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加贝酯联合奥曲肽对急性胰腺炎患者胃肠功能、免疫功能及炎性因子水平的影响*

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摘要 目的:探讨加贝酯联合奥曲肽对急性胰腺炎(AP)患者胃肠功能、血清炎性因子及免疫功能的影响。**方法:**选取2014年1月到2018年6月在我院接受治疗的AP患者100例,采用随机数字表法将所有患者分为对照组和观察组各50例。对照组给予注射用醋酸奥曲肽治疗,观察组在对照组的基础上给予注射用甲磺酸加贝酯治疗。对比两组患者治疗后临床疗效、胃肠功能恢复情况、血清炎性因子水平及免疫球蛋白lgG、lgM、lgA的变化情况。**结果:**治疗后观察组总有效率为83.24%,高于对照组的67.03%(P<0.05)。治疗后观察组排气恢复时间、排便恢复时间、肠鸣音消失时间、腹胀缓解时间、腹痛缓解时间均显著短于对照组(P<0.05)。治疗后两组肿瘤坏死因子-α(TNF-α)、C反应蛋白(CRP)、白细胞介素-6(IL-6)及白细胞介素-8(IL-8)水平较治疗前均明显下降(P<0.05),且治疗后观察组的TNF-α、CRP、IL-6及IL-8水平低于对照组(P<0.05)。治疗后两组的lgG、lgM、lgA水平均较治疗前均明显升高(P<0.05),治疗后观察组的lgG、lgM水平高于对照组(P<0.05)。**结论:**加贝酯联合奥曲肽治疗AP不仅能够有效抑制患者的炎症反应,改善其免疫功能,还能够促进患者胃肠功能恢复,提高临床疗效。

关键词:加贝酯;奥曲肽;急性胰腺炎;胃肠功能;免疫功能;炎症因子

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Effect of Gabexate Combined with Octreotide on Gastrointestinal Function, Immune Function and Inflammatory Factors in Patients with Acute Pancreatitis*

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ABSTRACT Objective: To investigate the effect of gabexate combined with octreotide on gastrointestinal function, serum inflammatory factors and immune function in patients with acute pancreatitis (AP). **Methods:** 100 cases of AP patients treated in our hospital from January 2014 to June 2018 were selected. All patients were divided into control group and observation group by random number table method, with 50 cases in each group. The control group was given octreotide acetate for injection, while the observation group was given gabexate mesylate for injection on the basis of the control group. The clinical efficacy,gastrointestinal function recovery, serum inflammatory factors and the changes of immunoglobulin lgG, lgM and lgA were compared between the two groups. **Results:** After treatment, the total effective rate of the observation group was 83.24%, which was higher than 67.03% of the control group (P<0.05). After treatment, the recovery time of exhaust, recovery time of defecation, disappearing time of bowel sound, relieving time of abdominal distention, and relieving time of abdominal pain were significantly shorter than those in the control group (P<0.05). After treatment, the levels of tumor necrosis factor-α (TNF-α), C reactive protein (CRP), interleukin-6 (IL-6) and interleukin-8 (IL-8) in the two groups were significantly lower than before treatment (P<0.05), and the levels of TNF-α, CRP, IL-6 and IL-8 in the observation group were lower than those of the control group after treatment. After treatment, the levels of lgG, lgM and lgA in both groups were significantly higher than before treatment (P<0.05). After treatment, the levels of lgG and lgM in observation group were higher than those of the control group (P<0.05). **Conclusion:** Gabexate combined with octreotide in the treatment of AP can not only effectively inhibit the inflammatory response of the patients,improve the immune function, but also promote the recovery of gastrointestinal function and improve the clinical efficacy.

Key words: Gabexate; Octreotide; Acute pancreatitis; Gastrointestinal function; Immune function; Inflammatory factors

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前言

急性胰腺炎(acute pancreatitis,AP)是由多种因素导致胰腺内胰酶被激活后发生自身消化现象,胰腺出现不同程度功能障碍,进而出现水肿、出血及坏死等症状的疾病[1-3]。临床根据病变程度将 AP 分为轻症 AP 和重症 AP 两大类,轻症 AP 出现恶心、呕吐、胰腺水肿等症状,患者预后良好;重症 AP 可继发感染、休克等症状,且伴随脏器功能障碍及严重代谢功能紊乱,病情凶险,患者预后差、病死率高。随着我国老龄化社会的到来,AP 的发病率逐年上升,AP 患者免疫功能低下,发病后病情进展迅速且并发症较多,严重威胁患者的生命健康[4-6]。奥曲肽是一种人工合成八肽环状化合物,可改善胰腺循环、抑制胰酶分泌,过往用于治疗 AP 中取得了一定效果[7,8]。加贝酯是一种临床常用抑制胰腺分泌的非肽类蛋白酶的抑制剂,可抑制活化的胰蛋白酶、减轻胰腺损伤[9,10]。本研究探讨加贝酯联合奥曲肽对 AP 患者胃肠功能、免疫功能及炎性因子水平的影响。研究报告整理如下。

1 资料与方法

1.1 一般资料

选取 2014 年 1 月到 2018 年 6 月在我院接受治疗的 AP 患者 100 例。纳入标准:(1)年龄≥ 60 岁;(2)均符合《急性胰腺炎诊治指南(2014)》[11]中 AP 的相关诊断标准,并通过临床症状及影像学检查确诊;(3) 全身脏器功能正常者;(4)患者及家属均知情同意并积极配合治疗。排除标准:(1)伴有严重恶性肿瘤疾病者;(2)伴有心梗、心竭或严重心律失常者;(3)伴有肠梗阻、功能性便秘等消化系统疾病者;(4)对加贝酯或奥曲肽过敏者;(5)临床资料不全者。采用随机数字表法将所有患者分为对照组和观察组各 50 例。对照组:男 29 例,女 21 例,年龄 41-69 岁,平均(53.21± 5.31)岁,发病至入院时间 3-10 h,平均(5.01± 0.97)h。其中轻症 AP 33 例,重症 AP 17 例;致病原因:暴饮暴食 21 例,饮酒过量 13 例,胆道疾病 10 例,高脂血症 6 例。观察组:男 27 例,女 23 例,年龄 40-67 岁,平均(54.24± 6.31)岁,发病至入院时间 2-10 h,平均(4.98± 1.06)h。其中轻症 AP 31 例,重症 AP 19 例;致病原因:暴饮暴食 18 例,饮酒过量 15 例,胆道疾病 11 例,高脂血症 6 例。两组患者一般资料比较均无明显差异(P>0.05),具有可比性。本次研究经我院医学伦理会审批通过。

1.2 方法

两组患者入院后均给予抗感染、胃肠减压、解痉止痛、纠正水电解质紊乱及营养支持等常规治疗。对照组在常规治疗的基础上给予注射用醋酸奥曲肽(国药准字 H20031207,成都天台山制药有限公司,规格:0.1 mg)治疗,0.3 mg 注入 50 mL 生理盐水混合后微泵滴注,2 次 /d,治疗 7 d。观察组在对照组的基础上给予注射用甲磺酸加贝酯(国药准字 H20093471,江苏吴中医药集团有限公司苏州制药厂,规格:0.1 g)治疗,0.3 g 注入 500 mL 葡萄糖注射液中混合后静脉滴注,1 次 /d,治疗 7 d。治疗期间密切关注患者各项生命体征及临床症状,若出现严重不良反应应停止治疗。

1.3 疗效评定标准

显效:血清及尿淀粉酶水平归于正常,临床症状完全消失;有效:血清及尿淀粉酶水平有所下降,临床症状明显好转;无效:血清及尿淀粉酶无下降或升高,临床症状无改善甚至加重。总有效率 = 显效率 + 有效率[12]。

1.4 观察指标

(1) 胃肠功能:对比两组患者治疗后排气恢复时间、排便恢复时间、肠鸣音消失时间、腹胀缓解时间、腹痛缓解时间;(2) 血清炎性因子:分别于治疗前后抽取患者空腹静脉血 3 mL,以 3000 r/min 的速度离心 10 min,提取上清液,通过酶联免疫吸附法测定血清炎性因子水平,包括肿瘤坏死因子 -α(tumor necrosis factor-α,TNF-α)、C 反应蛋白 (C reactive protein,CRP)、白细胞介素 -6(interleukin-6,IL-6)、白细胞介素 -8(interleukin-8,IL-8)水平,试剂盒均购于上海酶联生物科技有限公司,严格遵循试剂盒操作指南进行相关操作;(3) 免疫功能:采用全自动生化分析仪(日立 7600)检测血清中的 lgG、lgM、lgA 水平。

1.5 统计学方法

采用 SPSS21.0 软件进行统计学分析,男女比例、致病原因等计数资料以例数的形式表示,采用卡方检验,炎症因子指标、免疫功能指标等计量资料以($\bar{x}$± s)的形式表示,采用 t 检验。以 α=0.05 为检验标准。

2 结果

2.1 治疗后两组患者临床疗效对比

治疗后观察组总有效率高于对照组,差异有统计学意义(P<0.05)。详见表 1。

表 1 治疗后两组患者临床疗效对比[n(%)]

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

Groups	n	Excellence	Effective	Invalid	Total effective rate
Control group	50	15(30.00)	18(36.00)	17(34.00)	33(66.00)
Observation group	50	19(38.00)	23(46.00)	8(16.00)	42(84.00)
x^2					4.320
P					0.038

2.2 治疗后两组患者胃肠功能恢复情况对比

治疗后观察组排气恢复时间、排便恢复时间、肠鸣音消失时间、腹胀缓解时间、腹痛缓解时间均显著短于对照组(P<0.05),详见表 2。

表 2 治疗后两组患者胃肠功能恢复情况对比($\bar{x}\pm s$)

Table 2 Comparison of gastrointestinal function recovery between the two groups after treatment($\bar{x}\pm s$)

Groups	n	Recovery time of exhaust(h)	Recovery time of defecation(h)	Disappearing time of bowel sound(d)	Relieving time of abdominal distention(d)	Relieving time of abdominal pain(d)
Control group	50	29.88± 8.25	40.21± 10.36	4.09± 1.25	6.84± 2.14	9.03± 4.67
Observation group	50	15.25± 5.32#	22.36± 7.69#	1.92± 0.54#	2.67± 1.23#	4.11± 2.51#
t		10.538	9.783	11.269	11.946	6.562
P		0.000	0.000	0.000	0.000	0.000

Note: Compared with control group, #P<0.05.

2.3 治疗前后两组患者血清炎性因子水平比较

治疗前两组患者 TNF-α、CRP、IL-6 及 IL-8 水平比较均无明显差异(P>0.05),治疗后两组 TNF-α、CRP、IL-6 及 IL-8 水平较治疗前均有明显下降(P<0.05),且治疗后观察组的 TNF-α、CRP、IL-6 及 IL-8 水平低于对照组(P<0.05),详见表3。

表 3 治疗前后两组患者血清炎性因子水平比较($\bar{x}\pm s$)

Table 3 Comparison of serum inflammatory factors between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Times	TNF-α (μg/L)	CRP (mg/L)	IL-6 (μg/L)	IL-8 (μg/L)
Control group	50	Before treatment	35.68± 4.61	295.69± 56.84	88.63± 8.62	99.32± 19.20
		After treatment	27.51± 3.03*	105.64± 18.96*	55.25± 6.40*	61.59± 16.20*
Observation group	50	Before treatment	34.59± 4.35	294.29± 56.71	86.98± 7.98	98.50± 18.99
		After treatment	19.25± 2.69*#	75.50± 13.25*#	34.26± 5.02*#	45.68± 11.03*#

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

2.4 治疗前后两组患者免疫功能比较

治疗前两组患者的 lgG、lgM、lgA 水平比较均无明显差异(P>0.05),治疗后两组的 lgG、lgM、lgA 水平均较治疗前明显升高(P<0.05),治疗后观察组的 lgG、lgM 水平高于对照组(P<0.05),详见表 4。

表 4 治疗前后两组患者免疫功能比较($\bar{x}\pm s$)

Table 4 Comparison of immune function between the two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Times	lgG(g/L)	lgM(g/L)	lgA(g/L)
Control group	50	Before treatment	9.53± 0.49	1.35± 0.19	2.43± 0.36
		After treatment	15.03± 3.19*	1.66± 0.40*	3.09± 0.34*
Observation group	50	Before treatment	9.49± 0.53	1.38± 0.21	2.49± 0.33
		After treatment	20.51± 3.68*#	2.20± 0.46*#	3.08± 0.40*

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

3 讨论

AP 是临床常见多发急腹症之一，在急腹症中发病率位居第四,仅次于急性胆囊炎、急性阑尾炎及溃疡性穿孔,其发病机制主要是胰酶发生自身消化后导致胰腺出现功能障碍[13,14]。相关研究指出暴饮暴食、长期饮酒、胆管疾病等是 AP 发病的主要诱因,临床症状有恶心呕吐、发热、腹痛腹胀、排便困难、淀粉酶含量增高等,重症者可伴随一个或多个脏器损害,严重影响患者生命健康[15,16]。相关研究指出[17,18],AP 发生时患者体内存在明显的炎症反应,TNF-α、CRP、IL-6 及 IL-8 等炎症因子水平显著升高。其中 CRP 是一种全身性炎症反应急性期的非特异性标志物，能及时反映组织损伤程度及炎症程度,TNF-α 是促炎症形成因子,能有诱导 IL-6、IL-8 释放,加重胰腺及周围组织的损伤程度,增强胰蛋白酶活性,引发胰腺炎,而 IL-6 的产生也会促进 TNF-α 水平的升高。各种炎症之间相互作用可引起胰腺、心、肝、肾组织受损和微循环障碍,最终出现多脏器功能衰竭甚至导致死亡[19,20]。

本研究结果显示,治疗后两组 TNF-α、CRP、IL-6 及 IL-8 水平较治疗前均明显下降,且治疗后观察组以上炎症因子水平低于对照组,这说明加贝酯联合奥曲肽治疗 AP 能有效控制炎症反应,减轻胰腺受损程度。奥曲肽是一种药理作用与天然内源性生长抑素类似的人工合成八肽环状化合物,具有抑制胰酶分泌、松弛 Oddi 括约肌、降低胰管内压力、改善胰腺微循环之效,同时还能有效降低炎性因子水平,降低胰腺血流量,保护机体免受内毒素的损伤,促进肠道蠕动,加速肠道功能恢复[21,22]。加贝酯是近年来临床用于抑制胰酶分泌的一种非肽类蛋白的抑制剂,能有效降低胰蛋白酶、激汰释放酶、纤维蛋白溶酶的活性,从而抑制胰腺分泌,保护胰腺组织[23,24]。

相关研究还指出[25],当 AP 发生时患者的免疫功能处于紊乱的状态，而患者免疫功能紊乱可降低患者对致病菌的抵抗力,增加 AP 患者发生感染的几率,因此改善 AP 患者的免疫功能至关重要。lgG、lgM、lgA 是机体的免疫球蛋白,对于机体的免疫功能有重要的调节作用。本研究结果显示,治疗后两组的 lgG、lgM、lgA 水平均较治疗前明显升高，且治疗后观察组的 lgG、lgM 水平高于对照组,说明两种治疗方案均能改善患者的免疫功能,但加贝酯联合奥曲肽的改善程度更明显。这可能是由于加贝酯联合奥曲肽能够明显的改善患者的营养物质转化率和负氮平衡,促进机体恢复,同时还能促进骨髓细胞成熟,进而改善患者的免疫功能[26,27]。AP 患者常存在腹痛腹胀、排便困难等胃肠功能障碍,内毒素无法及时排出,导致消化道出现感染甚至衰竭,影响病情恢复,因此改善胃肠功能亦是治疗关键[28]。本研究结果显示,治疗后观察组的总有效率显著高于对照组,且排气恢复时间、排便恢复时间、肠鸣音消失时间、腹胀缓解时间、腹痛缓解时间均低于对照组,提示加贝酯联合奥曲肽治疗 AP 能在较短时间内改善患者临床症状,促进胃肠功能恢复,提高临床疗效。这主要是因为奥曲肽和加贝酯可从不同方向抑制胰腺分泌,进而保护胰腺组织,同时奥曲肽还可以促进肠道蠕动,因此两种药物联合可有效改善患者的胃肠功能[29,30]。

综上所述,加贝酯联合奥曲肽治疗 AP 患者的临床疗效良好,不仅能够有效抑制炎症反应,改善免疫功能,还能够加速胃肠功能恢复,从而有利于患者康复。

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