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连续性血液净化治疗联合乌司他丁对急性胰腺炎患者 TLR4、血浆炎症因子及白介素的影响 *

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摘要 目的:探究连续性血液净化联合乌司他丁对急性胰腺炎患者 TLR4、白介素及血浆炎症因子的影响。**方法:**选择 2014 年 1 月至 2016 年 1 月我院接诊的 72 例急性胰腺炎患者,并采用随机的方法分为实验组与对照组各 36 例。实验组与对照组均进行基础治疗和乌司他丁治疗,而实验组还要进行连续性血液净化治疗。记录治疗后 APACHE II 评分、住院时间、腹痛消失时间、血清淀粉酶恢复时间,测量患者治疗前和治疗一周后的 TLR4、血浆炎症因子及白介素水平。**结果:**(1)实验组患者治疗后住院时间、血清淀粉酶恢复时间、APACHE II 评分、腹痛消失时间均显著低于或少于对照组患者($P<0.05$)。(2)相较于治疗前,两组患者治疗一周后的 TLR4、CRP、IL-6 和 TNF- α 水平均显著降低($p<0.05$);实验组患者治疗一周后的 TLR4、CRP、IL-6 和 TNF- α 的水平均显著低于对照组($p<0.05$)。(3)实验组的治愈率(34.29%)和总有效率(74.29%)均显著高于对照组的治愈率(14.29%)和总有效率(48.57%)。**结论:**连续性血液净化治疗联合乌司他丁对急性胰腺炎患者的抗炎效果相较于单独使用乌司他丁疗效显著,能更好地降低炎症反应,使得 TLR4、血浆炎症因子及白介素等炎症因子降低。

关键词:乌司他丁;急性胰腺炎;炎症因子;血液净化治疗

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Influence of TLR4, Plasma Inflammatory Cytokines and Interleukins on Acute Pancreatitis Patients Bicontinuous Blood Purification Treatment Combined with Ulinastatin*

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ABSTRACT Objective: In order to study the influence of TLR4, plasma inflammatory cytokines and interleukins on acute pancreatitis patients bicontinuous blood purification treatment combined with ulinastatin. **Methods:** From January 2014 to 2016 January, 72 cases of patients who with acute pancreatitis admitted to our hospital, and it was randomly divided into observation group and control group, each of 36 cases. In the control group based on the foundation treatment with ulinastatin treatment, while the observation group in the control group therapy based on the use of continuous blood purification treatment. Recorded after treatment, APACHE II score, hospitalization time, abdominal pain disappearing time, serum amylase recovery time, were measured the level of before treatment and after a week of treatment of TLR4, plasma inflammatory factors and interleukin. **Results:** (1) Observation group after treatment APACHE II score, length of stay, abdominal pain disappeared time, serum amylase recovery time were significantly lower than or less than the control group ($P<0.05$). (2) The levels of TLR4, CRP, IL-6 and TNF- α in the two groups after treatment were significantly lower than those before treatment ($p<0.05$); The levels of TLR4, CRP, IL-6 and TNF- α in the observation group were significantly lower than those in the control group ($p<0.05$) after one week treatment. (3) The cure rate (34.29%) and total effective rate (74.29%) in the observation group were significantly higher than that in the control group (14.29%) and total effective rate (48.57%). **Conclusion:** Compared to the single use of ulinastatin and continuous blood purification treatment combined with ulinastatin on the treatment of patients with acute pancreatitis effect significantly, can reduce the inflammatory reaction and the TLR4, plasma inflammatory factor and interleukin inflammatory factors.

Key words: Ulinastatin; Acute pancreatitis; Inflammatory factors; Blood purification therapy

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前言

急性胰腺炎是常见的腹部外科危重急症,其发生受多因素影响,发病原理是激活的胰酶进入胰腺组织导致胰腺自身消化、胰腺及胰腺周围炎症反应,肠源性内毒素入血激活炎症细胞,引起多器官功能障碍以及全身性炎症反应^[1]。炎症反应是急性胰腺炎的主要临床表现,急性胰腺炎发病可能产生全身性炎症反应及炎性细胞因子的释放。根据目前的研究^[2,3],绝大多数急性胰腺炎患者血浆炎症因子都会较正常人明显升高。长久以来,针对急性胰腺炎患者的临床治疗方法以乌司他丁静脉滴注治疗为主,但目前连续性血液净化技术已经受到各医疗机构的广泛肯定^[4]。所以本研究选择 2014 年 1 月至 2016 年 1 月我院接诊的 70 例急性胰腺炎患者进行研究,探究连续性血液净化治疗联合乌司他丁对急性胰腺炎患者 TLR4、血浆炎症因子及白介素水平的影响。现报道如下:

1 资料与方法

1.1 一般资料

选取 2014 年 1 月至 2016 年 1 月我院接诊的急性胰腺炎患者 72 例,随机将其分为实验组与对照组各 36 例。实验组患者组成为男性 20 例,女性 16 例,年龄为 23~62 岁,平均年龄 41 ± 18 岁。该组患者的组成为:10 例暴饮暴食,12 例胆道疾病,5 例酗酒,9 例其他原因;并发症:高脂血症 21 例,急性肺损伤 12 例,休克 2 例,急性肾损伤 1 例,心衰 2 例。对照组中男性 21 例,女性 15 例,年龄为 24~67 岁,平均年龄 44 ± 16 岁。其中实验组中男性 19 例,女性 17 例,年龄为 23~62 岁,平均年龄 41 ± 18 岁。该组患者的组成为:7 例酗酒,7 例暴饮暴食,14 例胆道疾病,8 例其他原因;并发症:高脂血症 19 例,急性肺损伤 12 例,急性肾损伤 2 例,心衰 3 例。两组患者性别、年龄、APACHE II 评分、病因等一般临床资料无显著差异,具有可比性。

1.2 纳入标准

两组患者均根据 2013 年《中国急性胰腺炎诊治指南》的诊断标准纳入,并经影像学检查确诊;所有患者均自愿加入本研究;排除其它急腹症;排除免疫系统疾病患者;排除血液系统疾

病患者;排除肿瘤患者;排除服用其他药物影响血必净治疗效果患者;患者及其家属均签订知情同意书。

1.3 治疗方法

实验组和对照组均给予基础治疗和乌司他丁治疗,而实验组在此基础上进行连续性血液净化治疗。基础治疗:对患者采取低流量吸氧、禁食、胃肠减压、维持患者水电平衡以及酸碱平衡,同时进行抗感染、营养支持等措施。危急情况下给予患者呼吸机辅助通气,以维持其的生命体征。乌司他丁治疗:根据患者情况将 20~25 万 U 乌司他丁加入 500 mL 5%葡萄糖注射液中进行静脉滴注 1 次,并且根据患者临床症状的改变进行乌司他丁用量的调整。连续性血液净化方法:本研究采用的血滤机为金宝公司的全自动 Prismaflex 系床旁血滤机(血液滤器型号为 HF1000set),借助其创建体外循环系统,连续静脉-静脉血液滤过 15 h/d,同时根据患者身体状况调整置换液中电解质成分和浓度。置换液的流速控制为 2000~2500 mL/h,并将血流速度控制在 170~180 mL/min(可以根据患者的具体情况进行调整)。同时采用低分子肝素钠联合枸橼酸钠在血液滤过时进行抗凝处理。此外,定期用生理盐水冲洗患者所用滤器,并于治疗前和治疗一周后采集患者血液标本,测定各因子。

1.4 观察指标

记录治疗后 APACHE II 评分、住院时间、腹痛消失时间、血清淀粉酶恢复时间,测量患者治疗前和治疗一周后的 TLR4、血浆炎症因子及白介素浓度。

1.5 统计学方法

研究数据采用 SPSS19.0 统计学软件进行统计分析,计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,行 t 检验,计数资料以百分比(%)表示,行 χ^2 检验, $p < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者 APACHE II 评分、血清淀粉酶恢复时间等指标比较

两组患者 APACHE II 评分、血清淀粉酶恢复时间等指标比较显示:实验组患者治疗后 APACHE II 评分明显低于对照组患者得分,而观察组患者住院天数、腹痛消失天数、血清淀粉酶回复天数明显短于对照组患者($P < 0.05$)。(见表 1)

表 1 两组患者 APACHE II 评分、血清淀粉酶恢复时间等指标比较($\bar{x} \pm s$)

Table 1 Comparison of APACHE II score and serum amylase recovery time and other items between two groups ($\bar{x} \pm s$)

Groups	n	APACHE II score	Hospital stay(Days)	Abdominal pain disappear time (Days)	Plasma amylase recovery time(Days)
Observation Group	36	4.53 ± 0.89	8.67 ± 3.08	5.13 ± 1.36	5.24 ± 1.98
Control Group	36	7.62 ± 0.78	11.03 ± 1.24	7.69 ± 0.89	8.31 ± 0.86
t		15.4472	4.2051	9.3182	8.4136
8.4136		$P < 0.0001$	0.0001	$P < 0.0001$	$P < 0.0001$

2.2 两组患者治疗前后 TLR4、血浆炎症因子及白介素水平比较

两组患者治疗前后 TLR4、血浆炎症因子及白介素水平比较显示:两组患者治疗一周后的 TLR4、CRP、IL-6 和 TNF- α 的

水平均显著低于治疗前 ($p < 0.05$);实验组患者治疗一周后的 TNF- α 、CRP、TLR4、IL-6 的水平均显著低于对照组 ($p < 0.05$) (见表 2)。

表 2 两组患者治疗前后 TLR4、血浆炎症因子及白介素浓度比较($\bar{x} \pm s$)

Table 2 The comparison in levels of TLR4, plasma inflammatory factor and interleukin

Groups	n	Time	TLR4(pg/mL)	CRP(mg/L)	IL-6(pg/mL)	TNF- α (pg/mL)
Observation Group	36	Before Treatment	12.87 $\pm$ 2.57	226.1 $\pm$ 20.9	31.23 $\pm$ 6.45	33.05 $\pm$ 6.13
		1 week after treatment	5.04 $\pm$ 2.36 ^{ab}	175.5 $\pm$ 23.4 ^{ab}	18.53 $\pm$ 4.60 ^{ab}	14.68 $\pm$ 4.28 ^{ab}
Control Group	36	Before Treatment	12.20 $\pm$ 2.24	216.1 $\pm$ 21.4	32.03 $\pm$ 6.13	32.56 $\pm$ 5.37
		1 week after treatment	6.26 $\pm$ 2.31 ^b	188.5 $\pm$ 22.6 ^b	21.35 $\pm$ 4.15 ^b	20.64 $\pm$ 4.36 ^b

注:与对照组相比,^a $p < 0.05$;与治疗前相比,^b $p < 0.05$

Note: compared with the control group, ^a $p < 0.05$; compared with pretherapy, ^b $p < 0.05$

2.3 两组患者的临床疗效比较

两组患者的临床疗效比较显示:实验组的治愈率(34.29%)

和总有效率(74.29%)均显著高于对照组的治愈率(14.29%)和总有效率(48.57%)(见表3)。

表 3 两组患者治疗效果的比较 [例(%)]

Table 3 Compared clinical efficacy between the two groups [case(%)]

Groups	n	Cure	Effective	Invalid	Total effect
Observation Group	36	12(34.29)*	14(40.00)	9(25.71)	26(74.29)*
Control Group	36	5(14.29)	12(34.29)	18(51.43)	17(48.57)

注:与对照组相比,* $p < 0.05$ 。

Note: compared with the control group,* $p < 0.05$.

3 讨论

急性胰腺炎(AP)多为胆石症、血脂异常等多种原因导致胰腺酶原的异常激活而出现胰腺组织的自我消化^[9]。临床上急性胰腺炎患者表现为急性腹部疼痛,同时伴有恶心、呕吐等症状。随着生活水平的提高,人们饥饿发生情况的减少,胃溃疡的发病率有所下降。但是蛋白、脂质的大量摄入导致急性胰腺炎的发病率不断增高,是消化科临床上常见的急腹症之一^[6]。急性胰腺炎主要分为轻型急性胰腺炎和重型急性胰腺炎。轻型急性胰腺炎的临床症状较轻,经过内科保守治疗后,一般能得到较好的治愈。重型急性胰腺炎则主要表现为胰腺出血坏死,临床症状重,如果患者没有得到有效的诊断和治疗,可以出现患者死亡,不仅对患者的个人身体健康,而且对患者的生活质量造成极大的影响以及对患者家庭造成巨大的负担^[7,8]。由于急性胰腺炎的病死率极高,所以对于本病的有效治疗一直是临床工作者研究要攻克的难点。

急性胰腺炎主要症状是全身性炎症反应,患者白细胞过度激活,中性粒细胞向炎症部位迁移增加,瀑布式炎症反应使CRP、IL-6、TNF- α 等炎症因子过度释放,导致多器官功能衰竭的发生甚至死亡^[9]。多项研究^[10,11]显示 Toll 样受体(Toll-like receptors, TLRs)是炎症瀑布式反应的闸门。TLRs 属于 I 类跨膜受体,与信号的传导相关,TLR4 是脂多糖受体,具有介导胞内信号传递的作用,TLR4 的激活将导致多种分子的活化,最终导致 TNF- α 等一系列炎症因子激活,产生一系列炎症反应。CRP 是在机体遭受外伤或炎症反应引起的组织损伤时的一种急性相蛋白,患者发病后其水平会迅速升高,随着机体恢复,其水平下降也快,临床中常用其检测炎症反应和组织损伤^[12]。IL-6 是 T 细胞原性细胞因子,可降低 IL-2 和肿瘤坏死因子等前炎

性细胞因子水平,促进糖皮质激素及可溶性肿瘤坏死因子受体分泌,可促进多种细胞的生长和分化,是免疫调节网络中的关键因子^[13]。TNF- α 由活化的巨噬细胞和单核细胞产生,是人体的主要炎症介质。TNF- α 具有使靶细胞对多种细胞因子的反应性提高的作用,同时促进炎症反应^[14]。临床上常用的治疗药物乌司他丁是一种蛋白水解酶抑制剂,因为有强大的抗炎、将低组织细胞炎症损伤、改善组织微循环及灌注等作用而被广泛应用于危重患者;而连续性血液净化治疗可以清除细胞因子和炎症介质,具有恢复免疫调节和改善心、肺、肾等系统的功能^[15-17]。本研究则联合这两种方式对急性胰腺炎患者进行治疗,发现两组患者治疗一周后的 TLR4、CRP、IL-6 和 TNF- α 的水平均显著低于治疗前,实验组患者治疗一周后的 TLR4、CRP、IL-6 和 TNF- α 的水平均显著低于对照组,这说明单纯使用乌司他丁治疗急性胰腺炎有较好的疗效,但是连续性血液净化治疗联合乌司他丁对急性胰腺炎的疗效比单纯使用乌司他丁治疗更显著,这之前临床工作者研究的结果相符^[18-20]。因为疗效显著,所以连续性血液净化治疗联合乌司他丁治疗的患者在治疗后 APACHE II 评分、住院时间、腹痛消失时间、血清淀粉酶恢复时间均显著低于或少于单纯使用乌司他丁治疗的患者。最终实验组的治愈率为 34.29%、总有效率为 74.29%,均远远高于对照组的治愈率 14.29%和总有效率 48.57%。

综上所述,连续性血液净化治疗联合乌司他丁对急性胰腺炎患者相较于单独使用乌司他丁治疗作用明显,能更好地降低炎症反应,使得 TLR4、血浆炎症因子及白介素等炎症因子降低,对于患者的快速恢复具有重要意义,值得在临床中广泛应用。

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