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复方谷氨酰胺联合双歧杆菌三联活菌胶囊治疗腹泻型肠易激综合征患者的临床疗效 *

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摘要 目的:研究复方谷氨酰胺以及双歧杆菌三联活菌胶囊联用治疗腹泻型肠易激综合征患者的临床疗效。**方法:**选择 2016 年 1 月～2020 年 2 月安徽省濉溪县医院收治的 81 例腹泻型肠易激综合征患者,将其随机分为两组。对照组 41 例患者仅口服 420 mg 的双歧杆菌三联活菌胶囊,每天 3 次;观察组 40 例患者加用 500 mg 的复方谷氨酰胺,每天 3 次。检测两组治疗前后的血清内毒素、二胺氧化酶活性及 D- 乳酸水平;血清白介素 -6(Interleukin -6,IL-6)、肿瘤坏死因子 -α(Tumor necrosis factor alpha,TNF-α)、白介素 -8(Interleukin -8,IL-8)、高敏 C 反应蛋白(High sensitive C reactive protein,hs-CRP)水平;血浆生长抑素和血管活性肠肽水平并比较治疗后临床疗效及治疗过程中不良反应的发生情况。**结果:**治疗后,观察组的有效率为 97.5%,明显高于对照组(75.61%,*P*<0.05);两组的血清内毒素、二胺氧化酶活性及 D- 乳酸、IL-6、TNF-α、IL-8、hs-CRP 水平、血浆生长抑素和血管活性肠肽水平均较治疗前明显降低(*P*<0.05),且观察组以上指标均明显低于对照组(*P*<0.05)。观察组治疗期间的有 2 例嗜睡、头晕、乏力不适,发生率为 5.00 %,对照组有 2 例头晕,1 例头痛、口干,发生率为 7.32 %,两组对比无统计学意义(*P*>0.05)。**结论:**复方谷氨酰胺联合双歧杆菌三联活菌胶囊治疗腹泻型肠易激综合征患者的临床效果明显优于单用双歧杆菌三联活菌胶囊治疗,其可有效修复肠黏膜屏障损伤,可能与其减轻炎症反应并改善胃肠激素水平有关。

关键词:双歧杆菌三联活菌胶囊;复方谷氨酰胺;腹泻型肠易激综合征

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Clinical Effect of Compound Glutamine Combined with Bifidobacterium Sanlian Capsule on the Diarrhea Type Irritable Bowel Syndrome*

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ABSTRACT Objective: To investigate the clinical effecacy of compound glutamine combined with bifidobacterium sanlian capsule on diarrhea type irritable bowel syndrome. **Methods:** Eighty-one patients with diarrhea type irritable bowel syndrome were selected from Suixi County Hospital of Anhui Province from January 2016 to February 2020 were randomly divided into two groups randomly. The control group (n=41) only took 420 mg bifidus triple viable capsule three times a day, the observation group (n=40) added 500 mg compound glutamine three times a day. The levels of serum endotoxin, diamine oxidase activity and D-lactate, serum IL-6, TNF-α, IL-8, hs-CRP levels, plasma somatostatin and vasoactive intestinal peptide were measured before and after treatment, and also detected compare clinical efficacy after treatment and occurrence of adverse reactions during treatment. **Results:** After treatment, the effective rate of the observation group was 97.5 %, which was significantly higher than that of the control group (75.61 %, *P*<0.05). The serum endotoxin, diamine oxidase activity, D-lactic acid, IL-6, TNF-α, IL-8, hs-CRP levels, plasma somatostatin and vasoactive intestinal peptide levels of the two groups were significantly reduced (*P*<0.05), and the above indexes in the observation group were significantly lower than those in the control group (*P*<0.05). The observation group had 2 cases of drowsiness, dizziness, fatigue and discomfort during the treatment period, the incidence rate was 5.00 %, the control group had 2 cases of dizziness, 1 case of headache and dry mouth, the incidence rate was 7.32 %, there was no statistical significance between the two groups (*P*>0.05). **Conclusion:** The clinical effect of compound glutamine combined with Bifidobacterium triple live bacteria capsule in the treatment of patients with diarrhea irritable bowel syndrome is significantly better than that of bifidobacterium triple live bacteria capsule alone. Inflammation is related to improving gastrointestinal hormone levels.

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前言

肠易激综合征是一种极为常见的慢性功能性胃肠疾病，肠镜检查并没有器质性病变，主要的症状为腹部不适或腹胀、腹痛、或便秘或腹泻、或便秘与腹泻交替发生，有时患者的大便中会带有大量的黏液，腹痛等不适症状会在排便后有所减轻[1-4]。其病因和病机不明，常常给予对症治疗，但没有一种药物能完全有效地治疗各种类型的肠易激综合征，治疗效果往往无法令人满意[5,6]。因而，寻求有效的联合用药方案极为重要。

双歧杆菌三联活菌可以充分的补充机体的生理细菌，调节肠道菌群的正常平衡，抑制对肠道内致病菌的不断生长，改善消化功能，还能有效合成机体生长发育和正常代谢过程所必须的维生素，提高患者的免疫力[7]。复方谷氨酰胺是由白术、谷氨酰胺、茯苓以及甘草组成的一种复合制剂。其中，甘草具有与皮质激素较为相似的抗炎以及抗过敏效果；白术具有修复胃肠黏膜以及调节肠道蠕动的效果；谷氨酰胺是临床上常用的一种免疫营养物质，具有保护肠道黏膜、促进蛋白质合成以及参与免疫细胞的能量代谢等多种功能，在降低危重患者肠源性感染，增强肠道的免疫功能以及维持肠道黏膜上皮结构的完整性等方面有重要的功能[8]。本研究将复方谷氨酰胺以及双歧杆菌三联活菌胶囊联用，分析其对腹泻型肠易激综合征的疗效。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月～2020 年 2 月安徽省濉溪县医院收治的 81 例腹泻型肠易激综合征患者，纳入标准：符合相关的诊断标准[9]；经大便常规和培养、内镜检查、血液生化、钡剂灌肠造影以及腹部 B 超等检查，排除患有肠道器质性疾病；知情同意。排除标准：(1)有重大腹部外科手术史的患者；(2)严重精神疾病患者；(3)在本研究开展的过程中采取抗生素、解痉剂或者止泻剂等影响观察的患者；(4)患有其他严重的系统性疾病或者器质性肠道疾病或，如糖尿病、结缔组织病、甲状腺功能亢进等。用抽签法随机将其分为两组。观察组 40 例，男 16 例，女 24 例；年龄 20~73 岁，平均(43.19±4.52)岁；病程 4 个月 ~6 年，平均(1.39±0.24)年。对照组 41 例，男 17 例，女 24 例；年龄 20~73 岁，平均(42.57±5.38)岁；病程 4 个月 ~6 年，平均(1.34±0.27)年。两组的基线资料比较差异均无统计学意义(P>0.05)，具有可比性。

1.2 治疗方法

对照组仅口服 420 mg 的双歧杆菌三联活菌胶囊（上海信谊药厂，国药准字 S10950032)，每天 3 次；观察组加用 500 mg 的复方谷氨酰胺(地奥集团成都药业，国药准字 H51023598)，每天 3 次。均给药 2 w。治疗期间无病例脱落，所有患者均完成相应的治疗和检测。

1.3 观察指标

疗效标准[9]：(1)治愈：每天大便 1～2 次，症状(腹胀和腹痛等)完全消失，大便软便且成形，没有出现黏液便；(2)显效：每天大便 3～4 次，症状(腹胀和腹痛等)明显减轻，没有出现黏液便，大便基本成形；(3)有效：每天大便的次数为治疗前的一半以下，症状(腹胀和腹痛等)有所减轻，黏液便逐渐消失，大便逐渐成形；(4)无效：大便次数和症状无变化。

治疗前后，空腹采集 3 mL 静脉血，用 ELISA 法检测肠黏膜屏障功能指标：血清内毒素、二胺氧化酶活性及 D- 乳酸水平；并检测炎症指标：血清 IL-6、TNF-α、IL-8、hs-CRP 水平，用免疫放射法检测胃肠激素指标：血浆生长抑素和血管活性肠肽水平，试剂盒购自欣博盛生物公司。

对比两组治疗期间出现的不良反应如嗜睡、头晕、乏力不适，头痛、口干等发生情况。

1.4 统计学分析

采用 SPSS 21.0 进行数据分析，两组间计量资料对比用 t 检验，计数资料组间比较用 χ^2 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的对比

治疗后，观察组的有效率为 97.50 %，明显高于对照组(75.61 %，P<0.05)，见表 1。

表 1 两组临床疗效比较[例(%)]

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

Groups	n	Cure	Effective	Valid	Invalid	The total effect rate
Control group	41	16(39.02)	10(24.39)	5(12.19)	10(24.39)	31(75.61)
Observation group	40	22(55.00)	11(27.50)	6(15.00)	1(2.50)	39(97.50)*

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

2.2 两组治疗前后血清内毒素、二胺氧化酶活性及 D- 乳酸水平的对比

治疗后，两组的血清内毒素、二胺氧化酶活性及 D- 乳酸水平均明显低于治疗前(P<0.05)，且观察组的血清内毒素、二胺氧化酶活性及 D- 乳酸水平明显低于对照组(P<0.05)，见表 2。

2.3 两组治疗前后血清 IL-6、TNF-α、IL-8、hs-CRP 水平的对比

治疗后，两组的血清 IL-6、TNF-α、IL-8、hs-CRP 水平均较治疗前明显降低(P<0.05)，且观察组的血清 IL-6、TNF-α、IL-8、hs-CRP 水平明显低于对照组(P<0.05)，见表 3。

2.4 两组治疗前后血浆生长抑素和血管活性肠肽水平的对比

治疗后，两组的血浆生长抑素和血管活性肠肽水平均较较治疗前明显降低(P<0.05)，且观察组的血浆生长抑素和血管活性肠肽水平明显低于对照组(P<0.05)，见表 4。

表 2 两组治疗前后的血清内毒素、二胺氧化酶活性及 D- 乳酸水平的对比($\bar{x}\pm s$)

Table 2 Comparison of the serum endotoxin, diamine oxidase activity and D-lactate levels between the two groups before and after treatment ($\bar{x}\pm s$)

Groups	n		Endotoxin(u/L)	Diamine oxidase activity(u/L)	D-lactate (ng/L)
Control group	41	Before treatment	1.67±0.34	1.96±0.38	54.13±11.72
		After treatment	1.24±0.19#	1.50±0.22#	47.29±10.25#
Observation group	40	Before treatment	1.69±0.35	1.97±0.41	55.63±12.18
		After treatment	0.48±0.09*#	0.83±0.12*#	43.25±10.13*#

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

表 3 两组治疗前后血清 IL-6、TNF-α、IL-8、hs-CRP 水平的对比($\bar{x}\pm s$)

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

Groups	n	IL-6(ng/L)	TNF-α(ng/L)	IL-8(ng/L)	hs-CRP(mg/L)
Control group	41	17.94±2.75	40.36±5.27	32.59±6.17	6.24±1.45
		8.32±1.28#	15.83±3.26#	17.24±5.63#	2.93±0.79#
Observation group	40	18.15±2.63	39.85±6.14	32.25±6.38	6.27±1.39
		4.59±1.07*#	8.71±2.34*#	12.41±3.59*#	0.95±0.33*#

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

表 4 两组血浆生长抑素和血管活性肠肽水平对比($\bar{x}\pm s$)

Table 4 Comparison of the plasma levels of somatostatin and vasoactive intestinal peptide between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n		Somatostatin(ng/L)	Vasoactive intestinal peptide(pg/mL)
Control group	41	Before treatment	62.45±11.79	307.42±15.74
		After treatment	51.47±11.36#	273.48±12.26#
Observation group	40	Before treatment	63.04±12.28	308.25±16.62
		After treatment	22.25±3.42*#	202.51±11.43*#

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

2.5 两组不良反应对比

观察组治疗期间的有 2 例嗜睡、头晕、乏力不适，发生率为 5.00 %，对照组有 2 例头晕，1 例头痛、口干，发生率为 7.32 %，两组对比无统计学意义(P>0.05)。2 组患者血、尿常规及肝肾检测均无异常。

3 讨论

肠易激综合征是一种与内脏异物和肠道动力学异常有关的肠功能紊乱性疾病，其病理生理学基础主要是内脏感觉异常以及胃肠道动力异常，可能与饮食、精神、遗传、肠道菌群失调和免疫等多种因素有关[10-13]。复方谷氨酰胺肠溶胶囊的主要成分是中药白术、茯苓、甘草及 L- 谷氨酰胺等。谷氨酰胺可以为 ATP 的生成提供能量，加强黏膜蛋白质以及细胞的代谢、合成，促进肠黏膜细胞的再生以及更新，有效保护细胞的完整性；使肠黏膜的屏障功能明显增强，抑制肠内毒素和细菌的移位[14,15]；增加胃肠激素的分泌，升高患者肠黏膜内免疫球蛋白的含量，修复各种原因造成的肠道黏膜受损，有效保护肠道黏膜结构的完整性，从而促进肠道功能的重建[16-18]；还能降低血浆中的自由基水平，抑制炎症因子的释放，减轻炎症反应．从而有效降低组织受损的程度[19]。中药茯苓、甘草和白术取自中医古方的四君子汤，具有健脾、益气、和胃之功效，能对消化系统的功能进行整体有效的调节。相关药理研究表明茯苓有增强机体免疫功能以及镇静的效果；甘草有抗炎、调节免疫功能和解毒等效果，还可以止腹痛以及解除肠道平滑肌痉挛，有助于促进消化道上皮细胞的再生；白术可以保护胃肠黏膜，有效调整胃肠的运动功能，增强免疫功能，还能抗氧化应激。

研究表明肠易激综合征患者普遍存在肠黏膜通透性增加，肠黏膜屏障功能异常，造成大量的肠腔细菌经过患者的肠上皮屏障而进入到固有层，使肠道的免疫系统紊乱或激活[20-23]。肠黏膜屏障受损导致大量的二胺氧化酶释放会进入血流以及肠间隙，其水平异常升高[24,25]。D- 乳酸由胃肠道内固有的细菌生成，当肠道的通透性明显升高时，会造成 D- 乳酸进入血液循环，血清含量明显升高。肠道受到感染后，肠黏膜的通透性降低，细菌发生移位，内毒素会进入到血液循环[26,27]。本研究中，观察组的血清内毒素、二胺氧化酶活性及 D- 乳酸水平明显低于对照组，表明联用复方谷氨酰胺能可有效修复肠黏膜，减轻肠黏膜受损程度。

IL-8 可以促进中性粒细胞对于溶酶体酶的吞噬效果，还能

促进中性粒细胞聚集在炎症部位，从而诱发炎症反应[28]。TNF-α能刺激四烯酸代谢物和细胞因子等的分泌，还能有效吞噬细胞产物和补体片段，造成细胞凋亡，损坏蛋白质，导致水肿，造成胃肠黏膜受到损伤，而且能与γ-干扰素共同对肠上皮细胞产生破坏作用，导致肠上皮细胞发生凋亡以及黏膜通透性的增加[29]。IL-6由巨噬细胞、上皮细胞和淋巴细胞分泌，生物作用效果与IL-1β比较类似，可以使细胞间黏附分子的表达水平明显提高，从而使肠上皮细胞的通透性破坏。本研究中，观察组的血清IL-6、IL-8和TNF-α水平均明显低于对照组，表明联用复方谷氨酰胺能明显减轻炎症反应。颜美珠等[30]对50例肠易激综合征患者给予复方谷氨酰胺治疗，患者的血清CRP及IL-1β水平明显降低。与本研究结果相一致。分析其原因为复方谷氨酰胺联合双歧杆菌三联活菌胶囊治疗腹泻型肠易激综合征，双歧杆菌三联活菌胶囊可直接补充肠道优势菌，快速纠正肠道微生物的生态平衡，杀灭和抑制部分致病菌，降低肠道内的内毒素，同时复方谷氨酰胺作用于患者机体，能够增强肠粘膜屏障功能，阻止细菌和毒素进入，从而降低炎性反应，使得IL-6、IL-8和TNF-α水平降低，二者联合显著的纠正促炎症因子与抗炎症因子之间的比例失调现象，整体减轻炎症反应[31,32]。且本研究两组不良反应对比无差异，说明复方谷氨酰胺联合双歧杆菌三联活菌胶囊治疗腹泻型肠易激综合征患者安全有效，不良反应少。

综上所述，复方谷氨酰胺联合双歧杆菌三联活菌胶囊治疗腹泻型肠易激综合征患者的临床效果明显优于单用双歧杆菌三联活菌胶囊治疗，其可有效修复肠黏膜屏障损伤，可能与其减轻炎症反应并改善胃肠激素水平有关。

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（下转第 4125 页）

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