doi: 10.13241/j.cnki.pmb.2017.10.012

连续性血液净化对重症胰腺炎患者炎症因子、内毒素及肠道黏膜屏障功能的影响*

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摘要 目的: 研究连续性血液净化对重症胰腺炎患者炎症因子、内毒素及肠道黏膜屏障功能的影响。**方法:** 选取 2014 年 2 月至 2015 年 1 月本院收治的 86 例重症胰腺炎患者,按照投硬币法分为观察组(43 例)和对照组(43 例)。对照组采取常规治疗,观察组在此基础上加以连续性血液净化治疗。比较两组患者治疗前后炎症因子、内毒素、肠道黏膜屏障功能变化情况,分析两组患者临床症状缓解时间。**结果:** 治疗后,观察组血清白介素 -6(IL-6)、白介素 -8(IL-8)、白介素 -1β(IL-1β)、肿瘤坏死因子 -α (TNF-α)、内毒素、D- 乳酸、二胺氧化酶水平明显低于对照组(P<0.05),压痛、腹痛、腹胀症状缓解时间显著短于对照组(P<0.05)。**结论:** 连续性血液净化能有效改善重症胰腺炎患者炎症因子水平、内毒素及肠道黏膜屏障功能,促进患者临床症状快速恢复。

关键词: 连续性血液净化;重症胰腺炎;炎症因子;内毒素;肠道黏膜屏障功能

中图分类号: R576;R459.5 **文献标识码:** A **文章编号:** 1673-6273(2017)10-1849-03

Effects of Continuous Blood Purification on the Inflammatory Factors, Endotoxin and Intestinal Mucosal Barrier in Patients with Severe Pancreatitis*

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ABSTRACT Objective: To study the effects of continuous blood purification on inflammatory factors, endotoxin and intestinal mucosal barrier function in patients with severe acute pancreatitis. **Methods:** From February 2014 to January 2015, 86 patients with severe pancreatitis were divided into the observation group (43 cases) and the control group (43 cases) according to coin method. The control group was treated with conventional therapy, and the observation group was treated with continuous blood purification on the basis of control group. Then the changes of inflammatory factors, endotoxin and intestinal mucosal barrier function were compared between the two groups before and after treatment, and the relief time of clinical symptom of two groups was analyzed. **Results:** The serum levels of IL-6, IL-8, IL-1β, and TNF-α in the observation group were significantly higher than those in the control group (P <0.05). The levels of endotoxin, D-lactate and diamine oxidase in the observation group were significantly lower than those in the control group(P<0.05). The relieving time of tenderness, abdominal pain and bloating in the observation group was significantly shorter than that in the control group (P <0.05). **Conclusion:** Continuous blood purification could effectively improve the levels of inflammatory factors, endotoxin and intestinal mucosal barrier function in patients with severe acute pancreatitis, and promote the rapid recovery of clinical symptoms in patients with severe acute pancreatitis.

Key words: Continuous blood purification; Severe pancreatitis; Inflammatory factor; Endotoxin; Intestinal mucosal barrier function

Chinese Library Classification(CLC): R576; R459.5 Document code: A

Article ID: 1673-6273(2017)10-1849-03

前言

重症胰腺炎是一种临床较为常见的急腹症，具有病情凶险、病因复杂、病情进展快等特点,病死率超过 20%[1]。相关研究发现大部分重症胰腺炎患者血清 IL-1、IL-6、IL-8、TNF-α 等炎症因子水平呈现出明显升高的趋势,并且全身炎症反应综合征和重症胰腺炎患者的严重程度呈现出正相关趋势[2]。当患者的肠道黏膜屏障功能受损时,毒素、细菌在肠道中会发生移位,促炎介质在通透性升高的肠道屏障作用下流入血液循环,导致机体发生自毁性、内源性失控的全身炎症反应,进一步损害器官和组织,进而发生多器官功能障碍综合征[3,4]。近年来,伴随着人们对重症胰腺炎认识的不断加深,在治疗重症胰腺炎中采取连续性血液净化方式已获得了一定进展,可降低病死率及改善患者的预后[5]。为给临床在治疗重症胰腺炎中提供更多参考价值,本研究文就连续性血液净化对重症胰腺炎患者炎症因子、内毒素及肠道黏膜屏障功能的影响进行分析。

1 资料与方法

1.1 临床资料

选取 2014 年 2 月至 2015 年 1 月期间本院收治的 86 例重

* 基金项目:湖南省科技计划基金资助项目(2012SK3242)

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(收稿日期:2016-10-11 接受日期:2016-10-29)

症胰腺炎患者。纳入标准:① 患者的临床诊断均和重症胰腺炎诊断标准相符;② 当前未使用可能会对研究结果造成影响的药物;③ 患者依从性较好,愿意配合医护人员完成本次试验;④ 均可收集到较为完整的饮食资料。排除标准:① 伴有多器官功能障碍;② 伴有内分泌性疾病或严重并发症;③ 在整个试验过程中不能根据要求完成检查;④ 在治疗过程中患者的病情突然加重,难以再次加入本次试验者。整个研究签署患者知情同意书,获取了本院伦理委员会的批准。按照投硬币法将本次研究对象分为了观察组(43 例)和对照组(43 例)。其中观察组中有 28 例为男性,15 例为女性;年龄为 32~68 岁之间,平均(48.32± 2.12)岁;发病原因:8 例饮酒,11 例暴饮暴食,19 例胆道病史,5 例病因不明。对照组中有 26 例为男性,17 例为女性;年龄为 33~70 岁之间,平均(48.41± 2.18)岁;发病原因:9 例饮酒,13 例暴饮暴食,18 例胆道病史,3 例病因不明。两组患者的一般资料比较在年龄、性别、发病原因方面无明显差异性(P>0.05)

1.2 方法

对照组采取常规治疗, 治疗方式如下:(1) 营养支持治疗。(2)水电解质平衡的维持,抗休克。(3)止痛、解痉、镇静处理。(4)使用预防性抗生素,主要针对患者伴有肠源性革兰氏阴性杆菌易位现象,使用能通过血胰屏障的抗生素,主要有亚胺培南、舒巴坦、喹诺酮类等。(5)使用生长抑制素、导泻通便、禁食、胃肠减压、液体复苏处理。观察组患者在对照组治疗基础上加以连续性血液净化进行治疗,血管通路的建立,连续性血液净化系统为 Baxter BM25,为 AN69 膜滤器,为 1.6 m× 1.6 m 的面积,流量为 2000~3000 mL/h 的置换液流量,输入方式采取稀释形式,为 150~200 mL/min 的血流量。超滤器的调整按照患者病情进行操作。抗凝处理方式为枸橼酸钠联合低分子肝素,患者伴有弥漫性血管内凝血需予以无肝素血滤操作, 滤器需定期冲洗。治疗时间共需持续 3 d。

1.3 观察指标

比较两组患者在治疗前和治疗 3d 后炎症因子 [白介素 -6(Interleukin-6, IL-6)、白介素 -8(Interleukin-8,IL-8)、白介素 -1β(Interleukin-1β,IL-1β)、肿瘤坏死因子 -α (Tumor necrosis factor-α ,TNF-α)]内毒素、肠道黏膜屏障功能(D- 乳酸、二胺氧化酶)变化,分别在患者治疗前和治疗 3 d 后手机 6 mL 的静脉血放置在无菌塑料管中,放置在室温中,转速 3000 r/min,离心 15 min,将血清分离后放置在 -50℃低温箱中待测,炎症因子水平使用酶联免疫法进行检测, 采取分光光度法对内毒素、D- 乳酸、二胺氧化酶水平进行检测,由上海医药化学研究所提供内毒素检测试剂盒,D- 乳酸、二胺氧化酶试剂盒由 sigma 公司提供,均根据说明书进行严格操作。分析两组患者的主要症状、体征缓解时间,包括压痛、腹痛、腹胀所需缓解的时间。

1.4 统计学处理

本次实验数据处理选择 SPSS11.5 软件包进行, 计量资料用($\bar{x}$± s)来表示,采用 t 检验,计数资料用[n(%)]来表示,采取 X^2 检验,其 P<0.05 表明差异具有统计学意义。

2 结果

2.1 两组患者治疗前后炎症因子水平比较

治疗前, 两组患者的 IL-6、IL-8、IL-1β、TNF-α 炎症因子水平比较差异性不明显(P>0.05),治疗 3d 后,两组患者的 IL-6、IL-8、IL-1β、TNF-α 炎症因子水平和治疗前相比显著性降低(P<0.05),其中观察组的 IL-6、IL-8、IL-1β、TNF-α 炎症因子水平明显低于对照组(P<0.05),见表 1。

表 1 两组患者治疗前后炎症因子水平比较($\bar{x}$ ± s)

Table 1 Comparison of the serum inflammatory factors levels between two groups before and after treatment($\bar{x}$± s)

Groups	Case	IL-6(pg/mL)		IL-8(pg/mL)		IL-1β(pg/mL)		TNF-α(ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	43	22.43± 2.14	15.32± 1.31*#	25.67± 2.45	16.43± 1.57*#	301.13± 23.21	234.32± 21.33*#	3.02± 0.56	1.23± 0.12*#
Control group	43	22.41± 2.16	18.63± 1.65*	25.69± 2.41	20.76± 2.02*	301.16± 23.16	287.54± 22.45*	3.04± 0.52	2.21± 0.34*

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

2.2 两组患者治疗前后内毒素及肠道黏膜屏障功能的比较

治疗前,两组患者的内毒素、D- 乳酸、二胺氧化酶水平比较无显著性差异(P>0.05),治疗 3 d 后,两组患者的内毒素、D- 乳酸、二胺氧化酶水平较治疗前显著降低(P<0.05),其中观察组的内毒素、D- 乳酸、二胺氧化酶水平明显比对照组低(P<0.05),见表 2。

表 2 两组患者治疗前后内毒素及肠道黏膜屏障功能比较($\bar{x}$± s)

Table 2 Comparison of the serum endotoxin and intestinal mucosa barrier function between two groups before and after treatment($\bar{x}$± s)

Groups	Case	Endotoxin(EU/L)		D-lactate(mg/L)		Diamine oxidase(U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	43	0.41± 0.05	0.21± 0.02*#	1.67± 0.13	0.92± 0.05*#	7.32± 0.73	4.53± 0.41*#
Control group	43	0.42± 0.03	0.33± 0.03*	1.68± 0.14	1.12± 0.11*	7.35± 0.74	6.02± 0.58*

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

2.3 两组患者症状、体征缓解时间比较

观察组压痛、腹痛、腹胀症状缓解时间显著短于对照组，差异显著(P<0.05)，见表3。

表3 两组患者症状、体征缓解时间比较($\bar{x}\pm s$)

Table 3 Comparison of the relief time of symptoms and signs between two groups ($\bar{x}\pm s$)

Groups	Case	Tenderness remission time	Stomach ache remission time	Stomachache remission time
Observation group	43	4.56± 0.54*	3.42± 0.36*	3.46± 0.45*
Control group	43	6.21± 0.67	4.68± 0.72	5.32± 0.56

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

3 讨论

研究表明在重症胰腺炎患者中胰腺以及周围组织自身消化情况反应较为明显，并且多项指标的变化较大，主要表现为患者的IL-6、IL-8、IL-1β、TNF-α水平显著升高[6]。连续性血液净化能有效清除炎症介质以及细胞因子，可促进免疫调节得到恢复，有利于患者的肝脏、肾、肺、心等系统得到改善[7,8]。本次研究结果显示通过对重症胰腺炎患者予以常规治疗联合连续性血液净化治疗后，患者的IL-6、IL-8、IL-1β、TNF-α炎症因子水平较治疗前显著降低，且降低的效果优于常规治疗者，提示连续性血液净化可有效降低患者缓解患者的炎症反应，经合成膜纤维的渗透、对流、吸附等方式减少炎症介质浓度，进而调节炎症介质水平，有利于重症胰腺炎患者的炎症反应及预后得到改善。

连续性血液净化可有效改善重症胰腺炎患者的肠道黏膜通透性，与其能有效清除炎症介质相关[9,10]。也有研究者在研究中发现连续性血液净化可改善重症胰腺炎患者肠黏膜屏障功能的损伤程度，原因可能是连续性血液净化能抑制全身炎症反应综合征及氧化应激反应，进而对p38丝裂原活化蛋白激酶信号通路活性起着下调的作用，对诱导型一氧化氮合酶表达发挥着抑制作用，降低一氧化氮的生成，有利于连接蛋白表达和重排得到改善，进而对重症胰腺炎患者的肠黏膜屏障功能起着保护作用[11-13]。

肠道黏膜屏障功能障碍易引发毒素易位、肠内细菌，继发脓毒血症及感染，其中继发感染易导致重症胰腺炎患者面临死亡的威胁[14]。当肠道屏障功能遭受损伤时，D-乳酸会在通透性增加的肠黏膜作用下流入血循环，进而升高D-乳酸在血中的水平，因此对D-乳酸水平进行检测可对肠黏膜通透性和损害情况作出确切反应，常常在早期诊断中将此指标视为肠黏膜受损的标志物[15,16]。95%以上的二胺氧化酶在纤毛上皮细胞或小肠黏膜中存在，细胞内酶的活性较强，和蛋白合成及肠核酸存在密切关联性，一旦肠黏膜屏障功能受到损害时，肠细胞间隙血流和淋巴管会增加二胺氧化酶进入的含量，升高血二胺氧化酶水平，通过对血浆二胺氧化酶水平进行监测可对早期肠黏膜通透性做出灵敏反应，常常将其视为评价肠黏膜状态的重要指标[17,18]。此外，肠道中的内毒素和细菌在受损的肠黏膜引导下，会进入人体中形成肠源性内毒素血脂，因此在观察肠黏膜平屏障通透性中可通过对内毒素在血清中的水平进行监测进而做出反应[19]。相关研究显示在重症胰腺炎患者中，内毒素、D-乳酸、二胺氧化酶水平呈现出明显升高的趋势[20]。本次研究结果显示患者经常规治疗联合连续性血液净化治疗后，内毒素、D-乳酸、二胺氧化酶水平显著性降低，其降低的效果优于单纯常规治疗者，提示连续性血液净化可有效改善重症胰腺炎患者肠黏膜屏障功能，还可有效改善患者的全身机体状况，有利于患者预后的改善。此外，重症胰腺炎患者经常规治疗联合连续性血液净化治疗后，压痛、腹痛、腹胀症状缓解时间较短，明显短于常规治疗者，提示连续性血液净化能促进重症胰腺炎患者临床症状得到快速缓解。

综上所述，连续性血液净化能有效改善重症胰腺炎患者炎症因子水平、内毒素及肠道黏膜屏障功能，促进患者临床症状得到快速恢复。

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