

血必净注射液治疗脓毒症伴轻度急性呼吸窘迫综合征疗效及对多配体蛋白聚糖-1和氧化应激指标的影响

周长静, 周雅楠, 杨 蕾, 柴成国

哈励逊国际和平医院 急救医学部, 河北 衡水 053000

摘要: **目的** 探讨血必净注射液对脓毒症伴轻度急性呼吸窘迫综合征 (ARDS) 患者的治疗效果及对多配体蛋白聚糖-1 (SDC-1) 和氧化应激相关指标的影响。**方法** 选取2021年1月—2022年9月河北医科大学哈励逊国际和平医院收治的84例脓毒症伴轻度ARDS患者, 按照随机数字表法将患者分为对照组和试验组, 每组各42例。对照组患者给予早期复苏、抗感染、营养支持及对症治疗。试验组在对照组基础上加用血必净注射液, 每次取血必净注射液100 mL加0.9%氯化钠注射液100 mL, 静脉滴注, 每天2次, 连续治疗3 d。分别于治疗前后, 检测两组患者外周血C反应蛋白 (CRP)、白细胞介素6 (IL-6)、白细胞介素8 (IL-8)、肿瘤坏死因子- α (TNF- α)、丙二醛 (MDA)、超氧化物歧化酶 (SOD)、透明质酸 (HA)、SDC-1、硫酸乙酰肝素 (HS) 水平; 比较两组治疗前后Murray肺损伤评分 (MLIS)、全身性感染相关性器官功能衰竭 (SOFA) 评分、急性生理学及慢性健康状况II (APACHE II) 评分, 随访两组患者出院1个月生存情况。**结果** 试验组治疗总有效率 (85.71%) 高于对照组 (66.67%), 两组差异有统计学意义 ($P<0.05$)。治疗前, 两组IL-8、IL-6、TNF- α 、CRP、MDA、SOD、HA、SDC-1、HS比较, 差异无统计学意义 ($P>0.05$)。治疗后, 两组IL-8、IL-6、TNF- α 、CRP、MDA、HA、SDC-1、HS水平均较本组治疗前显著降低 ($P<0.05$), SOD较治疗前显著升高 ($P<0.05$); 且试验组IL-8、IL-6、TNF- α 、CRP、MDA、HA、SDC-1、HS水平较对照组明显降低 ($P<0.05$), SOD较对照组明显升高 ($P<0.05$)。治疗前, 两组SOFA、APACHE II、MLIS评分均无显著差异 ($P>0.05$)。治疗后, 两组SOFA、APACHE II、MLIS评分均较本组治疗前显著降低 ($P<0.05$), 且试验组SOFA、APACHE II、MLIS评分较对照组明显降低 ($P<0.05$)。出院后1个月, 试验组死亡率 (30.95%) 明显低于对照组 (52.38%), 差异有统计学意义 ($P<0.05$)。脓毒症伴轻度ARDS患者血管内皮糖萼 (EG) 降解物HA、SDC-1、HS水平与MLIS评分间呈正相关 ($r=0.733$, $P=0.036$; $r=0.831$, $P=0.011$; $r=0.826$, $P=0.013$)。受试者工作特征 (ROC) 曲线显示, SDC-1联合氧化应激指标检测对脓毒症伴轻度ARDS患者短期的预后预测价值更大。**结论** 血必净注射液通过减轻脓毒症伴轻度ARDS患者肺血管内皮EG的降解, 明显缓解ARDS, 有效改善患者短期预后。

关键词: 血必净; 脓毒症; 急性呼吸窘迫综合征; 多配体蛋白聚糖-1; 氧化应激

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Effect of Xuebijing Injection on treatment of sepsis with mild acute respiratory distress syndrome and its effect on multi ligand proteoglycan-1 and oxidative stress indexes

ZHOU Changjing, ZHOU Yanan, YANG Lei, CHAI Chengguo

Department of Emergency Medicine, Halison International Peace Hospital, Hengshui 053000, China

Abstract: Objective To investigate the therapeutic effect of Xuebijing Injection on sepsis patients with mild acute respiratory distress syndrome (ARDS) and its influence on multi ligand proteoglycan 1 (SDC-1) and oxidative stress related indicators. **Methods** From January 2021 to September 2022, 84 patients with sepsis and mild ARDS who were admitted to the Harrison International Peace Hospital were selected and divided into the control group and the experimental group according to the random number table, with 42 patients in each group. Patients in the control group were given early resuscitation, anti infection, nutritional support and symptomatic treatment. Patients in the experimental group were supplemented with Xuebijing Injection on the basis of

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第一作者: 周长静, 女, 本科, 主治医师, 研究方向为各种急危重症的诊治。E-mail: hlx15930374203@163.com

the control group. Each time, 100 mL of Xuebijing Injection and 100 mL of 0.9% Sodium Chloride Injection were taken, and intravenous infusion was performed twice a day for three consecutive days. Before and after treatment, C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor- α (TNF- α), malondialdehyde (MDA), superoxide dismutase (SOD), hyaluronic acid (HA), SDC-1, and heparan sulfate (HS) levels were detected in two groups of patients. Murray lung injury score (MLIS), systemic infection related organ failure (SOFA) score, acute physiology and chronic health status II (APACHE II) score were compared between the two groups before and after treatment, and follow up the one-month survival of the two groups of patients after discharge. **Results** The total effective rate of the experimental group (85.71%) was higher than that of the control group (66.67%), and the difference between the two groups was statistically significant ($P < 0.05$). Before treatment, there was no statistically significant difference of IL-8, IL-6, TNF- α , CRP, MDA, SOD, HA, SDC-1, and HS in two groups ($P > 0.05$). After treatment, the levels of IL-8, IL-6, TNF- α , CRP, MDA, HA, SDC-1, and HS in two groups were significantly reduced compared to before treatment ($P < 0.05$), while SOD was significantly increased compared to before treatment ($P < 0.05$). And the levels of IL-8, IL-6, TNF- α , CRP, MDA, HA, SDC-1, and HS in the experimental groups were significantly reduced compared to the control group ($P < 0.05$), while SOD was significantly increased compared to the control group ($P < 0.05$). Before treatment, there was no significant difference in SOFA, APACHE II, and MLIS scores between the two groups ($P > 0.05$). After treatment, the scores of SOFA, APACHE II, and MLIS in two groups were significantly reduced compared to before treatment in same group ($P < 0.05$), and the scores of SOFA, APACHE II, and MLIS in the experimental group were significantly reduced compared to the control group ($P < 0.05$). One month after discharge, the mortality rate in the experimental group (30.95%) was significantly lower than that in the control group (52.38%), with a statistically significant difference ($P < 0.05$). There is a positive correlation between the levels of endothelial glycocalyx (EG) degradation products HA, SDC-1, and HS in sepsis patients with mild ARDS and MLIS score ($r = 0.733, P = 0.036; r = 0.831, P = 0.011; r = 0.826, P = 0.013$). The receiver operating characteristic (ROC) curve shows that the combination of SDC-1 and oxidative stress indicators has greater predictive value for short-term prognosis in patients with sepsis and mild ARDS. **Conclusion** Xuebijing Injection can significantly alleviate the degradation of pulmonary endothelial EG in patients with sepsis and mild ARDS, and effectively improve the short-term prognosis of patients.

Key words: Xuebijing Injection; sepsis; acute respiratory distress syndrome; multi ligand proteoglycan 1; oxidative stress

脓毒症是各种原因引起的重症感染继发全身炎症反应综合征,发病机制尚未完全清楚,脓毒症的病情凶险,病死率高,且逐年增加。肺脏是脓毒症患者损伤最重、最容易受累的器官,急性呼吸窘迫综合征(ARDS)是脓毒症常见的并发症之一,由于肺泡上皮细胞和毛细血管内皮细胞受损,炎性细胞浸润,肺间质充血水肿,表现为顽固性低氧血症和呼吸衰竭^[1]。血管内皮糖萼(EG)是内皮细胞表面重要的功能层,对维持内皮功能起到重要作用,早期评估患者内皮细胞功能并有效保护是治疗脓毒症的重要环节^[2-3]。脓毒症伴ARDS西医多采用液体治疗和机械通气等措施,总体疗效不甚理想。血必净注射液不仅抑制炎症反应,而且减少内毒素对血管内皮细胞的影响,对于血管内皮细胞具有保护作用。由于血必净注射液有对抗内毒素、抗炎、抗氧化应激、调节免疫、保护血管内皮细胞等作用^[4],临床对脓毒症的治疗有良好疗效^[5-7]。本研究旨在观察血必净注射液对脓毒症伴轻度ARDS患者EG功能相关指标、炎症指标及氧化应激指标的影响,为临床脓毒症的治疗及用药提供参考。

1 资料与方法

1.1 一般资料

选取2021年1月—2022年9月河北医科大学哈励逊国际和平医院收治的84例脓毒症伴轻度ARDS患者为研究对象,其中男46例,女38例;年龄60~73岁,平均年龄(67.88 ± 5.12)岁。纳入标准:符合《脓毒症与感染性休克治疗国际指南》^[8]和轻度ARDS诊断标准^[9]。①1周内新发或加重的呼吸系统症状;②胸部影像学提示双肺浸润影,不能用积液、肺叶不张或结节完全解释;③给予常规氧疗($< 10 \text{ L} \cdot \text{min}^{-1}$)后, $200 \text{ mm Hg} < \text{氧合指数} (\text{PaO}_2/\text{FiO}_2) \leq 300 \text{ mmHg}$ ($1 \text{ mm Hg} = 133 \text{ Pa}$)。排除标准:①排除心力衰竭或液体过度负荷导致的肺水肿;②严重肝肾功能障碍和合并自身免疫系统疾病;③存在出血倾向或凝血功能紊乱。研究方案经本院医学伦理委员会批准(编号:2020-3-008),患者家属均签署知情同意书。

1.2 方法

对照组患者按照《脓毒症与感染性休克治疗国际指南》^[8]予以早期复苏、抗感染、高流量鼻导管给氧、机械通气(小潮气量通气策略)、营养支持及对

症治疗等。试验组在对照组治疗基础上加用血必净注射液(天津红日药业股份有限公司,国药准字Z20040033,规格:每支10 mL,批号:1901016、2003151、2102221),每次取血必净注射液100 mL加0.9%氯化钠注射液100 mL,静脉滴注,每天2次,连续治疗3 d。

1.3 观察指标

分别在治疗前及治疗3 d后,采集两组患者外周静脉血3 mL,采用日立7060全自动生化分析仪检测C反应蛋白(CRP)、白细胞介素-6(IL-6)、白细胞介素-8(IL-8)、肿瘤坏死因子- α (TNF- α)水平。同时采集患者静脉血5 mL,3 000 r·min⁻¹(离心半径10 cm)离心10 min;采用ELISA法检测丙二醛(MDA)、超氧化物歧化酶(SOD)、透明质酸(HA)、多配体蛋白聚糖-1(SDC-1)和硫酸乙酰肝素(HS)水平,各试剂盒均由武汉博士德生物工程有限公司提供。

分别于治疗前及治疗3 d后对两组患者Murray肺损伤评分(MLIS)、全身性感染相关性器官功能衰竭评分(SOFA)和急性生理学及慢性健康状况评分(APACHE II)进行评估。随访两组患者出院1个月生存情况。

观察药物的不良反应:包括皮肤瘙痒、皮疹、过敏性休克、面色苍白、大汗淋漓、紫绀等。

1.4 疗效判定

参照《临床疾病诊断依据治愈好转标准》^[10]判定。痊愈:体温36~37℃、呼吸频率<20次·min⁻¹、心率<90次·min⁻¹、白细胞计数(4~10)×10⁹·L⁻¹;显效:病情显著改善,但体温、呼吸频率、心率、白细胞

计数尚有1项未达痊愈标准;有效:病情有所改善,体温、呼吸频率、心率、白细胞计数等有所改善,但不明显;无效:未达上述标准或病情加重。

总有效率=(痊愈+显效+有效)例数/总例数

1.5 统计学方法

采用SPSS 23.0软件进行统计分析,符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本 t 检验。计数资料以百分率表示,组间比较采用 χ^2 检验。采用Pearson相关分析探讨EG损伤标志物HA、SDC-1和HS与脓毒症伴轻度ARDS患者肺损伤指标MLIS评分的相关性。采用受试者工作特征(ROC)曲线对脓毒症伴轻度ARDS患者短期预后进行预测。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者基线资料比较

按照随机数字表法将患者分为对照组和试验组,每组各42例。两组患者年龄、性别、体质量、MLIS评分、APACHE II评分、SOFA评分比较,差异均无统计学意义($P>0.05$),见表1。

2.2 两组患者炎症因子和氧化应激指标比较

治疗前,两组患者炎症因子IL-8、IL-6、TNF- α 、CRP和氧化应激指标SOD、MDA比较,无统计学意义($P>0.05$)。治疗后,两组患者IL-8、IL-6、TNF- α 、CRP、MDA均较本组治疗前显著下降($P<0.05$),SOD较本组治疗前显著升高($P<0.05$);且治疗后试验组IL-8、IL-6、TNF- α 、CRP、MDA较对照组明显降低($P<0.05$),SOD较对照组明显升高($P<0.05$),见表2。

2.3 两组患者EG损伤标志物HA、SDC-1、HS比较

治疗前,两组HA、SDC-1、HS比较,差异无统计

表1 两组基线资料比较

Table 1 Comparison of baseline data between two groups

组别	n/例	年龄/岁	女性/例(占比/%)	体质量/kg	MLIS评分	APACHE II评分	SOFA评分
对照	42	68.43±5.71	18(42.86)	73.33±7.29	13.12±4.30	28.97±6.71	4.48±1.80
试验	42	67.64±6.29	20(47.62)	74.51±6.64	11.93±3.47	30.04±5.83	4.22±1.76

表2 两组患者炎症因子和氧化应激指标比较($\bar{x} \pm s$)

Table 2 Comparison of inflammatory factors and oxidative stress indicators between two groups ($\bar{x} \pm s$)

组别	n/例	时间	IL-8/(ng·L ⁻¹)	IL-6/(ng·L ⁻¹)	TNF- α /(ng·L ⁻¹)	CRP/(mg·L ⁻¹)	SOD/(U·L ⁻¹)	MDA/(μ mol·L ⁻¹)
对照	42	治疗前	62.57±6.29	72.45±9.72	80.56±9.21	58.43±8.32	34.29±4.86	13.61±3.27
		治疗后	42.63±5.18*	37.15±6.53*	48.23±6.39*	27.04±6.73*	49.38±7.31*	8.22±2.28*
试验	42	治疗前	63.82±7.43	70.62±8.36	82.23±8.14	55.39±7.11	32.53±5.72	12.69±3.63
		治疗后	30.87±4.15**	30.78±4.40**	35.78±4.51**	16.48±4.22**	61.09±9.22**	6.03±2.49**

与同组治疗前比较:* $P<0.05$;与对照组治疗后比较:** $P<0.05$

* $P<0.05$ vs same group before treatment; ** $P<0.05$ vs control group after treatment

学意义($P>0.05$)。治疗后,两组HA、SDC-1、HS均较本组治疗前显著降低($P<0.05$),且试验组HA、SDC-1、HS较对照组明显降低($P<0.05$),见表3。

2.4 两组患者SOFA、APACHEII、MLIS评分及临床疗效、短期预后比较

治疗前,两组患者SOFA、APACHEII、MLIS评分比较,差异无统计学意义($P>0.05$);治疗后,两组患者SOFA、APACHE II、MLIS评分均较本组治疗前显著下降($P<0.05$);且试验组SOFA、APACHE II、MLIS评分较对照组明显降低($P<0.01$)。见表4。

试验组治疗总有效率(85.71%)显著高于对照组(66.67%),差异显著($P<0.05$)。出院后1个月,试验组死亡率为(30.95%)明显低于对照组(52.38%),差异显著($P<0.05$)。见表5。

2.5 脓毒症伴轻度ARDS患者HA、SDC-1、HS与MLIS评分的相关性分析

经Pearson相关性分析,脓毒症伴轻度ARDS患者HA、SDC-1、HS与MLIS评分之间呈正相关($r=0.733$, $P=0.036$; $r=0.831$, $P=0.011$; $r=0.826$, $P=0.013$)。脓毒症伴轻度ARDS患者EG损伤标志物水平越高,肺损伤越严重。

2.6 脓毒症伴轻度ARDS患者短期预后的ROC曲线分析

ROC曲线结果显示,SDC-1联合氧化应激指标检测对脓毒症伴轻度ARDS患者短期预后的预测曲线下面积为0.822,高于SDC-1曲线下面积(0.765)及氧化应激指标曲线下面积(0.724),SDC-1联合氧化应激指标对脓毒症伴轻度ARDS患者短期的预后预测价值更大。见图1。

表3 两组患者EG损伤标志物比较($\bar{x}\pm s$)

Table 3 Comparison of injury marker of endothelial glycocalyx between two groups ($\bar{x}\pm s$)

组别	n/例	时间	HA/($\mu\text{g}\cdot\text{L}^{-1}$)	SDC-1/($\mu\text{g}\cdot\text{L}^{-1}$)	HS/($\mu\text{g}\cdot\text{L}^{-1}$)
对照	42	治疗前	139.25 $\pm$ 11.85	114.36 $\pm$ 11.29	91.22 $\pm$ 9.46
		治疗后	116.31 $\pm$ 8.27*	105.75 $\pm$ 9.45*	75.06 $\pm$ 8.28*
试验	42	治疗前	137.52 $\pm$ 12.19	116.02 $\pm$ 13.64	89.16 $\pm$ 7.33
		治疗后	104.28 $\pm$ 9.83*#	93.72 $\pm$ 7.10*#	68.69 $\pm$ 6.32*#

与同组治疗前比较: * $P<0.05$; 与对照组治疗后比较: # $P<0.05$

* $P<0.05$ vs same group before treatment; # $P<0.05$ vs control group after treatment

表4 两组患者SOFA、APACHE II、MLIS评分比较($\bar{x}\pm s$)

Table 4 Comparison of SOFA, APACHEII, and MLIS scores between two groups ($\bar{x}\pm s$)

组别	n/例	时间	SOFA 评分	APACHE II评分	MLIS 评分
对照	42	治疗前	13.12 $\pm$ 4.30	28.97 $\pm$ 6.71	4.48 $\pm$ 1.80
		治疗后	7.24 $\pm$ 2.62*	16.50 $\pm$ 4.28*	2.91 $\pm$ 2.24*
试验	42	治疗前	11.93 $\pm$ 3.47	30.04 $\pm$ 5.83	4.22 $\pm$ 1.76
		治疗后	4.69 $\pm$ 2.28*#	13.35 $\pm$ 3.11*#	2.05 $\pm$ 1.63*#

与同组治疗前比较: * $P<0.05$; 与对照组治疗后比较: # $P<0.05$

* $P<0.05$ vs same group before treatment; # $P<0.05$ vs control group after treatment

表5 两组患者临床疗效及短期预后比较

Table 5 Comparison of therapeutic effect and short-term prognosis of between two groups

组别	n/例	痊愈/例(占比/%)	显效/例(占比/%)	有效/例(占比/%)	无效/例(占比/%)	总有效率/%	死亡/例(占比/%)
对照	42	6(14.28)	13(30.95)	9(21.43)	14(33.33)	28(66.67)	22(52.38)
试验	42	7(16.67)	15(35.71)	14(33.33)	6(14.29)	36(85.71)*	13(30.95)*

与对照组比较: * $P<0.05$

* $P<0.05$ vs control group

3 讨论

炎症反应失衡是脓毒症发生发展的核心环节,级联式炎症反应导致血管内皮细胞损害,表现以微循环血流动力学障碍、局部组织灌注以及内皮通透性改变为特点^[11];ARDS发病基础是肺血管内皮和

肺泡上皮急性损伤,引发炎症细胞浸润和肺血管通透性增加。还涉及细菌内毒素、炎症因子刺激肺泡上皮和血管内皮细胞受损,内皮细胞损伤激活脓毒症炎症-凝血通路加剧炎症反应及凝血功能异常,也影响毛细血管渗漏及组织器官灌注,导致多器官功

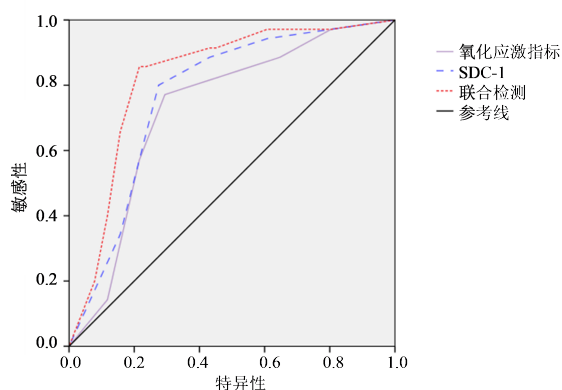


图1 SDC-1联合氧化应激指标对脓毒症伴轻度ARDS患者短期预后的ROC曲线

Fig. 1 ROC curves of SDC-1 combined with oxidative stress indexes for short-term prognosis in patients with sepsis and mild ARDS

能障碍^[12]。内皮功能障碍的恢复则作为疾病的治疗目标。

血管内皮EG是覆盖于微血管内皮表面的一层由糖蛋白、蛋白聚糖和糖胺聚糖组成的被膜屏障性结构,是微循环功能的重要调节器,在维持内皮细胞结构功能的稳定、抑制微血栓形成、调节微循环血流、调控血细胞与内皮细胞的作用、防止炎性细胞黏附、维护血管壁屏障功能的完整起关键作用^[13]。脓毒症时肺血管内皮EG出现降解和脱落,导致肺血管内皮细胞表面屏障破坏,肺毛细血管通透性和肺毛细血管阻力增加,肺循环压力增加,炎症级联反应被激活,扩大肺损伤^[14-15]。HA存在于血管内皮表面,肺泡周围组织中有分泌,HS升高较HA显著,SDC-1在血管中表达广泛,在脓毒症的发生与发展过程中起着重要作用。SDC-1脱落增强了炎症反应并且参与多种疾病的发生。炎性刺激下,SDC-1的脱落增加。本研究结果显示,治疗前两组IL-8、IL-6、TNF- α 、CRP、MDA、SOD、HA、SDC-1、HS比较,差异无统计学意义;治疗后,两组IL-8、IL-6、TNF- α 、CRP、MDA、HA、SDC-1、HS水平均较本组治疗前下降,SOD较治疗前升高,且组间比较差异均有统计学意义($P < 0.05$)。脓毒症伴ARDS微循环障碍的机制主要是肺内皮功能障碍和肺血管内皮EG降解,通过检测EG损伤标志物变化来评估疾病结局^[16-18]。脓毒症伴轻度ARDS患者HA、SDC-1、HS与MLIS评分之间呈正相关,脓毒症伴轻度ARDS患者内皮EG损伤标志物水平越高,肺损伤越严重。ROC结果显示,SDC-1联合氧化应激指标检测对脓毒症伴轻度ARDS患者短期预后有一定的预测价值。

血必净注射液是在血府逐瘀汤的基础上,选用红花、赤芍、川芎、丹参、当归等活血化瘀中药,针对“感染性多器官功能障碍综合征”,基于“菌、毒、炎并治”的原则,通过扶助正气而推动血行,改善气虚血瘀之证,具有溃散毒邪、活血化瘀、扶正固本、疏经通络的功用,能够调节免疫反应、拮抗内毒素及改善微循环障碍,临床上常应用于治疗脓毒症^[19-21]。目前研究大多集中在相关炎症因子表达水平的改善方面,对肺血管内皮细胞损伤及肺血管内皮EG降解的研究较少。本研究显示,试验组治疗总有效率(85.71%)显著高于对照组(66.67%, $P < 0.05$)。脓毒症EG受损,其降解的血液标志物明显增高,导致微血管通透性增高,促进白细胞与内皮细胞的黏附及迁移,促进炎症反应^[22-23]。血必净注射液通过保护肺血管内皮EG结构,减少脓毒症时肺内皮细胞的损伤,减少肺毛细血管渗漏,改善微循环障碍,进而改善脓毒症预后。从抗炎反应、抗氧化应激,保护肺血管内皮细胞,减轻肺血管内皮EG降解等途径达到治疗ARDS的疗效^[24]。治疗后,两组患者SOFA、APACHE II、MLIS评分较本组治疗前显著下降($P < 0.05$)。相关临床评价也发现,血必净注射液明显改变APACHE II评分等指标,并降低死亡率^[25],本研究中患者出院后1个月内随访,试验组死亡率为30.95%,明显低于对照组的52.38%($P < 0.05$),与相关报道结果一致。

血必净注射液在脓毒症干预治疗中具有独特的双向调节的特点,采用中医辨证论治和整体观念的原则,药效作用广泛,多靶点治疗该疾病效果良好。本研究有待扩大样本量,并开展多中心、随机、对照临床研究,进一步明确血必净注射液的疗效及安全性,同时开展更多实验研究探讨其具体作用机制和其中发挥作用的活性成分,为其临床应用提供参考与依据。

利益冲突 所有作者均声明不存在利益冲突

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