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双歧杆菌乳杆菌三联活菌片联合血必净注射液对急性胰腺炎患者炎性介质、细胞免疫指标及肠黏膜屏障功能的影响*

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摘要 目的:探讨血必净注射液联合双歧杆菌乳杆菌三联活菌片治疗急性胰腺炎(SAP)患者的临床疗效。**方法:**选取2016年9月~2019年4月期间我院收治的SAP患者119例,根据随机数字表法将患者随机分为对照组(n=59)和研究组(n=60),对照组给予血必净注射液治疗,研究组在对照组的基础上联合双歧杆菌乳杆菌三联活菌片治疗,比较两组临床疗效,炎性介质、细胞免疫指标水平、肠黏膜屏障功能及不良反应发生情况。**结果:**研究组治疗7d后总有效率高于对照组($P<0.05$)。两组治疗期间未见药品不良反应发生。两组血清内毒素、二胺氧化酶(DAO)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)以及C反应蛋白(CRP)、CD8⁺水平均降低,且研究组低于对照组($P<0.05$),CD4⁺/CD8⁺、CD4⁺、NK细胞水平升高,且研究组高于对照组($P<0.05$)。**结论:**SAP患者在血必净的基础上联合双歧杆菌乳杆菌三联活菌片治疗,可提高机体细胞免疫功能,改善炎性因子水平和肠黏膜屏障功能,且用药安全性较好,临床应用价值较高。

关键词:双歧杆菌乳杆菌三联活菌片;血必净注射液;急性胰腺炎;炎性介质;细胞免疫;肠黏膜屏障功能

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Effects of Bifidobacterium Lactobacillus Triple Viable Tablet Combined with Xuebijing Injection on Inflammatory Mediators, Cellular Immune Indexes and Intestinal Mucosal Barrier Function in Patients with Severe Acute Pancreatitis*

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ABSTRACT Objective: To explore the clinical effect of Xuebijing injection combined with Bifidobacterium Lactobacillus triple viable tablet in the treatment of acute pancreatitis (SAP). **Methods:** 119 patients with SAP who were admitted to our hospital from September 2016 to April 2019 were selected, they were randomly divided into control group (n=59) and study group (n=60) according to the method of random number table. The control group was treated with Xuebijing injection. The study group was treated with Bifidobacterium Lactobacillus triple viable tablet on the basis of the control group. The clinical efficacy, inflammatory mediators, cellular immune indexes, intestinal mucosal barrier function and adverse reactions were compared between the two groups. **Results:** The total effective rate of the study group was higher than that of the control group after 7 days treatment ($P<0.05$). The levels of serum endotoxin, diamine oxidase (DAO), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), C-reactive protein (CRP), CD8⁺ in the two groups were decreased, and those of the study group were lower than those of the control group ($P<0.05$). The levels of CD4⁺/CD8⁺, CD4⁺, NK cells were increased, and those of the study group were lower than those of the control group ($P<0.05$). There was no adverse drug reaction in the two groups. **Conclusion:** Bifidobacterium lactobacillus triple viable tablet combined with Xuebijing injection on SAP can improve the immune function, the level of inflammatory factors and the intestinal mucosal barrier function, which has good drug safety, and the clinical application value is high.

Key words: Bifidobacterium Lactobacillus triple viable tablet; Xuebijing injection; Severe acute pancreatitis; Inflammatory mediators; Cellular immunity; Intestinal mucosal barrier function

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前言

急性胰腺炎(Severe acute pancreatitis, SAP)主要是指多种因素导致的胰腺腺泡受损,激活的炎性细胞因子及胰酶大量释放,最终引发 SAP^[1]。该病临床主要表现为腹痛腹胀、恶心呕吐、胰酶升高以及发热等,若未能及时予以治疗,可伴有胰腺坏死、免疫功能低下等情况,并继发腹膜炎、感染、休克等多种并发症,病情凶险^[2,3]。现临床针对 SAP 的治疗尚无统一方案,多以控制感染、抑制炎症因子的释放等对症治疗为主。血必净注射液是临床常用于治疗危重疾病的药物,可发挥强效的抗内毒素、抗炎作用,降低 SAP 患者感染过程中的病理损害^[4,5],但仍有部分患者单用血必净注射液治疗后,效果欠佳。胃肠道是人体最大的细菌、病毒生产基地,在 SAP 的病情进展中,胃肠道功能可受到不同程度的影响,引起肠道菌群移位和继发性感染^[6]。双歧杆菌乳杆菌三联活菌片作为一种微生态制剂,可维持胃内微生态平衡,既往常用于治疗各类胃肠道疾病,疗效显著^[7]。本研究通过探讨 SAP 患者在血必净的基础上联合双歧杆菌乳杆菌三联活菌片治疗后的临床效果,以期临床 SAP 的选择提供参考。

1 资料与方法

1.1 一般资料

选取我院收治的 119 例 SAP 患者,选取时间:2016 年 9 月~2019 年 4 月。本次研究获得本院伦理学委员会批准进行。纳入标准:(1)SAP 诊断标准参考《重症急性胰腺炎(2014 版)》^[8];(2)经影像学或实验室检查确诊为 SAP;(3)急性生理学和慢性健康状况评分标准 II^[9](Scoring criteria for acute physiology and chronic health II, APACHE II)评分 ≥ 8 分者;(4)发病至入院时间 ≤ 48 h 者;(5)患者及其家属知情本研究且签署同意书。排除标准:(1)既往已有胰腺疾病史者;(2)合并急、慢性肠道疾病者;(3)妊娠或哺乳期妇女;(4)对本次研究药物存在过敏史者;(5)合并血液系统疾病、恶性肿瘤者;(6)合并精神疾患不配合治疗者;(7)合并心脑肝肾等脏器功能障碍者。根据乱数表法将患者随机分为研究组($n=60$)、对照组($n=59$),对照组男 32 例,女 27 例,年龄 28~64 岁,平均 (43.62 ± 3.08) 岁;APACHE II 评分 8~16 分,平均 (12.06 ± 1.34) 分;发病至入院时间 5~48h,平均 (26.71 ± 2.35) h;发病原因:酗酒 23 例,暴饮暴食 18 例,胆源性 18 例。研究组男 34 例,女 26 例,年龄 25~63 岁,平均 (42.98 ± 3.82) 岁;APACHE II 评分 8~17 分,平均 (12.54 ± 1.28) 分;发病至入院时间 6~46h,平均 (27.06 ± 2.54) h;发病原因:酗酒 25 例,暴饮暴食 20 例,胆源性 15 例。两组一般资料比较无差异($P>0.05$)。

1.2 方法

入院后均给予维持水电解质平衡、禁饮禁食、早期液体复苏补充容量、抗感染、胃肠减压、抑制胰酶分泌等早期干预,同时加强护理,严格监测患者生命体征。随后对照组给予天津红日药业股份有限公司生产的血必净注射液(国药准字 Z20040033,规格:每支装 10 mL),将血必净注射液(100 mL)与生理盐水(100 mL)混合,静脉滴注,2 次/d。研究组在对照组的基础上联合杭州远大生物制药有限公司生产的双歧杆菌四联活菌片(国药准字 S20060010,规格:每片重 0.5 g)2 g 治疗,研磨水化,自胃管注入,3 次/d,两组均治疗 7 d。

1.3 观察指标

(1)记录患者的临床疗效。疗效判定^[10]依据如下:治愈:实验室各项指标如血淀粉酶恢复正常,患者临床症状消失,胰腺 B 超结果显示恢复正常;显效:实验室各项指标如血淀粉酶明显恢复正常,胰腺 B 超结果显示基本恢复正常,患者临床症状明显改善;有效:实验室各项指标如血淀粉酶、临床症状有所改善,胰腺 B 超结果显示有所改善;无效:实验室各项指标如血淀粉酶、临床症状及胰腺 B 超结果均未见明显改善或恶化。总有效率=治愈率+显效率+有效率。(2)抽取患者 5 mL 空腹静脉血,抽血时间:治疗前、治疗 7 d 后清晨。经离心半径 8 cm,3900 r/min 离心 12 min,分离上清液,置于冰箱中(-40°C)待测。用酶联免疫吸附试验检测血清白介素-6(IL-6)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)以及 C 反应蛋白(C-reactive protein, CRP)水平,采用酶学分光光度法检测二胺氧化酶(Diamine oxidase, DAO)水平,采用鲎试剂比浊法检测内毒素。采均严格遵守试剂盒(南京建成生物工程有限公司)的说明书进行操作。采用美国 BD 公司生产的流式细胞仪检测细胞免疫指标:CD4⁺、CD8⁺、NK 细胞,计算 CD4⁺/CD8⁺。(3)记录两组不良反应。

1.4 统计学方法

本研究数据均采用 SPSS26.0 软件进行统计学分析,计数资料以率表示,采用 χ^2 检验,计量资料用 $(\bar{x}\pm s)$ 表示,比较应用 t 检验, $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 临床疗效比较

研究组治疗 7 d 后临床总有效率高于对照组($P<0.05$),详见表 1。

2.2 肠粘膜屏障功能比较

治疗前,两组血清 DAO、内毒素水平比较无差异($P>0.05$)。

表 1 患者临床疗效比较[例(%)]

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

Groups	Cure	Markedly effective	Effective	Invalid	Total effective rate
Control group($n=59$)	9(15.25)	18(30.51)	16(27.12)	16(27.12)	43(72.88)
Study group($n=60$)	15(25.00)	26(43.33)	11(18.33)	8(13.33)	52(86.67)
χ^2					5.783
P					0.016

05);治疗 7 d 后,两组血清内毒素、DAO 水平均降低,且研究组治疗前, 两组血清 IL-6、CRP、TNF- α 水平比较无差异 ($P>0.05$); 治疗 7 d 后, 两组血清 IL-6、CRP、TNF- α 水平均下降,且研究组低于对照组 ($P<0.05$),详见表 3。

2.3 炎症介质比较

表 2 肠粘膜屏障功能比较($\bar{x}\pm s$)

Table 2 Comparison of intestinal mucosal barrier function($\bar{x}\pm s$)

Groups	(EU/mL)		DAO(ng/L)	
	Before treatment	7d after treatment	Before treatment	7d after treatment
Control group(n=59)	7.01 $\pm$ 1.46	5.48 $\pm$ 1.27*	5.73 $\pm$ 1.12	4.14 $\pm$ 0.87*
Study group(n=60)	6.92 $\pm$ 1.53	3.87 $\pm$ 1.19*	5.66 $\pm$ 1.07	3.07 $\pm$ 1.05*
t	0.328	7.137	0.349	6.048
P	0.743	0.000	0.728	0.000

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

表 3 炎症介质比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory mediators($\bar{x}\pm s$)

Groups	IL-6(pg/mL)		CRP(mg/L)		TNF- α (pg/mL)	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment
Control group (n=59)	187.77 $\pm$ 23.81	148.76 $\pm$ 25.31*	158.21 $\pm$ 20.73	132.45 $\pm$ 21.44*	74.03 $\pm$ 12.35	53.38 $\pm$ 11.43*
Study group(n=60)	186.71 $\pm$ 20.92	101.38 $\pm$ 19.27*	157.28 $\pm$ 22.96	93.23 $\pm$ 19.38*	73.96 $\pm$ 10.47	38.52 $\pm$ 0.62*
t	0.258	11.502	0.232	10.472	0.033	10.056
P	0.979	0.000	0.817	0.000	0.973	0.000

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

2.4 细胞免疫指标比较

治疗前,两组 CD4⁺、CD8⁺、NK 细胞、CD4⁺/CD8⁺ 水平比较 CD8⁺、NK 细胞水平升高,且研究组高于对照组 ($P<0.05$),CD8⁺ 降低,且研究组低于对照组 ($P<0.05$);详见表 4。
差异无统计学意义 ($P>0.05$); 治疗 7d 后, 两组 CD4⁺、CD4⁺/

表 4 细胞免疫指标比较($\bar{x}\pm s$)

Table 4 Comparison of cellular immune indexes($\bar{x}\pm s$)

Groups	CD4 ⁺ (%)		CD8 ⁺ (%)		NK(%)		CD4 ⁺ /CD8 ⁺	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment
Control group (n=59)	24.53 $\pm$ 3.87	32.41 $\pm$ 5.38*	32.39 $\pm$ 3.36	26.54 $\pm$ 4.35*	9.66 $\pm$ 0.44	13.17 $\pm$ 0.63*	0.75 $\pm$ 0.19	1.22 $\pm$ 0.14*
Study group (n=60)	24.76 $\pm$ 4.69	43.66 $\pm$ 5.41*	31.68 $\pm$ 4.14	22.47 $\pm$ 4.23*	9.52 $\pm$ 0.39	16.61 $\pm$ 0.59*	0.78 $\pm$ 0.11	1.94 $\pm$ 0.12*
t	0.292	11.373	1.026	5.175	1.838	30.750	1.056	30.138
P	0.771	0.000	0.307	0.000	0.069	0.000	0.293	0.000

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

2.5 不良反应发生情况比较

两组治疗期间未见药品不良反应发生,亦未见心电图、血尿常规、肝肾功能均未见明显异常。

3 讨论

现临床有关 SAP 的发病机制尚不清晰,大多学者认为该病为自身胰腺功能异常所致^[11-13]。随着研究的深入,学者们也逐渐发现炎症因子引起的瀑布扩大式效应在 SAP 的病情进展中

占据主要地位^[14-16]。胰液外漏、炎症因子的大量释放,不仅会导致患者免疫功能降低,还可进一步破坏肠道黏膜屏障,导致细菌移位,引起肠道菌群紊乱,内毒素大量分泌,进入外周循环后可进一步反馈性的促进释放大量炎症因子,引起全身性炎症反应,导致多器官功能衰竭甚至死亡。血必净注射液在急性胰腺炎中应用较多,大量基础及临床实践证实,血必净注射液具有强效的抗内毒素作用,同时还可拮抗内源性炎性介质失控性的释放^[17,18]。由于 SAP 的发病机制复杂,单一的药物并不能达到

最理想的治疗效果,仍需优化治疗。近年来有研究指出益生菌制剂应用于脓毒症等危重疾病的治疗,可重建并维持肠道菌群的稳态,降低肠源性感染的发生风险^[19-21],但目前有关益生菌制剂应用于SAP的治疗中的报道尚不十分多见,本研究就此展开分析。

本次研究结果中研究组总有效率高于对照组,可见双歧杆菌乳杆菌三联活菌片联合血必净注射液治疗SAP疗效显著。分析其原因,血必净注射液的成分主要为川芎、赤芍、红花、丹参、当归等药材,现代药理研究显示,血必净注射液可改善微循环,可促进炎症吸收,减少炎症渗出,对SAP发生时的胰腺及胰腺外的器官具有良好的保护效果^[22,23]。双歧杆菌乳杆菌三联活菌片的主要成分为双歧杆菌、嗜酸乳杆菌以及肠球菌等三种益生菌,进入人体后可直接增加肠道正常菌群数量,使肠道菌群重新获取平衡状态,改善微循环,进而提高治疗效果^[24]。IL-6可诱导T淋巴细胞的活化,常用于反应急性期的炎症水平^[25];CRP是一种急性时相蛋白,可反映机体的炎症程度,且对于感染性疾病的敏感性较高;TNF- α 由活化的巨噬细胞产生,低浓度的TNF- α 是防御病原菌的重要微生物,而高浓度的TNF- α 则会导致一系列的炎症损伤^[26];DAO是一种高度活性的细胞内酶,可反映肠道机械屏障的完整性和受损伤程度^[27];内毒素要作用于机体的内皮细胞、中性粒细胞、血小板等,导致微循环障碍^[28]。以往有研究证实,SAP患者早期即存在过度的炎症反应和免疫抑制^[29]。因此,临床可对上述指标进行观察,以进一步确认SAP患者的预后和转归。本研究结果中两组患者肠黏膜屏障功能、炎症因子水平、免疫功能均有所改善,且双歧杆菌乳杆菌三联活菌片联合血必净注射液治疗者改善效果更佳。这可能是因为双歧杆菌乳杆菌三联活菌片进入肠道后,迅速恢复肠道菌群平衡,帮助建立肠道屏障,促进肠道吸收,提高患者免疫功能^[30];期间还可产生多种有机酸防止腐败菌生长,清除肠道内的氧自由基、抑制炎症反应。两组治疗期间未见药品不良反应发生,可见用药安全性较好。

综上所述,SAP患者在血必净的基础上联合双歧杆菌乳杆菌三联活菌片治疗可提高机体细胞免疫功能,改善炎症因子水平、肠黏膜屏障功能,且用药安全性较好,临床应用价值较高。

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