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枯草杆菌二联活菌肠溶胶囊联合泮托拉唑对 UC 患者炎症因子、肠黏膜功能及外周血 Th17、CD4⁺CD25⁺Treg 细胞表达的影响*

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摘要 目的: 观察枯草杆菌二联活菌肠溶胶囊联合泮托拉唑对溃疡性结肠炎(UC)患者炎症因子、肠黏膜功能及外周血 Th17、CD4⁺CD25⁺Treg 细胞表达的影响。**方法:** 研究对象选择 2014 年 7 月~2018 年 9 月期间来我院香山门诊部接受诊治的 80 例 UC 患者, 随机分为联合组(枯草杆菌二联活菌肠溶胶囊联合泮托拉唑治疗)、对照组(泮托拉唑治疗), 各 40 例。对比两组的疗效、炎症因子、肠黏膜功能及外周血中 Th17 及 CD4⁺CD25⁺Treg 细胞表达。记录两组治疗期间不良反应发生情况。**结果:** 联合组的临床总有效率为 92.50%(37/40), 对照组为 70.00%(28/40), 两组比较差异有统计学意义($P<0.05$)。两组不良反应发生率对比无差异($P>0.05$)。联合组治疗 6 个月后血清白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)、C 反应蛋白(CRP)水平均明显比对照组低($P<0.05$)。联合组治疗 6 个月后血清 D-乳酸含量、二胺氧化酶(DAO)水平均明显比对照组低($P<0.05$)。联合组治疗 6 个月后外周血中 Th17 细胞表达比对照组低, CD4⁺CD25⁺Treg 细胞表达比对照组高($P<0.05$)。**结论:** 枯草杆菌二联活菌肠溶胶囊联合泮托拉唑治疗 UC 患者, 可有效改善肠道环境, 使外周血中的 Th17 细胞表达降低, CD4⁺CD25⁺Treg 细胞表达增加, 并缓解炎症状态, 临床效果满意且安全性好。

关键词: 枯草杆菌二联活菌肠溶胶囊; 泮托拉唑; 溃疡性结肠炎; 炎症因子; 肠黏膜功能; Th17 细胞; Treg 细胞

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Effects of Bacillus Subtilis Enteric Coated Capsules Combined with Pantoprazole on Inflammatory Factors, Intestinal Mucosal Function and Expression of Th17 and Treg Cells in Peripheral Blood of Patients with UC*

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ABSTRACT Objective: To observe the effect of Bacillus subtilis enteric coated capsules combined with pantoprazole on inflammatory factors, intestinal mucosal function and expression of Th17, Treg cells in peripheral blood of patients with ulcerative colitis (UC). **Methods:** 80 patients with UC who came to Xiangshan Road outpatient department of our hospital from July 2014 to September 2018 were selected, and were randomly divided into control group (pantoprazole) and combination group (Bacillus subtilis enteric coated capsules combined with pantoprazole), 40 cases in each group. The efficacy, inflammatory factors, intestinal mucosal function and the expression of Th17 and CD4⁺CD25⁺ Treg cells in peripheral blood were compared between the two groups. The incidence of adverse reactions in the two groups was recorded. **Results:** The clinical total effective rate of the combination group was 92.50% (37 / 40), and that of the control group was 70.00% (28/40), the difference was statistically significant ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). The levels of serum interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), C-reactive protein (CRP) of the combination group at 6 months after treatment were significantly lower than those of the control group ($P<0.05$). The levels of serum D-lactic acid and diamine oxidase (DAO) of the combination group at 6 months after treatment were significantly lower than those of the control group ($P<0.05$). 6 months after treatment, expression of Th17 in the combination group was lower than that of the control group, and the expression of CD4⁺CD25⁺Treg cells in the combination group were higher than those of the control group ($P<0.05$). **Conclusion:** Bacillus subtilis enteric coated capsules combined with pantoprazole in the treatment of patients with UC can effectively improve the intestinal environment, reduce the expression of Th17 cells in peripheral blood, increase the

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expression of CD4⁺CD25⁺Treg cells, and reduce the inflammatory state. The clinical effect is satisfactory and the safety is good.

Key words: Bacillus subtilis enteric coated capsules; Pantoprazole; Ulcerative colitis; Inflammatory factors; Intestinal mucosal function; Th17 cells; Treg cells

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前言

溃疡性结肠炎(UC)为病因未明的慢性非特异性肠道炎症反应,临床多表现为腹痛、腹泻、血便,同时还可累及末端回肠及全结肠,病情严重者甚至引起结肠穿孔、下消化道出血等严重并发症,给患者生命安全带来严重威胁^[1-3]。泮托拉唑为质子泵抑制剂,既往常用于 UC 的治疗,可获得一定的治疗效果^[4]。但仍有部分患者存在症状改善不明显、长期用药不良反应大、停药后易复发等情况^[5]。近年临床研究发现^[6],肠道菌群失调现象在 UC 发病机制中起着重要作用,故临床尝试将益生菌用于 UC 的治疗中。枯草杆菌二联活菌肠溶胶囊属于益生菌的一种,可有效调节肠道菌群失调^[7]。本研究探讨枯草杆菌二联活菌肠溶胶囊联合泮托拉唑对 UC 患者的治疗效果,以期临床提供参考。

1 资料与方法

1.1 一般资料

研究对象选择 2014 年 7 月~2018 年 9 月期间来我院香山路门诊部接受诊治的 80 例 UC 患者,纳入标准:(1)均符合《中国炎症性肠病诊断治疗规范的共识意见》^[8]中 UC 诊断标准;经结肠镜、病理学检查确诊;(2)患者及其家属知情本研究且签署了同意书;(3)患者心肝肾等脏器功能无异常;(4)对本次研究药物无禁忌者。排除标准:(1)妊娠或哺乳期妇女;(2)感染性结肠炎、克罗恩病、缺血性肠炎、结肠癌等;(3)肠梗阻、肠穿孔者;(4)依从性差、未能遵从医嘱用药者;(5)患有精神疾病,无法配合沟通者。以上患者随机分为对照组、联合组,各 40 例。联合组男 23 例,女 17 例,平均年龄(36.28±3.72)岁;平均病程(1.26±1.19)年;病情严重程度:轻度 15 例,中度 14 例,重度 11 例。对照组男 22 例,女 18 例,平均年龄(36.71±4.59)岁;平均病程(1.39±1.27)年;病情严重程度:轻度 16 例,中度 15 例,重度 9 例。两组一般资料相比无差异($P>0.05$),具有可比性。研究方案经我院伦理学委员会批准。

1.2 方法

对照组口服泮托拉唑钠肠溶片(杭州中美华东制药有限公司,国药准字 H19990166,规格:40 mg)治疗,晨起服用,40 mg/次,1 次/d。联合组在对照组的基础上联合枯草杆菌二联活菌肠溶胶囊(北京韩美药品有限公司,国药准字 S20030087,规格:250 mg/粒)治疗,500 mg/次,3 次/d。两组均连续治疗 6 个月。

1.3 观察指标

(1)治疗 6 个月后对比两组临床疗效。其中显著好转:腹痛、腹泻、血便等临床症状消失,结肠镜检查发现肠黏膜基本恢复正常,大便常规检查无白细胞、红细胞。好转:结肠镜检查可见假息肉或肠黏膜炎症反应减轻,腹痛、腹泻、血便等临床症状有所改善。无效:症状未见改善甚至加重,结肠镜检查无改变。总有效率=显著好转率+好转率^[9]。(2)采集两组治疗前、治疗 6 个月后的空腹肘静脉血 6 mL,分为两管,一管经离心处理(离心半径 20 cm,3800 r/min 离心 15 min)后保存冰箱中待检。血清 D-乳酸含量、二胺氧化酶(DAO)采用改良酶学分光光度法测定,白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)、C 反应蛋白(CRP)采用酶联免疫吸附法检测,均严格遵守试剂盒(上海晶抗生物工程有限公司)说明书步骤进行操作。另一管采用 Ficoll 密度梯度离心法制备外周血单个核细胞,采用美国库尔特公司生产的 EPICS XL 流式细胞仪检测外周血中 Th17 及 CD4⁺CD25⁺Treg 细胞表达。(3)记录两组不良反应发生情况。

1.4 统计学方法

SPSS 25.0 进行数据分析。计量资料以($\bar{x} \pm s$)表示,采用 t 检验。计数资料以例(%)表示,采用 χ^2 检验。所有统计均采用双侧检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 疗效对比

联合组的临床总有效率为 92.50%(37/40),对照组为 70.00%(28/40),两组比较差异有统计学意义($P<0.05$)。如表 1 所示。

表 1 两组疗效对比 [例(%)]

Table 1 Comparison of curative effect between the two groups [n(%)]

Groups	Significant improvement	Improvement	Invalid	Total effective rate
Control group(n=40)	9(22.50)	19(47.50)	12(30.00)	28(70.00)
Combination group(n=40)	15(37.50)	22(55.00)	3(7.50)	37(92.50)
χ^2				6.646
P				0.010

2.2 两组炎症因子指标对比

两组治疗 6 个月后血清 IL-8、TNF- α 、CRP 水平均明显比治疗前低($P<0.05$),同时联合组治疗 6 个月后血清 IL-8、

TNF- α 、CRP 水平均明显比对照组低($P<0.05$)。如表 2 所示。

2.3 两组肠黏膜功能指标对比

两组治疗 6 个月后血清 D-乳酸含量、DAO 水平均明显比

治疗前低($P<0.05$),同时联合组治疗 6 个月后血清 D-乳酸含量、DAO 水平均明显比对照组低($P<0.05$)。如表 3 所示。

表 2 两组炎症因子指标对比($\bar{x}\pm s$)Table 2 Comparison of inflammatory factors between the two groups($\bar{x}\pm s$)

Groups	IL-8(pg/mL)		TNF- α (ng/mL)		CRP(ng/mL)	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group(n=40)	30.51 $\pm$ 3.49	19.51 $\pm$ 3.49*	37.15 $\pm$ 4.35	24.69 $\pm$ 5.63*	42.67 $\pm$ 5.63	29.35 $\pm$ 4.41*
Combination group(n=40)	30.42 $\pm$ 4.15	12.45 $\pm$ 2.24*	37.86 $\pm$ 5.11	13.24 $\pm$ 3.49*	42.02 $\pm$ 6.19	21.26 $\pm$ 3.35*
t	0.105	10.767	0.669	10.932	0.496	9.239
P	0.917	0.000	0.505	0.000	0.652	0.000

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

表 3 两组肠黏膜功能指标对比($\bar{x}\pm s$)Table 3 Comparison of intestinal mucosal function indexes between the two groups($\bar{x}\pm s$)

Groups	D--lactic acid(mmol/L)		DAO(U/L)	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group(n=40)	5.24 $\pm$ 0.35	3.95 $\pm$ 0.28*	8.23 $\pm$ 1.31	7.44 $\pm$ 1.15*
Combination group(n=40)	5.29 $\pm$ 0.32	3.04 $\pm$ 0.21*	8.28 $\pm$ 1.24	5.83 $\pm$ 0.97*
t	0.667	16.444	0.175	6.768
P	0.507	0.000	0.861	0.000

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

2.4 两组外周血中 Th17 及 CD4⁺CD25⁺Treg 细胞表达对比

两组治疗 6 个月后外周血中 Th17 细胞表达比治疗前低, CD4⁺CD25⁺Treg 细胞表达比治疗前高($P<0.05$),同时联合组治

疗 6 个月后外周血中 Th17 细胞表达比对照组低, CD4⁺CD25⁺Treg 细胞表达比对照组高($P<0.05$)。如表 4 所示。

表 4 两组外周血中 Th17 及 CD4⁺CD25⁺Treg 细胞表达对比($\bar{x}\pm s, \%$)Table 4 Comparison of Th17 and CD4⁺CD25⁺Treg cells expression in peripheral blood of two groups($\bar{x}\pm s, \%$)

Groups	Th17		CD4 ⁺ CD25 ⁺ Treg cell	
	Before treatment	6 months after treatment	Before treatment	6 months after treatment
Control group(n=40)	2.62 $\pm$ 0.39	2.05 $\pm$ 0.33*	2.63 $\pm$ 0.28	4.82 $\pm$ 0.33*
Combination group(n=40)	2.67 $\pm$ 0.41	1.47 $\pm$ 0.29*	2.68 $\pm$ 0.25	6.25 $\pm$ 0.46*
t	0.559	8.350	0.842	15.975
P	0.578	0.000	0.402	0.000

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

2.5 两组不良反应发生率对比

治疗期间,对照组有 1 例口干、1 例皮疹、1 例嗜睡,不良反应发生率为 7.50%(3/40);联合组有 2 例口干、1 例皮疹、1 例嗜睡,不良反应发生率为 10.00%(4/40);两组比较无差异($\chi^2=0.157, P=0.692$)。不良反应经停药处理后消失。

3 讨论

UC 具有病程长、复发率高、易迁延等特点,同时该病也属于结肠癌的癌前病变,UC 患者患癌风险显著高于正常人,严重影响患者日常生活,需及时给予积极有效治疗^[10]。相关流行病学报道结果显示^[11],西方国家 UC 发病率高达 10~15/105。近年来国内报告亦日渐增多,累计超过 12 万例次/年,已成为临

床慢性腹泻和消化系统疾病的主要病因^[12]。UC 的具体发病机制尚不十分明确,多认为与肠道菌群失调引发的黏膜免疫功能受损密切相关^[13]。正常肠道菌群在致病因素影响下被打乱,肠道微生态平衡失调,诱发易感宿主肠道黏膜发生免疫反应,引发炎症介质大量释放,致使肠道出现级联反应引发肠道黏膜损伤^[14-16]。因此,改善肠道菌群环境、减轻炎症反应、提高机体免疫耐受已成为 UC 的主要治疗目标。泮托拉唑在胃壁细胞酸性条件下可被激活并转化为环次磺胺,并与 H⁺-K⁺-ATP 酶上巯基相结合,进而发挥减少胃酸分泌、减轻黏膜损害的作用^[17,18]。但罗丽红^[19]等学者的研究则指出,泮托拉唑治疗 UC 虽近期疗效尚可,但不良反应大,且易复发。考虑到肠道菌群平衡失调在 UC 疾病进展中的重要性,笔者尝试将枯草杆菌二联活菌肠溶胶囊

用于 UC 的辅助治疗中。枯草杆菌二联活菌肠溶胶囊含有枯草杆菌和粪肠球菌,是临床上用以改善肠道菌群平衡的常用药物^[20]。

本研究结果显示,联合组的临床总有效率高于对照组,提示枯草杆菌二联活菌肠溶胶囊联合泮托拉唑治疗 UC 患者,临床效果确切。枯草杆菌二联活菌肠溶胶囊口服后可使肠道内菌群恢复正常,抑制致病菌在人体内繁殖,而泮托拉唑在促进胃肠道功能恢复的同时,还有利于肠道对枯草杆菌二联活菌肠溶胶囊的快速吸收,二者联合应用有效提高 UC 的疗效^[21,22]。本研究结果显示,联合组治疗 6 个月后血清 IL-8、TNF- α 、CRP、D-乳酸含量、DAO 水平以及外周血中 Th17 细胞表达均明显比对照组低,CD4⁺CD25⁺Treg 细胞表达比对照组高。提示枯草杆菌二联活菌肠溶胶囊联合泮托拉唑治疗可改善机体免疫功能及肠粘膜功能,缓解体内炎症反应。既往研究结果显示^[23],Th17 细胞产生的细胞因子可作用于肠道内皮细胞,使其产生多种促炎效应介质如 IL-8、TNF- α 、CRP 等,上述促炎因子可介导肠黏膜病理损伤,诱发 UC 的肠粘膜反应。CD4⁺CD25⁺Treg 细胞具有抑制自身反应性 T 细胞、维持自身免疫耐受以及阻止自身免疫性疾病的发生等功能^[24]。D-乳酸是细菌代谢和裂解的产物,DAO 可反映小肠粘膜结构和功能,当肠粘膜屏障功能受损时,肠粘膜通透性增加,细菌移位致使 D-乳酸、DAO 大量产生^[25]。枯草杆菌二联活菌肠溶胶囊通过胃酸屏障到达肠道崩解后释放活菌,可暂时定植于肠道内,发挥生物夺氧作用,促使氧还原电位及局部氧浓度降低,肠道保护屏障恢复,提高内源性保护屏障,从而形成适合正常优势菌群生长的环境,增强肠道免疫能力^[26,27]。同时枯草杆菌二联活菌肠溶胶囊可诱导免疫耐受,防止炎症反应的发生,减少 IL-8、TNF- α 、CRP 等炎症介质的释放,恢复肠道免疫平衡^[28,29]。既往有研究结果显示^[30],采用益生菌可恢复肠道菌群平衡系统,有效缓解临床症状,提高抵抗力。与本研究结果大致类似。临床实践中泮托拉唑易引起口干、皮疹、嗜睡等不良反应,本研究中两组不良反应发生率对比无统计学差异,可见治疗方案均安全性较好。本次研究样本量偏少,且未进行随访研究观察两组患者复发情况,有待进一步的大样本量、增加随访考察的研究。

综上所述,枯草杆菌二联活菌肠溶胶囊联合泮托拉唑治疗 UC 患者,可促进肠道功能恢复,减轻机体炎性反应,并使外周血中的 Th17 细胞表达降低,CD4⁺CD25⁺Treg 细胞表达增加,临床效果满意且安全性好。

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