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血必净注射液联合持续血液净化治疗重症脓毒症的效果 及对血清 IL-6、TNF- α 的影响

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摘要 目的:研究血必净注射液联合持续血液净化治疗重症脓毒症的效果及对血清白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)的影响。**方法:**将2012年1月至2013年12月我院收治124例重症脓毒症患者随机分为治疗组和对照组,每组62例。对照组给予常规抗感染、对症支持、脏器保护治疗,治疗组在此基础上加用血必净注射液联合持续血液净化治疗。于治疗前及治疗第7天记录并比较两组患者多器官功能障碍(MODS)发生率、脓毒症休克率、死亡率、好转率、氧合指数(动脉血氧分压(PaO₂)/吸入氧浓度(FiO₂))、血清IL-6、TNF- α 水平以及急性生理和慢性健康评分II(APACHE II)。**结果:**经7天治疗后,两组MODS发生率、IL-6、TNF- α 水平以及APACHE II评分较治疗前均显著降低,PaO₂/FiO₂水平较治疗前显著提高(均 $P < 0.05$);治疗组脓毒症休克率较治疗前显著降低($P < 0.05$);治疗组MODS发生率、脓毒症休克率、死亡率、IL-6、TNF- α 水平以及APACHE II评分均显著低于对照组,好转率以及PaO₂/FiO₂水平显著高于对照组(均 $P < 0.05$)。**结论:**血必净注射液联合持续血液净化治疗重症脓毒症能维护多器官功能、降低MODS及脓毒症休克发生率,提高动脉血气氧合指数等疗效。

关键词:血必净注射液;血液净化;重症脓毒症;白介素-6;肿瘤坏死因子- α

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The Curative Effect of Xuebijing Injection Combined With Continuous Blood Purification on Severe Sepsis and Its Influence on Serum IL-6 and TNF- α

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ABSTRACT Objective: To research the curative effect of Xuebijing injection combined with continuous blood purification on severe sepsis and its influence on the level of serum IL-6 and TNF- α . **Methods:** 124 patients with severe sepsis who were treated in our hospital from January 2012 to December 2013 were randomly divided into treatment group and control group, each group had 62 cases. The patients in control group were treated with traditional medicine such as antibiotics, symptomatic and supporting medicine, and medicine for organ protection, the patients in treatment group were given Xuebijing injection combined with continuous blood purification therapy besides traditional medicine. The incidence of MODS, septic shock rate, mortality, improvement rate, and levels of PaO₂ or FiO₂, serum IL-6, TNF- α and the APACHE II score of the two groups before treatment and after 7 days of therapy were recorded and compared. **Results:** After 7 days of therapy, the incidence of MODS, the levels of serum IL-6, TNF- α and APACHE II score in both groups decreased, PaO₂/FiO₂ levels significantly increased compared with before treatment ($P < 0.05$); Septic shock rate of treatment group significantly decreased compared with before treatment ($P < 0.05$); The incidence of MODS, septic shock rate, mortality, serum IL-6, TNF- α levels and APACHE II score of treatment group were significantly lower than those of the control group, improvement rate and PaO₂/FiO₂ levels was higher than those of the control group ($P < 0.05$). **Conclusion:** Xuebijing injection combined with continuous blood purification can maintain multiple organ function, reduce the incidence of MODS and septic shock, and improve arterial blood gas oxygenation index in treating severe sepsis.

Key words: Xuebijing injection; Blood purification; Severe sepsis; IL-6; TNF- α

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前言

脓毒症是一种以全身性的感染引起器官功能损害的复杂性临床综合征,而重症脓毒症是因感染导致全身炎症反应的基础上并发组织灌注低压或不足、脏器功能障碍的综合征,具有

高的发病率及病死率^[1,2]。临床证实脓毒症存在细菌或高度可疑感染灶,脓毒症是因感染而起,但其发生及发展有着自身独特的病理过程以及规律^[3]。因此,脓毒症是机体应对感染性因素所起的反应,病情的进一步恶化将引发多器官功能障碍(multiple organ dysfunction syndrome, MODS)和脓毒性休克,有高达50%~60%的病死率^[4,5]。有研究结果显示,在重症脓毒症的病理和生理过程中细胞因子有着决定性的作用,机体在患有脓毒症时将释放大量的细胞因子、炎症递质,从而引发瀑布效应,发生

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MODS^[67]。相关医学研究表明,人体在感染严重的情况下炎症因子血清白介素-6(Interleukin, IL-6)、肿瘤坏死因子- α (TNF- α)的浓度显著升高,并且其水平与脓毒症患者的严重程度呈现正相关关系^[9]。当前,从脓毒症的病理和生理发展过程的角度来有效阻断血清 IL-6、TNF- α 等细胞因子的过度释放的研究较少。本研究拟观察血必净注射液联合持续血液净化治疗重症脓毒症的效果及其对血清 IL-6、TNF- α 的影响,现将结果报道如下。

1 资料与方法

1.1 研究对象

选择 2012 年 1 月至 2013 年 12 月我院收治的 124 例重症脓症患者。纳入标准:①符合重症脓毒症的诊断标准^[10];②急性生理和慢性健康评分 II (APACHE II) ≥ 12 分。排除标准:①伴有慢性心、肺、肝、肾以及凝血功能等器官性的系统疾病;②艾滋病感染者;③恶性肿瘤患者;④结缔组织疾病;⑤对血必净注射液过敏者。其中男性 70 例,女性 54 例,年龄 19~86 岁,平均年龄(61.7 $\pm$ 6.3)岁;包括原发性疾病重症肺炎 15 例、肿瘤外科 5 例、神经外科 50 例、神经内科 36 例、创伤外科 18 例。将 124 例重症脓症患者按随机数字表法分为两组:治疗组 62 例,其中男 36 例,女 26 例,平均年龄(61.6 $\pm$ 5.9)岁,包括原发性疾病重症肺炎 8 例、肿瘤外科 2 例、神经外科 25 例、神经内科 18 例、创伤外科 9 例。对照组 62 例,其中男 34 例,女 28 例,平均年龄(61.8 $\pm$ 6.2)岁,原发性疾病重症肺炎 7 例、肿瘤外科 3 例、神经外科 25 例、神经内科 18 例、创伤外科 9 例。两组患者的性别、年龄、原发病以及 APACHE II 评分等资料比较差异不具有统计学意义($P > 0.05$),资料均衡可比。

1.2 治疗方法

两组患者均给予常规的抗感染、对症支持、脏器保护等治疗,治疗组在此基础上加用静脉滴注血必净注射液(天津红日药业生产,生产批号:1007191,10 ML/支,每毫升含有 1 g 生药)100 ML,2 次/天,同时行持续 24 小时的病床旁高流量的静脉血液净化治疗,共 7 天。

1.3 观察指标

在治疗前及治疗第 7 天记录两组患者 MODS 发生率、脓毒症休克率、死亡率、好转率、以及动脉血气氧合指数包括 PaO_2 及 FiO_2 :采用血液气体分析仪(blood gas analyzer)测定动脉血氧分压(PaO_2)水平,氧浓度分析仪(oxygen analyzer)测定气体的吸入氧浓度(FiO_2)水平。通过酶联免疫吸附法来检测血清 IL-6、TNF- α 水平,并比较不同时间的 APACHE II 评分^[11]。

1.4 统计学分析

采用 SPSS20.0 统计软件录入数据,计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)来表示,计数资料以率来表示。两组资料比较时,两独立样本的计量资料采用 t 检验,定性资料采用 χ^2 检验进行统计分析。检验水准 $\alpha=0.05$ 。

2 结果

2.1 两组治疗前后 MODS 发生率、脓毒症休克率、死亡率、好转率比较

经 7 天治疗后,两组 MODS 发生率较治疗前均显著降低($P < 0.05$),治疗组的脓毒症休克率较治疗前显著降低($P < 0.05$),治疗组 MODS 发生率、脓毒症休克率、死亡率均显著低于对照组($P < 0.05$),好转率显著高于对照组($P < 0.05$),详见表 1。

表 1 两组治疗前后 MODS 发生率、脓毒症休克率、死亡率、好转率比较[n=62,n(%)]

组别 Groups	时间 Time	MODS 发生率 Incidence of MODS	脓毒症休克率 Septic shock rate	死亡率 Mortality	好转率 Improvement rate
治疗组 Treatment group	治疗前 Before treatment	35(56.5)*	11(17.7)*	—	—
	治疗第 7 天 After 7 days of therapy	19(30.6) [#]	2(3.2) [#]	3(4.8) [#]	28(45.2) [#]
对照组 Control group	治疗前 Before treatment	36(58.1)*	13(21.0)	—	—
	治疗第 7 天 After 7 days of therapy	33(53.2)	8(12.9)	13(21.0)	14(22.6)

注:与治疗第 7 天比较,* $P < 0.05$;与对照组比较,[#] $P < 0.05$ 。

Note: Compared with after 7 days of therapy, * $P < 0.05$;compared with the control group, [#] $P < 0.05$.

2.2 两组治疗前后 PaO_2 / FiO_2 、IL-6、TNF- α 水平以及 APACHE II 评分比较

经 7 天治疗后,两组 IL-6、TNF- α 水平以及 APACHE II 较治疗前均显著降低($P < 0.05$),氧合指数 PaO_2 / FiO_2 水平较治疗

前显著提高($P < 0.05$),研究组 IL-6、TNF- α 水平以及 APACHE II 评分均显著低于对照组($P < 0.05$),氧合指数 PaO_2 / FiO_2 水平较对照组显著提高,改善明显($P < 0.05$),详见表 2。

表 2 两组治疗前后 PaO_2 / FiO_2 、IL-6、TNF- α 水平以及 APACHE II 评分比较[n=62,n(%)]

Table 2 Comparison of level of PaO_2 / FiO_2 , IL-6, TNF- α and APACHE II score before and after treatment in two groups[n=62,n(%)]

组别 Groups	时间 Time	PaO_2 / FiO_2	IL-6 (ng/L)	TNF- α (ng/L)	APACHE II (score)
治疗组 Treatment group	治疗前 Before treatment	185.1 $\pm$ 42.8*	235.4 $\pm$ 43.5*	183.0 $\pm$ 19.2*	36 $\pm$ 9*
	治疗第 7 天 After 7 days of therapy	300.9 $\pm$ 49.8 [#]	144.5 $\pm$ 33.6 [#]	51.0 $\pm$ 17.8 [#]	17 $\pm$ 3 [#]
对照组 Control group	治疗前 Before treatment	188.0 $\pm$ 50.8*	236.3 $\pm$ 43.9*	180.0 $\pm$ 24.0*	37 $\pm$ 8*
	治疗第 7 天 After 7 days of therapy	248.0 $\pm$ 52.9	204.8 $\pm$ 30.0	104.1 $\pm$ 22.0	29 $\pm$ 4

注:与治疗第 7 天比较,* $P < 0.05$;与对照组比较,[#] $P < 0.05$ 。

Note: compared with after 7 days of therapy, * $P < 0.05$;compared with the control group, [#] $P < 0.05$.

3 讨论

脓毒症是由一系列的免疫、炎性细胞以及衍生出的多种细胞因子、炎性介质,氧自由基及凝血物质等参与的复杂病理-生理反应^[1]。这种反应过程被学术界称为“炎症反应瀑布”,其能够导致人体多个器官系统产生功能障碍甚至衰竭^[2]。现代医学研究认为^[3],细胞因子在重症脓毒症患者的发病急发展过程中有重要作用,尤其是系统性的炎症反应构成脓症患者病情发展的基础,若不及时控制,极易导致炎症反应失控;此时细胞因子无法表达,造成组织功能受损。MODS 是系统性炎症反应进一步发展的严重阶段,此时全身性的严重反应已经发生,即使启动因素削弱甚至消除,炎症反应仍可能继续^[4]。因此,及时有效的控制炎症反应是治疗脓毒症患者的关键所在。重症脓毒症死亡率较高,它的生理-病理特征是一系列的炎症细胞被激活,同时释放大量的促炎因子。在炎症因子的反应过程中,IL-6 是始动因子,能够促发细胞因子网络释放出弹性蛋白酶并促进中性粒细胞的分化,诱导多种急性期的蛋白合成以及分泌,同时全程参与炎症反应,促进炎症的进展^[5]。因此,选择 IL-6 作为观察指标有着重要的临床意义。TNF- α 是单核巨噬细胞以及内皮细胞产生的,在机体受到感染、休克、创伤等应激反应下能够大量释放,是最主要的炎症反应的启动因子,能刺激中性粒细胞的聚集,释放大量的水解酶、蛋白酶以及氧自由基,对组织细胞造成损伤,并刺激单核巨噬细胞分泌出 IL-6 炎症介质^[6]。因此,TNF- α 作为主要观察指标。

血必净注射液是由红花、川芎、赤芍、当归和丹参等合成,具有清热凉血、疏通经络、活血化瘀、溃散毒邪功效的中草药制剂^[7]。许多相关研究表明,血必净注射液能够减少炎性因子释放量,对抗毒素、细菌,降低内毒素水平,清除氧自由基,调节免疫功能,从而阻断机体过度炎症反应,改善肺部缺氧-再灌注带来的损伤,改善肺的氧合指数,缓解过度通气作用,临床上广泛应用于重症脓毒症以及 MODS 的治疗^[8]。持续性的血液净化治疗重症脓毒症,能够有效清除各种大、中分子的炎症因子,如 IL-6、TNF- α 等,具有稳定血流动力学的作用,同时还兼具改善机体组织供养、增强细胞摄氧能力、改善微循环及组织灌注的功效,使脓毒症病情发展进程得以控制^[7]。两者联用符合重症脓毒症的治疗原则。本次研究结果显示,经 7 天治疗后,治疗组 MODS 发生率、脓毒症休克率、死亡率、血清 IL-6、TNF- α 水平以及 APACHE II 评分均显著低于对照组($P < 0.05$),好转率及氧合指数 $\text{PaO}_2/\text{FiO}_2$ 水平均显著高于对照组($P < 0.05$)。两组 MODS 发生率、IL-6、TNF- α 水平以及 APACHE II 评分均较治疗前均显著降低($P < 0.05$),氧合指数 $\text{PaO}_2/\text{FiO}_2$ 水平较治疗前显著提高($P < 0.05$),与相关研究结果一致^[19,20]。表明常规治疗对重症脓毒症有一定效果,但加用血必净注射液联合持续血液净化治疗效果更显著。结果表明,血必净注射液联合持续血液净化治疗能够有效抑制炎症性细胞因子释放,减轻机体在应激反应下的炎症反应,有效提高重症脓毒症患者的氧合指数,改善其肺功能,APACHE II 评分的显著降低,MODS 发生率的显著降低,说明二者联用能够有效提高重症脓毒症的治疗疗效,改善预后。

综上所述,血必净注射液可以抑制细胞因子的过度释放,持续血液净化能消除炎性介质,两者联用治疗重症脓毒症能抑制炎症细胞因子过度释放、维护多器官功能、降低 MODS 以及

脓毒症休克的发生率,提高动脉血气氧合指数等效果。

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