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双歧杆菌三联活菌片对溃疡性结肠炎患者免疫功能及 Fas/FasL 表达的影响 *

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摘要 目的:研究双歧杆菌三联活菌片对溃疡性结肠炎患者免疫功能及 Fas/FasL 表达的影响。**方法:**选取 2014 年 7 月至 2015 年 6 月本院收治的 84 例溃疡性结肠炎患者,根据患者入院顺序分为观察组(42 例)和对照组(42 例)两组。对照组采取美沙拉秦肠溶片进行治疗,观察组在此基础上结合双歧杆菌三联活菌片进行治疗。分析两组患者治疗前和治疗 2 个月后炎症因子水平、T 细胞亚群以及 Fas/FasL 表达情况,并比较两组患者的临床疗效。**结果:**观察组总的有效率显著高于对照组($P<0.05$)。治疗后,观察组的血清白介素-1(IL-1)、白介素-6(IL-6)、白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)水平显著低于对照组($P<0.05$), $CD4^+$ 、 $CD4^+/CD8^+$ T 细胞亚群显著高于对照组, $CD8^+$ 、Fas/FasL 表达显著低于对照组,差异均有统计学意义($P<0.05$)。**结论:**使用双歧杆菌三联活菌片治疗溃疡性结肠炎患者能改善患者的免疫功能及 Fas/FasL 表达,减轻炎症反应,临床效果良好。

关键词:双歧杆菌三联活菌片;溃疡性结肠炎;免疫功能;Fas/FasL

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Effect of Bifidobacterium Triple Viable Tablets on the Immune Function and Expression of Fas/FasL of Patients with Ulcerative Colitis*

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ABSTRACT Objective: To study the effect of bifidobacterium triple viable tablets on the immune function and expression of Fas/FasL of patients with ulcerative colitis. **Methods:** 84 patients with ulcerative colitis who were treated from July 2014 to June 2015 in our hospital were selected and divided into the observation group (42 cases) and control group (42 cases) according to the order of admission. The control group was treated with mesalazine enteric-coated tablets, and the observation group was treated with bifidobacterium triple viable tablets. The levels of inflammatory cytokines, T lymphocyte subpopulation and Fas/FasL expression, clinical efficacy were analyzed before and after treatment between two groups. **Results:** The total efficacy of observation group was significantly higher than that of the control group ($P<0.05$). After treatment, the serum interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α) levels of observation group were lower than those of the control group ($P<0.05$). The quantity of $CD4^+$ and $CD4^+/CD8^+$ T cells of observation group were significantly higher than those of the control group, The expression of $CD8^+$ and Fas/FasL were significantly lower than those of the control group ($P<0.05$). **Conclusion:** Bifidobacterium triple viable tablets could relieve the inflammatory response, improve the immune function and Fas / FasL expression and had better clinical efficacy.

Key words: Bifidobacterium triple viable slices; Ulcerative colitis; Immune function; Fas/FasL

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前言

溃疡性结肠炎也被称为非特异性溃疡性结肠炎,是一种慢性疾病,主要特征为弥漫性粘膜炎症,会对乙状结肠和直肠造成累及性影响,也可能分布在整个结肠,临床主要表现为腹痛、粘液脓血便、腹泻,是一种反复发作的慢性疾病,此病的发病率在我国呈现出逐年增加的趋势^[1]。大部分学者认为溃疡性结肠

炎是一种自身免疫性疾病,此病的病因和环境、感染、免疫、精神、遗传等因素相关^[2]。有关文献报道称在治疗溃疡性结肠炎中使用双歧杆菌三联活菌片具有较好的治疗效果,对肠道菌群组成可发挥调节性作用,有利于肠道微环境的改善^[3]。为给临床在治疗溃疡性结肠炎中提供更多可借鉴之处,本已经就双歧杆菌三联活菌片对溃疡性结肠炎患者免疫功能及 Fas/FasL 表达的影响予以研究,现报道如下。

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1 资料与方法

1.1 临床资料

选取 2014 年 7 月至 2015 年 6 月本院收治的 84 例溃疡性结肠炎患者。纳入标准:① 患者的临床诊断和《对全国炎症性肠病诊断治疗规范的共识意见》^[4] 中所制定的溃疡性结肠炎标准相符;② 意识清醒;③ 无肾病、肝病变性衰竭;④ 在最近一个月

内使用过益生菌、免疫调节药、酸奶、抗菌药物等。排除标准:① 家族遗传病史;② 精神障碍史;③ 胃肠道手术史;④ 肠肿瘤、急慢性腹泻、肠结核、肠易激综合征等肠道疾病。整个研究患者知情同意,并得到本院伦理委员会的批准。两组患者的性别、年龄、病程等基本资料比较差异无统计学意义($P>0.05$),具有可比性,见表 1。

表 1 两组患者一般临床资料比较

Table 1 Comparison of the general information between the two groups

Groups	Cases	Sex		Age (year)	Course of disease(d)	Disease classification		
		Male	Female			Mild	Moderate	Serious
Observation group	42	26(61.90)	16(38.10)	62.57± 2.11	3.47± 0.58	26(61.90)	9(21.43)	7(16.67)
Control group	42	24(57.14)	18(42.86)	62.64± 2.15	3.51± 0.62	27(64.29)	8(19.05)	7(16.67)

1.2 治疗方法

所有患者在入院后予以心理干预、饮食指导、常规检查。对照组在此基础上采取美沙拉秦肠溶片(生产厂家:黑龙江天宏药业股份有限公司,规格:0.25 g/片,生产批号:20140312)进行治疗,饭后温水口服,1 g/次,4 次/d。观察组在对照组治疗基础上采取双歧杆菌三联活菌肠溶片(生产厂家:上海信谊药厂有限公司,规格:0.5 g/片,生产批号:20140222)进行治疗,4 片/次,3 次/天。所有患者均需连续治疗 2 个月。

1.3 观察指标

1.3.1 疗效判定 根据患者的脓血便、腹泻、腹痛、肛门烧灼四个方面的临床症状评判患者治疗 2 个月后的临床疗效,其评判标准如下:患者的临床症状消失,经内镜检查肠黏膜恢复至正常状态则为临床治愈;患者治疗后临床症状基本消失,部分假息肉形成及肠黏膜伴有轻度炎症则为显效;肠黏膜病变及临床症状均有所好转则为有效;临床症状以及经内镜检查均无改善则为无效。总有效 = 治愈 + 显效 + 有效。

1.3.2 血清炎症因子水平检测 比较两组患者治疗前和治疗 2 个月后血清炎症因子水平[白细胞介素 -1(IL-1)、白细胞介素 -6(IL-6)、白介素 -8(IL-8)、肿瘤坏死因子 - α (TNF- α)]变化,在清

晨抽取患者空腹静脉血 3 mL,将其放置在 EDTA 抗凝试管中,转速为 3000 r/min,离心时间为 10 min,分离血清后放置在 -50℃ 低温箱中待测,使用酶联免疫法检测 IL-1、IL-6、IL-8、TNF- α 水平,均根据试剂盒说明书完成整个操作过程。

1.3.3 外周血 T 细胞亚群以及 Fas/FasL 表达情况 分析两组患者治疗前和治疗 2 个月后外周血 T 细胞亚群以及 Fas/FasL 表达情况,在清晨抽取患者空腹静脉血 3 mL,将其放置在 EDTA 抗凝试管中,转速为 3000 r/min,离心时间为 10 min,分离血清后放置在 -50℃ 低温箱中待测,检测外周血 T 细胞亚群以及 Fas/FasL 表达均采取 T 细胞亚群分类及定量法完成。

1.4 统计学处理

本实验数据处理选择 SOSS11.5 软件包进行,计量资料用($\bar{x} \pm s$)来表示,采用 t 检验,计数资料用[n(%)]来表示,采取 χ^2 检验,其 $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者治疗的临床疗效比较

观察组总的有效率显著高于对照组 [90.48%(38/42) vs 64.29%(27/42)],差异具有统计学意义($P<0.05$),见表 2。

表 2 两组患者治疗的临床疗效比较[例(%)]

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

Groups	Cases	Cure	Excellent	Effective	Invalid	Total efficacy
Observation group	42	21(50.00)	11(26.19)	6(14.29)	4(9.52)	38(90.48)*
Control group	42	11(26.19)	3(7.14)	13(30.95)	15(35.71)	27(64.29)

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

2.2 两组患者治疗前后血清 IL-1、IL-6、IL-8、TNF- α 水平比较

治疗前,两组患者的血清 IL-1、IL-6、IL-8、TNF- α 水平比较差异无统计学意义 ($P>0.05$); 治疗后, 两组患者的血清 IL-1、

IL-6、IL-8、TNF- α 水平较治疗前显著降低($P<0.05$),观察组患者的血清 IL-1、IL-6、IL-8、TNF- α 水平显著低于对照组($P<0.05$),见表 3。

表 3 两组患者治疗前后血清 IL-1、IL-6、IL-8、TNF- α 水平比较($\bar{x} \pm s$, pg/mL)

Table 3 Comparison of the serum IL-1, IL-6, IL-8, TNF- α levels between the two groups before and after treatment($\bar{x} \pm s$, pg/mL)

Groups	Cases	Time	IL-1	IL-6	IL-8	TNF- α
Observation group	42	Before treatment	27.28± 2.33	23.32± 2.43	31.24± 2.87	28.43± 2.32
		After treatment	13.21± 1.56**	11.33± 1.02**	19.21± 1.65**	16.55± 1.56**
Control group	42	Before treatment	27.31± 2.38	22.37± 2.41	31.27± 2.91	28.49± 2.34
		After treatment	18.98± 1.54*	16.98± 1.76*	24.65± 2.04*	23.32± 1.76*

Note: Compared with before treatment, * $P<0.05$, Compared with control group after treatment, ** $P<0.05$.

2.3 两组患者治疗前后 T 细胞亚群及 Fas/FasL 表达比较

治疗前,两组患者的 CD4⁺、CD8⁺、CD4⁺/CD8⁺T 细胞亚群及 Fas/FasL 表达比较差异无统计学意义(P>0.05);治疗后,两组患者的 CD4⁺、CD4⁺/CD8⁺T 细胞亚群较治疗前显著升高(P<0.05),

CD8⁺、Fas/FasL 表达较治疗前显著降低 (P<0.05), 且观察组的 CD4⁺、CD4⁺/CD8⁺T 细胞亚群显著高于对照组(P<0.05), CD8⁺、Fas/FasL 表达显著低于对照组(P<0.05),见表 4。

表 4 两组患者治疗前后 T 细胞亚群及 Fas/FasL 表达比较($\bar{x} \pm s$)

Table 4 Comparison of the T cell subgroup and Fas/FasL expression between the two groups before and after treatment($\bar{x} \pm s$)

Groups	Cases	Time	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺	Fas(%)	FasL(%)
Observation group	42	Before treatment	37.43± 2.32	31.32± 1.45	1.18± 0.14	29.43± 2.33	19.43± 1.44
		After treatment	45.21± 3.11* [#]	26.54± 1.14* [#]	1.71± 0.22* [#]	13.56± 1.32* [#]	8.12± 0.56* [#]
Control group	42	Before treatment	37.37± 2.31	31.34± 1.46	1.19± 0.15	29.46± 2.31	19.51± 1.48
		After treatment	40.53± 2.41*	29.23± 1.18*	1.51± 0.18*	17.98± 1.87*	12.45± 1.12*

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

3 讨论

溃疡性结肠炎是多因素所致的复发性疾病,病因尚不明确,病变部位常常在直肠和乙状结肠处,也可能会蔓延至近端结肠,情况较为严重时可能会累及末段肠以及全结肠,病变表现为连续性分布^[5,6]。目前,溃疡性结肠炎的治疗主要以缓解患者病情,恢复肠道营养至正常状态为主,进而改善患者的生活质量^[7,8]。溃疡性结肠炎患者的肠道黏膜组织中伴有多种激活的免疫细胞浸润,这些免疫细胞可表达高水平的细胞因子受体、趋化因子受体等^[9,10]。

双歧杆菌三联活菌片是一种较为常见的口服益生菌,能直接对定植在肠黏膜中并且可大量繁殖,增加肠道有益菌,经生物拮抗竞争肠黏膜细胞上的结合位点作用,对其他有害菌的繁殖能发挥抑制总,使微生态和肠道菌群处于动态平衡状态^[14,16]。经双歧杆菌三联活菌片作用对肠黏膜有关淋巴组织活性能起着激活的效应,加强肠黏膜防御屏障以及免疫功效^[17]。除此之外,双歧杆菌三联活菌片对肠黏膜上皮能发挥保护及修复的功效,能有效缓解有毒物质以及细菌给肠黏膜造成的损伤,使其渗透性降低^[18,19]。IL-1、IL-6、IL-8、TNF- α 等炎症因子均在肠黏膜炎症的发生发展过程中发挥重要作用^[11-13]。本研究通过对溃疡性结肠炎患者予以双歧杆菌三联活菌片联合美沙拉秦肠溶片治疗后,患者的 IL-1、IL-6、IL-8、TNF- α 水平均得到显著性降低,其降低的效果显著优于单纯美沙拉秦肠溶片治疗,提示双歧杆菌三联活菌片可有效抑制溃疡性结肠炎患者的炎症反应,并且随着病情好转,患者血清 IL-1、IL-6、IL-8、TNF- α 水平会明显下降。同时,双歧杆菌三联活菌片能诱导 Th1 反应,对外周血 CD4⁺T 细胞亚群能发挥直接的刺激性效果,能促进调节剂使体内 Th1/Th2 平衡状态得以恢复,确保 CD4⁺/CD8⁺ 比值处于正常水平^[20]。本次研究结果显示患者经双歧杆菌三联活菌片联合美沙拉秦肠溶片治疗后 CD4⁺、CD4⁺/CD8⁺ 显著高于单纯的美沙拉秦肠溶片治疗,CD8⁺、Fas/FasL 表达也得到显著想降低,表明双歧杆菌三联活菌片能使 CD4⁺/CD8⁺ 比值恢复至正常水平,有利于 Fas/FasL 表达水平的恢复,进而诱导淋巴细胞凋亡。

总之,使用双歧杆菌三联活菌片治疗溃疡性结肠炎患者能改善患者的免疫功能及 Fas/FasL 表达,减轻炎症反应,临床效果良好。

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