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清胰利胆颗粒联合床旁 CRRT 疗法对 SAP 患者炎症因子、免疫功能及外周血 Foxp3、ROR γ t mRNA 表达的影响*

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摘要 目的:探讨清胰利胆颗粒联合床旁连续性肾脏替代治疗(CRRT)对重症急性胰腺炎(SAP)患者炎症因子、免疫功能及外周血叉状头 / 翅膀状螺旋转录因子(Foxp3)、维甲酸相关孤独受体 γ t(ROR γ t)mRNA 表达的影响。**方法:**选取 2017 年 3 月~2019 年 12 月期间我院收治的 SAP 患者 80 例,根据随机数字表法分为对照组(n=40)和研究组(n=40),对照组患者予以床旁 CRRT 疗法治疗,研究组在对照组的基础上联合清胰利胆颗粒治疗,比较两组疗效、炎症因子、免疫功能、外周血 Foxp3、ROR γ t mRNA 相对表达量及不良反应。**结果:**研究组治疗后临床总有效率为 87.50%(35/40),高于对照组患者的 70.00%(28/40)($P<0.05$)。研究组治疗后免疫球蛋白 G(IgG)、免疫球蛋白 A(IgA)、免疫球蛋白 M(IgM)、Foxp3 mRNA 相对表达量较治疗前升高,且高于对照组($P<0.05$)。两组治疗后白介素-6(IL-6)、白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)、ROR γ t mRNA 相对表达量较治疗前降低,且研究组低于对照组($P<0.05$)。两组在治疗过程中均未出现严重不良反应。**结论:**清胰利胆颗粒联合床旁 CRRT 疗法治疗 SAP,疗效显著,可有效改善患者炎症因子、免疫功能,其主要作用机制可能与外周血 Foxp3、ROR γ t mRNA 相对表达量有关。

关键词:清胰利胆颗粒;连续性肾脏替代治疗;重症急性胰腺炎;炎症因子;免疫功能;叉状头 / 翅膀状螺旋转录因子;维甲酸相关孤独受体 γ t

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Effect of Qingyilidan Granule Combined with Bedside CRRT on Inflammatory Factors, Immune Function and the Expression of Foxp3 and RoR γ t mRNA in Peripheral Blood of Patients with Severe Acute Pancreatitis*

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ABSTRACT Objective: To investigate the effect of qingyilidan granule combined with continuous renal replacement therapy (CRRT) on inflammatory factors, immune function and the relative expression of forked head/wing spiral transcription factor (Foxp3) and retinoic acid related lone receptor γ t (ROR γ T) mRNA in patients with severe acute pancreatitis (SAP). **Methods:** 80 SAP patients who were admitted to our hospital from March 2017 to December 2019 were selected, they were randomly divided into two groups: control group (n=40) and study group (n=40). Patients in the control group were treated with CRRT beside the bed. The study group was treated with Qingyi Lidan Granule on the basis of the control group. The efficacy, inflammatory factors, immune function, The relative expression of mRNA Foxp3, ror γ t and adverse reactions of the two groups were compared. **Results:** The total clinical effective rate was 87.50% (35/40) in the study group, which was higher than 70.00% (28/40) in the control group ($P<0.05$). The relative expression of immunoglobulin G (IgG), immunoglobulin A (IGA), immunoglobulin M (IgM), Foxp3 mRNA in the study group was higher than that in the control group ($P<0.05$). The relative expressions of Interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α) and ror γ t mRNA in the two groups were lower than those in the control group ($P<0.05$). There were no adverse reactions in the two groups. **Conclusion:** Qingyilidan granule combined with bedside CRRT can effectively improve the inflammatory factors and immune function of pa-

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tients with SAP, and its main mechanism may be related to the relative expression of Foxp3 and γ t mRNA in peripheral blood.

Key words: Qingyilidan granules; Continuous renal replacement therapy; Severe acute pancreatitis; Inflammatory factors; Immune function; Forked head/wing spiral transcription factor; Retinoic acid related lone receptor γ t

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前言

重症急性胰腺炎(SAP)是指由多种病因引起的胰酶激活,继而导致胰腺局部炎症反应的一类疾病^[1,2]。SAP发病急骤,病死率极高,近年来随着医疗技术的进步,其治愈率有所提高,但总体死亡率仍高达17%^[3,4]。SAP的治疗方案尚未完全统一,多以阻止疾病进展、抑制胰酶及消化酶分泌、控制机体炎症反应为主^[5]。连续性肾脏替代治疗(CRRT)是通过体外循环血液净化技术连续、缓慢清除水分和溶质的一种治疗方式,是危重症抢救中最常用的血液净化技术之一^[6,7],但仍有不少患者经CRRT治疗后难以达到理想预期,尚需优化治疗。清胰利胆颗粒具有行气解郁、活血止痛、解毒通便的功效,常用于急性胰腺炎(AP)、急性胃炎等疾病的治疗^[8]。本研究通过对我院收治的部分SAP患者予以清胰利胆颗粒联合床旁CRRT疗法,取得了较好的疗效,现整理报道如下。

1 资料与方法

1.1 一般资料

纳入标准:(1)诊断标准参考《急性胰腺炎诊治指南(2014)》^[9],并经影像学等手段确诊;(2)对本次研究使用药物无禁忌症者;(3)具有CRRT指征者;(4)签署知情同意书。排除标准:(1)妊娠或哺乳期妇女;(2)合并精神障碍,无法正常沟通交流者;(3)合并肝肾功能障碍者;(4)合并凝血功能障碍者;(5)合并免疫缺陷、急慢性感染者;(6)合并恶性肿瘤者。选取2017年3月~2019年12月期间我院收治的SAP患者80例,根据随机数字表法分为对照组($n=40$)和研究组($n=40$),其中对照组女16例,男24例,年龄30~59岁,平均 (43.67 ± 4.29) 岁;病程2~9d,平均 (5.64 ± 0.92) d;体质量指数 $21 \sim 27 \text{ kg/m}^2$,平均体质量指数 $(23.59 \pm 0.82) \text{ kg/m}^2$;SAP诱因:暴饮暴食11例,酗酒10例,胆道疾病史9例,其他10例。研究组女13例,男27例,年龄33~64岁,平均 (43.92 ± 5.28) 岁;病程3~9d,平均 (5.82 ± 1.03) d;体质量指数 $22 \sim 27 \text{ kg/m}^2$,平均体质量指数 $(23.82 \pm 0.97) \text{ kg/m}^2$;SAP诱因:暴饮暴食13例,酗酒11例,胆道疾病史10例,其他6例。两组一般资料对比无差异($P>0.05$)。

1.2 方法

两组患者入院后均给予胃肠减压、禁食、补液、抑酶、解痉

止痛、抗炎、抑酸、维持水电解质平衡等基础治疗,在此基础上,对照组给予床旁CRRT治疗,采用购自德国爱德华生命科学公司的AQUARIUS血滤机,置换液流速设置为 $1 \sim 4 \text{ L/h}$,血流量设置为 $200 \sim 300 \text{ mL/min}$ 之间,并根据患者具体生化指标调整电解质含量。先给予连续性血液净化,2d后若患者病情平稳,则给予日间透析,每次12h,连续进行3d。研究组患者在对照组的基础上联合清胰利胆颗粒[抚松县中药有限责任公司,国药准字Z22022250,规格:袋装10g(含糖型);每袋装4g(无糖型)]治疗,1袋/次,3次/d,保留灌肠给药,连续治疗5d。血液净化过程中采用肝素抗凝。

1.3 观察指标

(1)记录两组治疗后的临床疗效。总有效率=显效率+有效率,显效:血淀粉酶恢复至正常水平,患者临床症状、体征消失;有效:血淀粉酶水平降低但未恢复至正常水平,患者临床症状、体征有所改善;无效:血淀粉酶水平未降低,患者临床症状、体征未见明显改善甚至加重^[10]。(2)于治疗前后抽取两组清晨空腹静脉血5mL,经 3500 r/min ,离心14min,离心半径12cm,分离上清液,置于冰箱(-30°C)中待测。参考苏州吉玛基因股份有限公司生产的试剂盒说明书步骤,采用酶联免疫吸附试验检测炎症因子指标:白介素-6(IL-6)、白介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)。参考浙江夸克生物科技有限公司生产的试剂盒说明书步骤,采用免疫比浊法检测免疫球蛋白G(IgG)、免疫球蛋白A(IgA)、免疫球蛋白M(IgM)水平。采用实时荧光定量PCR扩增法检测叉状头/翅膀状螺旋转录因子(Foxp3)mRNA、维甲酸相关孤独受体 γ t(ROR γ t)mRNA相对表达量。(3)记录两组治疗期间不良反应状况。

1.4 统计学方法

本研究数据采用SPSS25.0软件进行统计分析,计量资料用 $(\bar{x} \pm s)$ 表示,比较应用t检验,计数资料以率表示,采用 χ^2 检验, $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组疗效比较

研究组治疗后临床总有效率为87.50%(35/40),高于对照组患者的70.00%(28/40)($P<0.05$),详见表1。

表1 两组疗效比较例(%)

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

Groups	Markedly effective	Effective	Invalid	Total efficiency
Control group($n=40$)	10(25.00)	18(45.00)	12(30.00)	28(70.00)
Study group($n=40$)	15(37.50)	20(50.00)	5(12.50)	35(87.50)
χ^2				5.000
P				0.025

2.2 两组免疫功能指标比较

两组治疗前 IgG、IgA、IgM 比较无差异 ($P>0.05$); 研究组治

疗后 IgG、IgA、IgM 较治疗前升高, 且高于对照组 ($P<0.05$); 详见表 2。

表 2 两组免疫功能指标比较($\bar{x} \pm s$, g/L)Table 2 Comparison of immune function indexes between the two groups($\bar{x} \pm s$, g/L)

Groups	IgG		IgA		IgM	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=40)	10.73± 1.51	10.96± 1.61	1.56± 0.76	1.63± 0.58	1.63± 0.59	1.69± 0.64
Study group(n=40)	10.58± 1.47	14.79± 1.42*	1.62± 0.82	2.17± 0.73*	1.69± 0.64	2.14± 0.85*
t	0.450	11.284	0.339	3.663	0.436	2.675
P	0.654	0.000	0.735	0.000	0.664	0.009

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

2.3 两组炎症因子水平比较

两组治疗前 IL-6、IL-8、TNF- α 比较无差异 ($P>0.05$); 两组

治疗后 IL-6、IL-8、TNF- α 较治疗前降低, 且研究组低于对照组 ($P<0.05$); 详见表 3。

表 3 两组炎症因子水平比较($\bar{x} \pm s$, ng/L)Table 3 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$, ng/L)

Groups	IL-6		IL-8		TNF- α	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=40)	22.69± 3.47	16.83± 2.24*	24.83± 3.68	18.27± 2.01*	2.79± 0.24	2.31± 0.21*
Study group(n=40)	22.78± 3.52	10.32± 2.51*	23.94± 3.25	13.02± 2.29*	2.84± 0.26	1.56± 0.19*
t	0.115	12.239	1.146	10.987	0.894	16.750
P	0.909	0.000	0.255	0.000	0.374	0.000

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

2.4 两组 Foxp3 mRNA、ROR γ t mRNA 相对表达量比较

两组治疗前 Foxp3 mRNA、ROR γ t mRNA 相对表达量比较差异无统计学意义 ($P>0.05$); 两组治疗后 Foxp3 mRNA 相对表

达量较治疗前升高, 且研究组高于对照组 ($P<0.05$); ROR γ t mRNA 相对表达量较治疗前下降, 且研究组低于对照组 ($P<0.05$); 详见表 4。

表 4 两组 Foxp3 mRNA、ROR γ t mRNA 相对表达量比较($\bar{x} \pm s$)Table 4 Comparison of Foxp3 mRNA and ROR γ t mRNA expression between the two groups($\bar{x} \pm s$)

Groups	Foxp3 mRNA relative expression		ROR γ t mRNA relative expression	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=40)	0.89± 0.12	1.97± 0.22*	1.16± 0.12	0.72± 0.11*
Study group(n=40)	0.86± 0.09	2.65± 0.24*	1.19± 0.15	0.51± 0.09*
t	1.265	13.209	0.988	9.345
P	0.210	0.000	0.316	0.000

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

2.5 两组不良反应发生率比较

两组患者在治疗过程中均未出现皮疹、恶心呕吐、头痛、乏力、腹泻等不良反应。

3 讨论

SAP 作为临床常见的急腹症, 具有发病急骤、病情进展迅速、致死率高等特点^[11]。现临床有关 SAP 的具体发病机制尚不十分明确, 现有的观点主要包括 "氧化应激学说" "胰酶自身

消化理论" "Th2 细胞的偏移" 等, 随着研究的深入, 不少学者发现 SAP 病情进展的严重程度与血清中炎症因子的浓度具有相关性, 并认为 SAP 的发生总体上是炎症发生发展以及免疫功能严重失衡的一个过程^[12,13]。因此, 寻找清除炎症因子、提高机体免疫功能的有效方案, 也是 SAP 治疗研究的热点。CRRT 是临床治疗 SAP 的常用方案之一, 可有效发挥纠正电解质紊乱、调节酸碱平衡、清除炎症介质和内毒素的作用, 从而阻止疾病进展^[14,15]。清胰利胆颗粒具有活血化瘀、疏肝利胆、解毒通便

之效,临床亦常用于 AP 的辅助治疗中^[16]。

本次研究结果显示,研究组治疗后临床总有效率高于对照组,提示清胰利胆颗粒联合床旁 CRRT 疗法治疗 SAP,可进一步提高治疗效果。CRRT 以透析为基础,可最大限度的将机体内代谢废物和多余水分清除,维护机体酸碱、水电解质平衡以及血流动力学稳定,改善各脏器功能,进而改善 SAP 患者的预后^[17-19]。而清胰利胆颗粒是由大黄、牡蛎、赤芍、姜黄、金银花、延胡索、牡丹皮、柴胡等中药经现代工艺制成的中药制剂,其中大黄泻热通腑,柴胡疏肝解郁,延胡索疏肝理气,金银花疏散退热,牡丹皮及赤芍活血、散瘀、清热,姜黄活血化瘀,牡蛎攻毒散结,诸药合用,共奏通腑攻下、活血化瘀、清热解毒之效^[20]。目前研究发现^[21-23],胰腺炎急性期时,IL-6、IL-8、TNF- α 等炎性细胞因子水平显著升高,参与胰腺的炎症损伤过程,因此其可预测胰腺炎炎症反应状态。而 IgA、IgG、IgM 等免疫功能指标水平显著降低,提示机体的免疫功能下降,会促进疾病进展^[24]。本研究中两组患者炎症因子、免疫功能指标水平均有所改善,且研究组改善效果更佳。提示清胰利胆颗粒联合床旁 CRRT 疗法治疗 SAP 患者可有效提高机体的免疫功能,减轻患者炎症反应,有利于患者病情的康复。现代药理研究表明^[25-27],牡蛎中含大量糖原,补充糖原可改善机体循环功能,并具有保肝作用,从而能减轻胰腺负担;赤芍含有丰富的苷类化合物,具有抗凝、抗动脉粥样硬化、保护心脏和肝脏、抗炎、提高机体免疫功能等功效;金银花具有良好的抗菌消炎作用。以往研究表明^[28-30],Treg/Th17 的平衡调节在免疫系统疾病中有着重要地位,Treg 可维持机体免疫功能稳定,Th17 具有介导、扩大机体炎症反应的作用,与脓毒症、SAP 等多种疾病的发生密切相关;而 Foxp3 mRNA 相对表达量可有效反映 Treg 细胞水平,Th17 细胞水平则可通过 ROR γ t mRNA 相对表达量来反映。本研究中治疗后研究组 Foxp3 mRNA 相对表达量高于对照组,ROR γ t mRNA 则低于对照组。笔者推测清胰利胆颗粒发挥作用的机制可能与外周血 Foxp3、ROR γ t mRNA 相对表达量有关,但是关于 Foxp3 和 ROR γ t mRNA 的作用机制还需要后续研究进行深入分析。另两组在治疗过程中均未出现不良反应,表明清胰利胆颗粒联合床旁 CRRT 疗法安全可靠。

综上所述,清胰利胆颗粒联合床旁 CRRT 疗法治疗 SAP,疗效显著,可有效改善患者炎症因子、免疫功能,其主要作用机制可能与外周血 Foxp3、ROR γ t mRNA 相对表达量有关。

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