照组给予多烯磷脂酰胆碱治疗,研究组在对照组的基础上联合双歧杆菌三联活菌胶囊治疗,比较两组临床疗效、肝功能、脂糖代谢及炎症因子,记录两组治疗期间不良反应情况。**结果:**研究组治疗12周后的临床总有效率为82.26%(51/62),高于对照组的63.93%(39/61)($P$<0.05)。两组治疗12周后谷氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)、总胆红素(TBIL)、白介素-6(IL-6)、C反应蛋白(CRP)、肿瘤坏死因子-α(TNF-α)均下降,且研究组低于对照组($P$<0.05)。研究组治疗12周后空腹血糖(FPG)、总胆固醇(TC)、低密度脂蛋白(LDL-C)、甘油三酯(TG)均降低,且研究组低于对照组($P$<0.05)。高密度脂蛋白(HDL-C)升高,且研究组高于对照组($P$<0.05)。两组不良反应发生率对比未见显著性差异($P$>0.05)。**结论:**双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱治疗NAFLD,用药安全性较好,疗效确切,可有效改善患者肝功能、炎症因子水平及脂糖代谢。

**关键词:**多烯磷脂酰胆碱;双歧杆菌三联活菌胶囊;非酒精性脂肪性肝病;肝功能;脂糖代谢;炎症因子

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# Effects of Bifidobacterium Triple Viable Capsule Combined with Polyene Phosphatidylcholine on Liver Function, Metabolism of Lipopolysaccharide and Inflammatory Factors in NAFLD Patients*

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**ABSTRACT Objective:** To investigate the effect of Bifidobacterium triple viable capsule combined with polyene phosphatidylcholine on liver function, lipid and glucose metabolism and inflammatory factors in patients with nonalcoholic fatty liver disease (NAFLD). **Methods:** 123 patients with NAFLD in our hospital were selected. The patients were randomly divided into control group (n=61) and study group (n=62) according to the method of random number table. The control group was treated with polyene phosphatidylcholine, and the study group was treated with Bifidobacterium triple viable Capsule on the basis of the control group. The clinical effect, liver function, lipid and sugar metabolism and inflammatory factors of the two groups were compared, and the adverse reactions during the treatment were recorded. **Results:** The total clinical effective rate of the study group was 82.26% (51/62), which was higher than 63.93% (39/61) of the control group ($P$<0.05). After 12 weeks of treatment, Glutamate aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) were all decreased in the two groups, which were lower in the study group than in the control group ($P$<0.05). The Total cholesterol (TC), high density lipoprotein (HDL-C), triglyceride (TG), ow density lipoprotein (LDL-C), fasting blood glucose (FPG) in the study group were all lower than those in the control group ($P$<0.05). There was no significant difference in the incidence of adverse reactions between the two groups ($P$>0.05). **Conclusion:** Bifidobacterium triple viable capsule combined with polyene phosphatidylcholine can effectively improve the liver function, inflammatory factor level and glycolipid metabolism of patients with NAFLD.

**Key words:** Polyene phosphatidylcholine; Bifidobacterium triple viable capsule; Nonalcoholic fatty liver disease; Liver function; Lipopolysaccharide metabolism; Inflammatory factors

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## 前言

非酒精性脂肪性肝病( NAFLD)是指除酒精和其他明确引起肝损因素所致,最终引起肝细胞内脂肪堆积和变性的病理综合征,临床主要表现为消化不良、乏力、肝区隐痛、肝脾增大等[1,2]。NAFLD 是消化科常见病和多发病,患者多伴有中心性肥胖、2 型糖尿病以及脂质代谢紊乱等[3]。现临床针对 NAFLD 的治疗尚无统一方案,多以保肝、降脂等药物治疗为主[4]。多烯磷脂酰胆碱为治疗肝脏的常用药物,可辅助性改善肝损伤[5],但仍有不少患者经单用多烯磷脂酰胆碱治疗后,效果欠佳,尚需优化治疗。近年来不少学者发现肠道菌群在 NAFLD 的疾病进展中发挥重要作用[6]。双歧杆菌三联活菌胶囊可以帮助调整人体肠道菌群的平衡,是消化类的常用药物[7]。本研究通过对我院收治的 NAFLD 患者给予双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱治疗,疗效确切。

## 1 资料与方法

### 1.1 基线资料

选取我院收治的 NAFLD 患者 123 例, 选取时间:2016 年 8 月 ~2019 年 5 月。本次研究已获得我院伦理学委员会批准。纳入标准:(1) 诊断标准参考《非酒精性脂肪性肝病诊疗指南(2010 版)》[8];(2)肝脏影像学确诊为弥漫性脂肪肝,无饮酒史或乙醇量不超过 140g/ 周;(3) 知情本研究且签署了同意书;(4)入组前 1 个月未接受过相关治疗者。排除标准:(1)合并药物性肝炎、病毒性肝炎、自身免疫性肝病以及酒精性肝病等;(2)各种原因导致的明确肝硬化失代偿期者;(3) 心脑肾等重要脏器严重障碍者;(4)妊娠及哺乳期妇女;(5)伴有精神疾患无法沟通交流者;(6)甲状腺功能减退症患者;(7)对本次研究药物存在禁忌症者。根据乱数表法将患者分为研究组(n=62)、对照组(n=61),其中研究组男 37 例,女 25 例,年龄 41~74 岁,平均(53.37± 4.61)岁;病程 1~5 年,平均(2.86± 1.17)年;体质量指数 21.2~26.9 kg/m$^2$,平均(23.85± 0.72)kg/m$^2$。对照组男 33 例,女 28 例,年龄 43~72 岁,平均(53.68± 4.92)岁;病程 1~6 年,平均(2.79± 1.08)年;体质量指数 21.3~26.5 kg/m$^2$,平均(23.83± 0.92)kg/m$^2$。两组一般资料比较无差异($P$>0.05)。

### 1.2 治疗方法

对照组给予多烯磷脂酰胆碱(赛诺菲(北京)制药有限公司,国药准字 H20059010,规格:228 mg)治疗,口服,456 mg/ 次,3 次 /d。研究组则在对照组的基础上联合双歧杆菌三联活菌胶囊(上海上药信谊药厂有限公司,国药准字 S10950032,规格:0.21 g)治疗,630 mg/ 次,2 次 /d。均治疗 12 周。

### 1.3 观察指标

(1)抽取患者空腹静脉血 4 mL,抽血时间:治疗前、治疗 12 周后清晨, 3900 r/min 离心 15 min,离心半径 12 cm,取上清液待测。采用美国 BECKMAN CX8 型全自动生化分析仪及配套试剂盒检测低密度脂蛋白(LDL-C)、空腹血糖(FPG)、高密度脂蛋白(HDL-C)、谷氨酸氨基转移酶(ALT)、总胆固醇(TC)、天冬氨酸氨基转移酶(AST)、总胆红素(TBIL)、甘油三酯(TG)。采用酶联免疫吸附试验检测白介素 -6(IL-6)、C 反应蛋白(CRP)、肿瘤坏死因子 -α(TNF-α)水平,严格遵守试剂盒(武汉博士德生物科技有限公司)说明书进行操作。(2)记录两组治疗期间不良反应状况。(3)记录两组患者治疗 12 周后的临床疗效。

### 1.4 疗效判定标准

显效:肝脏 B 超提示脂肪肝消失或脂肪肝程度下降 2 级,AST、ALT、TBIL 中有 1 项或多项恢复正常范围;有效:肝脏 B 超提示脂肪肝程度下降 1 级,AST、ALT、TBIL 中改善程度 >50%但未恢复至正常; 无效:肝脏 B 超提示未见改善甚至加重,AST、ALT、TBIL 中改善程度 <50%。总有效率 = 显效率 + 有效率。

### 1.5 统计学方法

研究数据录入 SPSS24.0 软件处理。计数资料以率表示,行卡方检验。计量资料用均数± 标准差($\bar{x}\pm s$)表示,行 t 检验。α=0.05 为检验水准。

## 2 结果

### 2.1 疗效比较

治疗 12 周后, 研究组的临床总有效率为 82.26%(51/62),高于对照组的 63.93%(39/61)($P$<0.05);详见表 1。

表 1 临床疗效比较 例(%)

Table 1 Comparison of clinical effects n(%)

| Groups | Markedly effective | Effective | Invalid | Total effective rate |
|---|---|---|---|---|
| Control group(n=61) | 13(21.31) | 26(42.62) | 22(36.07) | 39(63.93) |
| Study group(n=62) | 19(30.65) | 32(51.61) | 11(17.74) | 51(82.26) |
| $x^2$ | | | | 5.259 |
| $P$ | | | | 0.022 |

### 2.2 肝功能指标比较

两组治疗前 AST、ALT、TBIL 比较无差异($P$>0.05);两组治疗 12 周后 AST、ALT、TBIL 均下降, 且研究组低于对照组($P$<0.05);详见表 2。

### 2.3 脂糖代谢指标比较

两组治疗前 TC、TG、LDL-C、HDL-C、FPG 比较无差异($P$>0.05); 对照组治疗前、治疗 12 周后 TC、TG、LDL-C、HDL-C、FPG 比较差异无统计学意义($P$>0.05);研究组治疗 12 周后 TC、TG、LDL-C、FPG 均降低, 且研究组低于对照组($P$<0.05), 研究组治疗 12 周后 HDL-C 升高, 且研究组高于对照组($P$<0.05);详见表 3。

表 2 肝功能指标比较($\bar{x}\pm s$)

Table 2 Comparison of liver function indexes($\bar{x}\pm s$)

| Groups | AST(U/L) | | ALT(U/L) | | TBIL(mmol/L) | |
|---|---|---|---|---|---|---|
| | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment |
| Control group(n=61) | 51.91± 5.43 | 33.50± 5.57* | 69.29± 9.01 | 42.19± 5.51* | 14.92± 2.44 | 11.35± 1.76* |
| Study group(n=62) | 51.75± 6.89 | 24.10± 5.83* | 68.67± 8.66 | 25.68± 4.94* | 15.09± 2.39 | 8.05± 1.53* |
| t | 0.143 | 9.140 | 0.389 | 17.503 | 0.390 | 11.103 |
| *P* | 0.887 | 0.000 | 0.698 | 0.000 | 0.697 | 0.000 |

Note: compared with before treatment, *$P$<0.05.

表 3 脂糖代谢指标比较($\bar{x}\pm s$)

Table 3 Comparison of glycolipid metabolism indexes($\bar{x}\pm s$)

| Groups | TC(mmol/L) | | TG(mmol/L) | | LDL-C(mmol/L) | | HDL-C(mmol/L) | | FPG(mmol/L) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment |
| Control group(n=61) | 5.35± 0.56 | 5.17± 0.87 | 2.24± 0.26 | 2.05± 0.28 | 3.05± 0.26 | 2.91± 0.19 | 1.54± 0.21 | 1.59± 0.25 | 6.12± 0.59 | 6.04± 0.48 |
| Study group(n=62) | 5.41± 0.62 | 4.05± 0.51* | 2.31± 0.23 | 1.28± 0.12* | 2.97± 0.31 | 1.16± 0.14* | 1.49± 0.23 | 1.85± 0.27* | 6.15± 0.43 | 5.26± 0.32* |
| t | 0.563 | 8.727 | 1.582 | 19.878 | 1.549 | 58.219 | 1.258 | 5.539 | 0.323 | 10.620 |
| *P* | 0.575 | 0.000 | 0.116 | 0.000 | 0.124 | 0.000 | 0.211 | 0.000 | 0.748 | 0.000 |

Note: compared with before treatment, *$P$<0.05.

### 2.4 炎症因子指标比较

两组治疗前 IL-6、CRP、TNF-α 比较无差异($P$>0.05)；两组治疗 12 周后 IL-6、CRP、TNF-α 均降低，且研究组低于对照组($P$<0.05)；详见表 4。

表 4 炎症因子指标比较($\bar{x}\pm s$)

Table 4 Comparison of inflammatory factors($\bar{x}\pm s$)

| Groups | IL-6(ng/L) | | CRP(mg/L) | | TNF-α(ng/L) | |
|---|---|---|---|---|---|---|
| | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment | Before treatment | 12 weeks after treatment |
| Control group(n=61) | 76.38± 5.76 | 58.12± 6.27* | 17.26± 3.27 | 12.03± 3.25* | 231.30± 27.18 | 174.59± 24.08* |
| Study group(n=62) | 75.46± 6.34 | 26.25± 5.03* | 17.19± 4.32 | 8.42± 3.34* | 230.30± 30.25 | 103.86± 29.12* |
| t | 0.842 | 31.119 | 0.101 | 6.074 | 0.193 | 14.667 |
| *P* | 0.401 | 0.000 | 0.920 | 0.000 | 0.847 | 0.000 |

Note: compared with before treatment, *$P$<0.05.

### 2.5 不良反应比较

对照组出现 2 例腹泻、5 例腹胀、3 例恶心呕吐，不良反应发生率为 16.39%(10/61)；研究组出现 6 例腹胀、4 例恶心呕吐、3 例腹泻，不良反应发生率为 20.97%(13/62)；两组不良反应发生率对比未见显著性差异($x^2$=0.423，$P$=0.515)。

## 3 讨论

NAFLD 为全球最常见的肝病之一，在西方发达国家，约有 20%~30%的人患有该类疾病[10,11]。现临床有关 NAFLD 的生理病理学机制尚不十分明确，多数学者认为 NAFLD 发病的主要机制在于 " 二次打击 "，第一次打击为脂类在肝脏细胞的细胞质内大量聚集，第二次打击为触发的细胞毒素引起[12-14]，但以往临床常用的保肝、降脂等药物治疗并不能理想的阻止疾病进展[15]。随着对 NAFLD 的深入研究，不少学者发现肠道菌群结构改变在 NAFLD 的发生发展中起着重要作用[16,17]。NAFLD 患者常伴有不同程度的肠道菌群失调现象，且患者肠道中肠杆菌数量较健康者明显上升，乳杆菌、双歧杆菌和拟杆菌数量减少，导致 NAFLD 患者消除内毒素能力下降，易并发肠源性内毒素血症，加重 NAFLD 的病情[18,19]，同时反复的内毒素血症又可刺激机体炎性因子大量分泌，加重肝细胞的受损，形成恶性循环[20]。双歧杆菌三联活菌胶囊是临床常用的微生态制剂，可改善肠腔内环境，增强黏膜通透性[21,22]。

本次研究结果显示，研究组治疗 12 周后的临床总有效率 82.26%高于对照组 63.93%，可见 NAFLD 患者经双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱治疗后，疗效确切，可进一步提高治疗效果。分析其原因，多烯磷脂酰胆碱进入肝细胞以后，与肝细胞膜相结合，不仅可起到稳定细胞膜的作用，还有助于修复受损的肝细胞，促进肝组织再生，调节肝脏能量平衡，发挥良好的护肝效果[23]。本次研究使用的双歧杆菌三联活菌的主要成分均为人体补充有益菌，可建立强大的生物屏障，维持肠道微生态平衡[24,25]。由于肝脏在解剖及功能上与肠道关系密切，肝脏 70% 的血供来自于大肠回输到门静脉的血液[26]。而本研究中采用联合治疗的 NAFLD 患者，其肝功能改善效果更为显著，可能是因为益生菌可通过调节肠道菌群抑制入侵细菌、产生抗菌因子 - 短链脂肪酸来减轻致病菌对 NAFLD 的肝损伤[27]。以往研究证实，NAFLD 进展过程主要由炎症介导的，同时可伴有肝组织损伤、糖脂代谢紊乱等，其中 IL-6 可诱发肝内炎症与免疫反应，介导肝细胞的损伤；TNF-α 主要通过刺激内毒素促进 IL-6 等炎症因子的合成，介导肝细胞炎症；而 CRP 作为急性时相反应蛋白，同样也可以反映机体炎症程度[28,29]。本次研究中，联合治疗者的糖脂代谢、炎性因子水平改善均优于单用多烯磷脂酰胆碱治疗者，这可能是因为双歧杆菌三联活菌胶囊在提供有益菌的同时，还可抑制致病菌的生成，减少肠源性毒素的产生，减轻肝脏脂质沉积，从而减轻肝脏炎症，调节机体代谢平衡[30]。另两组不良反应发生率比较无差异，可见用药安全性较好。

综上所述，双歧杆菌三联活菌胶囊联合多烯磷脂酰胆碱治疗 NAFLD，用药安全性较好，疗效确切，可有效改善患者肝功能、炎性因子水平及糖脂代谢。

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