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加贝酯联合生长抑素治疗胰腺炎近期疗效及对炎症因子、D- 乳酸的影响 *

毛 庆 李海山△ 蔡兆辉 左 爽 张 琪

（合肥市第二人民医院急诊科 安徽 合肥 230011）

摘要 目的：探讨加贝酯联合生长抑素治疗胰腺炎近期疗效及对炎症因子、D- 乳酸的影响。**方法：**选择 2017 年 1 月至 2010 年 1 月在我院接受治疗的急性胰腺炎患者 80 例为研究对象，按照随机数表法分为对照组（n=40）和试验组（n=40）。对照组采用生长抑素治疗，实验组采用加贝酯联合生长抑素治疗，比较两组临床疗效、腹部体征与胃肠道功能恢复时间、血清 CRP、TNF-α、IL-6、D- 乳酸水平及血淀粉酶、尿淀粉酶、脂肪酶水平。并统计两组不良反应发生情况。**结果：**试验组组总有效率为 75.00%（30/40），试验组总有效率为 92.50%（37/40），两组比较有统计学意义（*P*<0.05）。试验组腹部体征消失时间及胃肠道功能恢复时间均明显短于对照组，差异有统计学意义（*P*<0.05）。治疗前，两组 CRP、TNF-α、IL-6、D- 乳酸水平及血淀粉酶、尿淀粉酶、脂肪酶水平比较无统计学差异（*P*>0.05）；治疗后，试验组血清 CRP、TNF-α、IL-6、D- 乳酸水平及血淀粉酶、尿淀粉酶、脂肪酶水平均明显低于对照组（*P*<0.05）。两组患者均发生不同程度的多器官功能衰竭、假性囊肿已经胰周感染，其试验组发生率为 7.5%（3/40），对照组发生率为 17.5%（7/40），两组比较具有统计学意义（*P*<0.05）。**结论：**加贝酯联合生长抑素治疗胰腺炎可有效改善患者炎症因子水平及肠粘膜功能，更利于快速控制病情，从而显著提高临床疗效。

关键词：加贝酯；生长抑素；急性胰腺炎；近期疗效；D- 乳酸

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Efficacy of Gabexate Combined with Somatostatin in the Treatment of Pancreatitis and Its Effect on Inflammatory Factors and D-LA*

MAO Qing, LI Hai-shan△, CAI Zhao-hui, ZUO Shuang, ZHANG Qi

(Department of Emergency, Hefei Second People's Hospital, Hefei, Anhui, 230011, China)

ABSTRACT Objective: To investigate the short-term efficacy of Gabexate combined with somatostatin in the treatment of pancreatitis and its effect on inflammatory factors and d-lactic acid. **Methods:** 80 patients with acute pancreatitis who were treated in our hospital from January 2017 to January 2010 were selected as the study subjects and randomly divided into the control group (n=40) and the experimental group (n=40). The control group was treated with somatostatin, and the experimental group was treated with Gabexate combined with somatostatin. The clinical efficacy, abdominal signs and recovery time of gastrointestinal function, serum CRP, TNF-α, IL-6, d-lactic acid levels, blood amylase, urinary amylase and lipase levels of the two groups were compared. And statistics of the two groups of adverse reactions. **Results:** The total effective rate was 75.00% (30/40) in the control group and 92.50% (37/40) in the experimental group. The comparison between the two groups was statistically significant (*P*<0.05). The disappearance time of abdominal signs and recovery time of gastrointestinal function in the experimental group were significantly shorter than those in the control group, with statistically significant differences (*P*<0.05). Before treatment, there was no statistical difference in the levels of CRP, TNF-α, IL-6, d-lactic acid, blood amylase, urinary amylase and lipase between the two groups (*P*>0.05). After treatment, serum levels of CRP, TNF-α, IL-6, d-lactic acid, blood amylase, urinary amylase and lipase in the test group were significantly lower than those in the control group (*P*<0.05). Two groups of patients are different degree of multiple organ failure, pseudocyst had peripancreatic infection, the incidence of the experimental group was 7.5% (3/40), the incidence of the control group was 17.5% (7/40), comparing the two groups have statistical significance (*P*<0.05). **Conclusion:** Gabexater combined with somatostatin in the treatment of pancreatitis can effectively improve the level of inflammatory factors and intestinal mucosal function of patients, more conducive to the rapid control of the disease, thus significantly improving the clinical efficacy.

Key words: Gabexater; Somatostatin; Acute pancreatitis; Short-term efficacy; D - lactic acid

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作者简介：毛庆（1979-），男，硕士，主治医师，研究方向：急诊临床诊疗，电话：13956912717

△ 通讯作者：李海山，副主任医师，电话：13205510170，E-mail: hjddxq@163.com

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前言

胰腺炎是发生在胰腺部为非感染性炎症，临床将其分为急性与慢性，其中急性胰腺炎较为常见，主要以突发性左上腹痛为首发症状，部分患者伴有恶心呕吐、腹胀便秘等症状，同时具有发病急、病情发展迅速、预后较差等特点[1,2]。临床发现，急性胰腺炎的主要病因为胰管堵塞所导致胰酶在胰腺中被激活，使其胰腺组织受损，从而引发胰腺组织发生急性炎症反应[3]。Abhinav Agrawal 等研究发现，急性胰腺炎病情能够在短时间恶化，从而诱发全身炎症反应综合征以及多器官功能障碍综合征，严重影响患者预后，因此早期采取有效治疗对患者具有重要的临床意义[4]。生长抑素能够有效抑制胰酶分泌，对胰腺细胞具有一定的保护作用[5]。研究显示，急性胰腺炎患者在使用生长抑素治疗后其不适症状明显好转[6]。Ewa Łubowska-Pająk 等学者发现生长抑素虽然能够减少胰腺组织损伤，但对其并发症的发生无明显影响[7]。加贝酯是一种非肽类蛋白酶抑制剂，可抑制胰酶蛋白酶原激活，从而缓解胰腺组织的病变[8]。研究发现，加贝酯在降低急性胰腺癌死亡率方面无过多影响，但可有效降低其并发症症，由此可见，生长抑制素联合加贝酯治疗急性胰腺炎具有一定的协同作用[9]。对此本研究通过探讨加贝酯联合生长抑素治疗急性胰腺炎近期疗效及对炎症因子、D- 乳酸的影响，从而近一步了解二者联合使用对胰腺炎的临床效果及作用机制。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月至 2010 年 1 月在我院接受治疗的急性胰腺炎患者 80 例为研究对象，纳入标准：(1)符合《急性胰腺炎诊治指南(2014 版)》中相关急性胰腺炎的诊断标准[10]，且血、尿淀粉酶均伴有不同程度的升高，同时伴有持续性的腹痛；(2)于发病 24h 内就诊；(3)符合生长抑素以及加贝酯治疗适应征。排除标准：(1)伴有严重肝、肾功能不全患者；(2)伴有恶性肿瘤者；(3)患有急性肠炎、急性肠梗阻、消化道溃疡等患者；(4)患有其他胰腺疾病患者。80 例患者按照随机数表法分为对照组和试验组，每组 40 例，年龄 36~62 岁，男性患者 37 例，女性患者 43 例，两组基线资料比较无统计学差异(P>0.05)，详见表 1。

表 1 两组基线资料比较[($\bar{x}\pm s$)，(例，%)]

Table 1 Comparison of two groups of baseline data[($\bar{x}\pm s$),(n,%)]

Groups	n	Age(years)	Sex		pathogenesis				
			male	femininiy	Course of the disease(h)	gallstone	Fat source	alcoholic	Ranson score
Control group	40	43.14± 3.75	21(52.50)	19(47.50)	10.43± 1.83	26(65.00)	3(7.50)	11(27.50)	1.76± 0.38
Treatment group	40	41.37± 4.11	16(40.00)	24(60.00)	11.61± 2.02	24(60.00)	4(10.00)	12(30.00)	1.67± 0.41

1.2 方法

两组均给予胃肠减压、抗炎、补液抗休克等常规治疗。对照组才基础上给予生长抑素治疗，取翰康注射剂 6 mg 与 48 mL 生理盐水中充分混合，首先给予负荷量，前 6 min 以 20 mL/h 速度泵入，后续以 2 mL/h 泵入。观察组以对照组为基础，联合使用加贝酯治疗，取 0.3 g 药量加入 500 mL 的 5%葡萄糖溶液中，静脉滴注，每日一次。两组均连续治疗 1 周。

1.3 观察指标

观察治疗后两组临床疗效；于治疗前后观察两组腹部体征、胃肠道功能恢复时间；比较两组治疗前后采用酶联免疫分析法测定血清 CRP、TNF-α、IL-6，使用分光光度法测定 D- 乳酸水平，用酶比色发测定血淀粉酶、尿淀粉酶、脂肪酶水平。并统计两组不良反应发生情况。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料用($\bar{x}\pm s$)表示，选用 t 检验，计数资料用[例(%)]表示，用 χ^2 检验比较，P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床疗效比较

对照组总有效率为 75.00%(30/40)，试验组总有效率为 92.50%(37/40)，两组比较有统计学意义(P<0.05)，见表 2。

表 2 两组临床结果比较[(例，%)]

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

Groups	n	Recovery	Effective	Invalid	Total efficiency
Control group	40	8(20.00)	22(55.00)	10(25.00)	30(75.00)
Treatment group	40	20(50.00)	17(42.50)	3(7.50)	37(92.50)a

Note: Compared with Treatment group, aP<0.05.

2.2 两组临床体征比较

试验组腹部体征消失时间及胃肠道功能恢复时间均明显短于对照组，比较有统计学差异(P<0.05)，见表 3。

2.3 两组炎症因子与 D- 乳酸水平比较

治疗前，两组 CRP、TNF-α、IL-6 及 D- 乳酸水平比较无统计学差异(P>0.05)；经治疗，两组患者上述指标水平均显著降低，且试验组明显低于对照组(P<0.05)，见表 4。

表 3 两组临床体征比较($\bar{x}\pm s$,d)

Table 3 Comparison of two groups of clinical signs ($\bar{x}\pm s$, d)

Groups	n	Abdominal signs disappear time	Recovery time of gastrointestinal function
Control group	40	4.83±0.73	3.01±0.52
Treatment group	40	3.37±0.62 [a]	2.14±0.35 [a]

Note: Compared with Treatment group, [a]P<0.05.

表 4 两组炎症因子与 D- 乳酸水平比较($\bar{x}\pm s$)

Table 4 Comparison of two groups of inflammatory cytokines and D-lactic acid of levels ($\bar{x}\pm s$)

Groups	n	Time	CRP(mg/L)	TNF-α(ng/L)	IL-6(ng/L)	D-LA(mg/L)
Control group	40	Before treatment	90.46±10.32	41.41±5.84	86.32±11.53	12.73±2.17
		After treatment	34.29±5.73[b]	28.54±3.18[b]	42.83±8.11b	5.83±1.04b
Treatment group	40	Before treatment	92.93±11.83	40.68±6.11	88.21±10.37	13.02±1.94
		After treatment	18.64±3.94 ab	17.95±4.25 [ab]	31.46±7.23 ab	3.46±0.83 [ab]

Note: Compared with Treatment group, [a]P<0.05; Compared with same group before treatment, [b]P<0.05.

2.4 两组淀粉酶与脂肪酶水比较

治疗前,两组血淀粉酶、尿淀粉酶、脂肪酶水平比较无统计学差异(P>0.05);经治疗,两组患者上述指标水平均显著降低,且试验组明显低于对照组(P<0.05),见表 5。

表 5 两组淀粉酶与脂肪酶水平比较($\bar{x}\pm s$, U/L)

Table 5 Comparison of two groups of amylase and lipase of levels ($\bar{x}\pm s$, U/L)

Groups	n	Time	Serum amylase	Urine amylase	Lipase
Control group	40	Before treatment	953.15±124.54	3548.29±425.68	249.18±30.58
		After treatment	274.15±41.58 [b]	1789.54±247.14 [b]	74.93±10.17 [b]
Treatment group	40	Before treatment	985.29±131.21	3613.31±487.92	252.47±32.24
		After treatment	148.64±26.17 [ab]	1073.41±144.58 [ab]	38.35±6.57 [ab]

Note: Compared with Treatment group, [a]P<0.05; Compared with same group before treatment, [b]P<0.05.

2.5 两组不良反应情况比较

两组患者均发生不同程度的多器官功能衰竭、假性囊肿已经胰周感染,其试验组发生率为 7.5%(3/40),对照组发生率为 17.5%(7/40),两组比较具有统计学意义(P<0.05)。

3 讨论

胰腺炎是临床常见的急腹症,具有较高的并发症率及死亡率,其发病机制较为复杂,但多数认为胰腺炎是因多种因素参与且复杂的一个病例过程[12]。众多学者通过对其发病机制研究发现,主要机制为胆胰管的共同通路,诱发结石梗阻,使胰腺出现自身消化,激活补体系统和激肽,使微循环产生障碍,从而造成炎症反应,导致细胞细胞凋亡、坏死[13-15]。据相关文献显示,胰腺炎在任何发病机制下,最终都会引起机体全是或局部发生炎症反应,炎症反应则会加重疾病的发生发展,从而形成恶性循环[16]。由此可见,胰酶的早期活化,炎症因子的产共同作用使胰腺炎患者早期出现病理损伤,而未及时有效治疗,随之病情发展,肠源性的徐俊移位则会导致严重的感染,从而出现严重的多器官衰竭。

目前临床对于胰腺炎的治疗主要采用胰酶抑制剂。生长抑素是治疗胰腺炎的常用药物,在改善患者临床方面具有显著效果。生长抑素属于一种肽激素,普遍存在与机体肠胃道神经、胃粘膜及胰岛中,具有多种功能,能够与胰腺细胞表面的生长抑素受体相结合,抑制腺苷酸环化酶活性,从而减少了细胞内的合成,减低胰腺外分泌功能;同时可减少腹腔以及胰腺血流量,使入血胰酶量减少;通过激素样作用松弛 Oddi 括约肌,缓解和阻断胰腺自身的消化;诱导胰腺组织 EGF 表达,促进正常胰腺细胞增生,修复胰腺;此外还可降低迷走神经兴奋性,使乙酰胆碱释放受阻,从而抑制神经性胰腺外分泌功能[17-21]。生长抑素上述功能在胰腺炎的治疗中发挥了重要作用。从本研究结果可见,患者经生长抑素治疗后,其临床症状明显好转,其淀粉酶及脂肪酶水平均降低, 观察治疗后患者炎症因子水平也有所好转,提示生长抑素可促进患者早期恢复,缓解临床症状,此结论与相关文献一致。另有研究显示,生长抑素在改善坏死性胰腺炎胰腺组织微循环方面效果却不显著[22]。Lyu Y 等研究认为,生长抑素可通过抑制胰液的分泌从而降低胰腺炎的死亡率,但对其并发症影响并不显著[23]。

国外研究认为,胰腺炎治疗中的关键环节为阻断胰酶异常激活、炎症介质释放以及消除已激活的胰酶和入血的炎症介质[24]。加贝酯是一种非肽类蛋白酶抑制剂,其分子量较小,因此可进入胰管,从而能够抑制胰液中胰酶活性;同时对 Oddi 括约肌运动具有抑制效果;有关文献报道,加贝酯可有效缓解胰腺组织的病变, 与抑制α- 白球蛋白相结合的胰蛋白酶活性有关,

对脂肪组织坏死具有明显的改善效果,同时还可降低血清淀粉酶、脂肪酶活性[25-28]。本研究结果显示,患者通过加贝酯联合生长抑素治疗后,其总有效率显著提高,临床症状改善时间明显缩短,且血清淀粉酶、脂肪酶水平明显降低,提示贝酯联合生长抑素在治疗胰腺炎利于损伤的胰腺快速恢复。

临床多项资料显示,胰腺内胰酶在损伤组织的同时会激活其体内的炎症细胞,从而使其释放大量的炎症因子,促进炎症细胞释放过量的炎症介质,从而导致胰腺炎的发生发展。CRP是机体组织在炎症反应和组织损伤所产生的一种急性反应性蛋白,通过激活补体及吞噬细胞的吞噬起到调理的作用,在机体免疫过程中具有一定的保护作用,其水平的高低与胰腺炎病情的炎症重度及预后相关。TNF-α是胰腺炎发病过程中较为重要的细胞因袭,能够诱导IL-2、IL-6等炎症因子的表达,导致机体产生相应的联机反应。IL-6是一种功能较为广泛的多效性细胞因子,可调节多种细胞生长及分化;通过增加机体血管的通透性、活化补体等引起机体胰腺持续坏死,同时会促进TNF-α分泌,使胰腺损伤加重。本结果显示,经治疗患者血清CRP、TNF-α及IL-6均显著降低,且联合治疗的效果更甚,提示生长抑素与加贝酯的联合在短时间内调节了细胞免疫水平,抑制细胞因子与炎症介质的释放,从而改善了患者血清炎症因子水平,其联合使用发挥了协同作用,使药效增强,进而增强了机体对炎症的抵抗以及对蛋白酶的抑制。

Pan X等团队研究认为[29],肠屏障功能障碍与胰腺炎的发生发展有密切关系。D-乳酸是通过胃肠道的固有细菌产生,其水平的高低能够直观反映出肠粘膜通透性的变化。在病情发生时,是导致肠道膜的通透性增加,使D-乳酸进入血液循环,从而使其血清水平浓度增加。本研究中,患者联合应用加贝酯与生长抑素显著降低了血清D-乳酸水平,且效果明显优于生长抑素治疗。分析其原因可能是,加贝酯与生长抑素的联合,广泛抑制了胰蛋白、弹性蛋白酶的活性及释放,有助于减少胰腺损伤,同时加贝酯能够减少肠道通透详性,改善机体肠粘膜功能,保护了肠粘膜屏障。

综上所述,加贝酯联合生长抑素治疗胰腺炎可有效改善患者炎症因子水平及肠粘膜功能,更利于快速控制病情,从而显著提高临床疗效。

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