

犀角地黄汤治疗老年脓毒症患者的临床研究

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【摘要】目的 观察犀角地黄汤对老年脓毒症患者炎症介质释放和预后的影响。**方法** 采用前瞻性随机对照研究方法。选择2015年3月至2017年2月南京中医药大学附属常熟中医院老年科收治的脓毒症患者74例, 将患者按随机数字表法分为中药治疗组和对照组, 每组37例, 中药治疗组2例在试验期间转入其他科室继续治疗, 2例自动出院, 1例转院; 对照组3例转院, 1例自动出院, 1例入组后7 d内死亡, 1例在试验期间转入其他科室继续治疗, 最终中药治疗组32例、对照组31例患者完成研究。两组均给予脓毒症常规治疗, 中药治疗组在常规治疗基础上给予犀角地黄汤浓缩水煎液100 mL〔犀角(用水牛角代替)30 g、生地黄24 g、芍药12 g、牡丹皮9 g〕口服或鼻饲, 对照组给予等量生理盐水, 均每日1次, 连续治疗1个疗程共7 d后评价其疗效。比较两组患者治疗前及治疗后3、7、14 d血清白细胞介素(IL-1 β 、IL-6)、肿瘤坏死因子- α (TNF- α)、白细胞计数(WBC)、C-反应蛋白(CRP)、乳酸水平的差异, 并观察两组ICU住院率、ICU住院时间及28 d病死率。用Kaplan-Meier生存曲线分析两组28 d存活率。**结果** 两组治疗后IL-1 β 、IL-6、TNF- α 均呈先升高后降低的趋势。治疗后14 d中药治疗组IL-1 β 明显低于对照组(ng/L: 83.27 \pm 21.84比96.73 \pm 26.33), 治疗后7 d起中药治疗组IL-6、TNF- α 已明显低于对照组〔IL-6(ng/L): 48.27 \pm 24.13比62.15 \pm 24.34, TNF- α (μ g/L): 1.41 \pm 0.31比1.96 \pm 0.29〕, 直到治疗后14 d中药治疗组IL-6、TNF- α 仍然低于对照组〔IL-6(ng/L): 29.25 \pm 18.57比56.24 \pm 23.61, TNF- α (μ g/L): 1.35 \pm 0.28比1.83 \pm 0.22, 均 P <0.05)。两组间各时间点WBC、CRP比较差异均无统计学意义(均 P >0.05)。对照组治疗后乳酸均逐渐降低, 中药治疗组治疗后呈先降低后升高的趋势, 且中药治疗组治疗后3 d起即明显低于治疗组(mmol/L: 1.26 \pm 0.43比2.01 \pm 0.59, 均 P <0.05)。中药治疗组ICU住院率、ICU住院时间和28 d病死率均明显低于对照组〔56.25%(18/32)比83.87%(26/31), (10.2 \pm 5.4)d比(13.5 \pm 5.8)d, 9.37%(3/32)比29.03%(9/31)〕。Kaplan-Meier生存曲线分析显示, 中药治疗组28 d存活率明显高于对照组(P =0.045)。**结论** 犀角地黄汤可降低脓毒症患者血清IL-1 β 、IL-6、TNF- α 及乳酸水平, 降低ICU住院率, 缩短ICU住院时间, 改善老年脓毒症患者预后。

【关键词】 犀角地黄汤; 脓毒症; 巨噬细胞; 有氧糖酵解

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Clinical research on effect of Xijiaodihuang decoction for treatment of elderly patients with sepsis Zhang Mo, Li Minzhu, Lu Jun, Chen Mingqi, Jiang Hua, Wang Xing, Yan Jing

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【Abstract】Objective To observe the effect of Xijiaodihuang decoction on the release of inflammatory mediators and prognosis in elderly patients with sepsis. **Methods** A prospective randomized controlled study was conducted. Seventy-four patients with sepsis admitted to the Department of Geriatrics of Changshu Hospital of Traditional Chinese Medicine (TCM) Affiliated to Nanjing University of TCM from March 2015 to February 2017, and they were divided into a TCM treatment group and a control group randomly, 37 cases in each group, there were 2 patients transferred to other department during the period of study to continue treatment, 2 patients discharged automatically and 1 case transferred to other hospital in the TCM treatment group; and there were 3 patients transferred to other hospital, 1 patient discharged automatically, 1 patient dead in 7 days after entering the control group and 1 patient transferred to other department during the period of observation to continue treatment in the control group. Finally, 32 patients were in TCM treatment group and 31 patients in the control group, completing the study. All patients in the two groups received conventional treatment of sepsis, patients in the TCM treatment group took Xijiaodihuang decoction 100 mL concentrated [rhinoceros horn (replaced with buffalo horn) 30 g, rehmannia root 24 g, peony 12 g, tree peony bark 9 g] taken orally or by nasal feeding, and patients in the control group received the same amount of normal saline, the two groups were treated 1 time a day for consecutive 7 days to complete 1 therapeutic course, then the treatment efficacy was evaluated in the two groups. The differences of serum interleukins (IL-1 β , IL-6), tumor necrosis factor- α (TNF- α), white blood cells (WBC), C-reaction protein (CRP), lactate levels between the two groups were compared before treatment and on the 3rd, 7th and 14th day after treatment, the incidence of staying in intensive

care unit (ICU), time of staying in ICU and 28-day mortality were also observed. The 28-day survival rate between two groups was analyzed by Kaplan-Meier survival curve. **Results** After treatment in the two groups, the levels of IL-1 β , IL-6 and TNF- α had a tendency of increase at first and then decrease. After treatment for 14 days, the IL-1 β was significantly lower in the TCM treatment group than that of the control group (ng/L: 83.27 \pm 21.84 vs. 96.73 \pm 26.33), the levels of IL-6 and TNF- α in TCM treatment group were obviously lower than those in the control group since 7 days after treatment [IL-6 (ng/L): 48.27 \pm 24.13 vs. 62.15 \pm 24.34, TNF- α (μ g/L): 1.41 \pm 0.31 vs. 1.96 \pm 0.29]. IL-6 and TNF- α were still lower than those in the control group until 14 days after treatment [IL-6 (ng/L): 29.25 \pm 18.57 vs. 56.24 \pm 23.61, TNF- α (μ g/L) 1.35 \pm 0.28 vs. 1.83 \pm 0.22, all $P < 0.05$]. There was no significant difference in WBC and CRP between the two groups before and after treatment (both $P > 0.05$). After treatment, the lactate in the control group was gradually decreased, while in the TCM treatment group, the lactate level after treatment presented a tendency firstly decreased and then elevated, and after treatment for 3 days in TCM treatment group, the level of lactate began markedly lower than that in the control group (mmol/L: 1.26 \pm 0.43 vs. 2.01 \pm 0.59, $P < 0.05$). The ICU hospitalization rate and ICU length of stay in the TCM treatment group were significantly lower than those in the control group [56.25% (18/32) vs. 83.87% (26/31), (10.2 \pm 5.4) days vs. (13.5 \pm 5.8) days], and the 28-day mortality was also obviously lower in TCM treatment group than that in control group [9.37% (3/32) vs. 29.03% (9/31)]. Kaplan-Meier survival curve analysis showed that the 28-day survival rate in TCM treatment group was significantly higher than that in control group ($P = 0.045$). **Conclusion** Xijiaodihuang decoction can reduce the levels of IL-1 β , IL-6, TNF- α and lactate in serum, reduce the incidence of staying in ICU, decrease the time of staying in ICU and improve the prognosis of elderly patients with sepsis.

[Key words] Xijiaodihuang decoction; Sepsis; Macrophage; Aerobic glycolysis

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脓毒症是宿主对感染应答失调所致的威胁生命的器官功能障碍^[1]。近年来,抗感染、营养支持、多器官功能保护等脓毒症的综合治疗水平取得了长足进步,然而,脓毒症患者的病死率仍较高^[2]。研究表明,急性期过度的全身炎症反应及后期的免疫耐受甚至免疫麻痹,是脓症患者病死率增加的主要原因之一,尤其对于基础疾病多、免疫功能易紊乱的老年患者。本研究首次将犀角地黄汤应用于老年脓症患者,通过观察其对患者全身炎症反应及预后的影响,初步探讨其可能的作用机制,为中医药治疗脓毒症提供新思路。

1 资料与方法

1.1 研究对象的选择:采用前瞻性随机对照研究方法。选择 2015 年 3 月至 2017 年 2 月本院老年科收治的符合纳入标准的脓症患者 74 例。

1.1.1 纳入标准:①符合脓毒症的诊断标准:2016 年以前采用脓毒症 1.0 诊断标准即感染引起的全身炎症反应综合征(SIRS),且具备以下标准 2 项或 2 项以上:体温 $>38\text{ }^{\circ}\text{C}$ 或 $<36\text{ }^{\circ}\text{C}$,心率 >90 次/min;呼吸频率 >20 次/min或动脉血二氧化碳分压(PaCO₂) <32 mmHg(1 mmHg=0.133 kPa),白细胞计数(WBC) $>12\times 10^9$ /L或 $<4\times 10^9$ 或未成熟粒细胞 $>10\%$;2016 年以后采用脓毒症 3.0 诊断标准即感染引起的序贯器官衰竭评分(SOFA)较基线水平升高 ≥ 2 分,若患者无基础器官功能障碍,则 SOFA 评分的基线为 0 分^[3]。②年龄 ≥ 60 岁。

1.1.2 排除标准:①对治疗药物过敏。②机械性肠梗阻或胃肠道对中药制剂不耐受或患者拒绝服用中药。③合并其他慢性炎症等并发症。

1.1.3 伦理学:本研究符合医学伦理学标准,并经南京中医药大学附属常熟中医院医学伦理委员会批准,所有入选患者或家属均签署知情同意书。

1.2 分组及治疗方法:按随机数字表法将患者分为对照组和中药治疗组,每组 37 例。入组 1 d 留取患者血标本后,均迅速按照“拯救脓毒症运动”指南^[2]进行常规治疗,包括生命体征监测、早期液体复苏、抗感染、营养支持等。如达到入住重症加强治疗病房(ICU)指征,则转入 ICU 继续治疗。血流动力学不稳定者给予血管活性药物维持血压,继发急性呼吸窘迫综合征(ARDS)者给予无创或有创机械通气,继发急性肾损伤(AKI)者给予连续性肾脏替代治疗(CRRT)。中药治疗组在常规治疗基础上给予犀角地黄汤浓缩水煎液 100 mL〔犀角(水牛角代替)30 g、生地黄 24 g、芍药 12 g、牡丹皮 9 g〕;对照组给予生理盐水 100 mL,经口服或鼻胃管饲入,均每日 1 次,连续服用 1 个疗程共 7 d。如患者在入组后 7 d 内转入 ICU,则在 ICU 期间继续给予中药或生理盐水至第 7 天。中药汤剂和生理盐水均密闭不透光封存。

1.3 观察指标:于治疗前及治疗后 3、7、14 d,采集两组患者外周静脉血 2~3 mL,3 000 转/min(离心半径 10 cm)离心 10 min,取上清液,-80 $^{\circ}\text{C}$ 超低温

表 1 两组患者一般资料比较

组别	例数 (例)	性别(例)		年龄 (岁, $\bar{x} \pm s$)	APACHE II 评分(分, $\bar{x} \pm s$)	SOFA 评分 (分, $\bar{x} \pm s$)	MAP (mmHg, $\bar{x} \pm s$)	PaO ₂ /FiO ₂ (mmHg, $\bar{x} \pm s$)
		男性	女性					
对照组	31	18	13	70.2 ± 7.5	22.7 ± 6.6	8.8 ± 3.1	79.2 ± 10.9	296.4 ± 39.7
中药治疗组	32	17	15	69.5 ± 6.8	23.5 ± 8.2	8.6 ± 2.3	75.3 ± 12.4	289.1 ± 46.7

组别	例数 (例)	SCr (μmol/L, $\bar{x} \pm s$)	感染来源[例(%)]				
			呼吸系统	泌尿系统	腹腔及消化系统	循环系统及血行感染	导管
对照组	31	95.6 ± 25.9	21(67.7)	2(6.5)	4(12.9)	2(6.5)	2(6.5)
中药治疗组	32	91.3 ± 27.2	20(62.5)	3(9.4)	5(15.6)	3(9.4)	1(3.1)

注: 1 mmHg=0.133 kPa

表 2 两组炎症介质及血气分析指标水平比较($\bar{x} \pm s$)

组别	时间	例数(例)	IL-1β (ng/L)	IL-6 (ng/L)	TNF-α (μg/L)	WBC (×10 ⁹ /L)	CRP (mmol/L)	乳酸 (mmol/L)
对照组	治疗前	31	93.62 ± 35.33	47.15 ± 16.03	1.55 ± 0.32	15.60 ± 4.95	32.14 ± 13.57	3.57 ± 1.48
	治疗后 3 d	31	98.04 ± 32.98 ^a	59.95 ± 21.48 ^a	2.03 ± 0.36 ^a	14.18 ± 4.11	29.17 ± 12.22	2.01 ± 0.59
	治疗后 7 d	31	101.41 ± 29.58 ^a	62.15 ± 24.34 ^a	1.96 ± 0.29 ^a	10.19 ± 3.53 ^a	18.82 ± 6.73 ^a	1.72 ± 0.22 ^a
	治疗后 14 d	31	96.73 ± 26.33	56.24 ± 23.61	1.83 ± 0.22 ^a	8.21 ± 3.17 ^a	9.28 ± 3.18 ^a	1.29 ± 0.35 ^a
中药治疗组	治疗前后	32	92.15 ± 33.43	49.40 ± 18.21	1.54 ± 0.33	14.32 ± 3.71	34.58 ± 11.40	3.69 ± 1.59
	治疗后 3 d	32	99.58 ± 34.12 ^a	52.34 ± 23.27	2.12 ± 0.38 ^a	15.13 ± 4.63	33.29 ± 11.92	1.26 ± 0.43 ^b
	治疗后 7 d	32	96.35 ± 21.80	48.27 ± 24.13 ^b	1.41 ± 0.31 ^b	11.21 ± 3.64 ^a	17.29 ± 8.21 ^a	1.07 ± 0.27 ^{ab}
	治疗后 14 d	32	83.27 ± 21.84 ^b	29.25 ± 18.57 ^{ab}	1.35 ± 0.28 ^{ab}	9.17 ± 3.75 ^a	9.24 ± 2.27 ^a	1.13 ± 0.32 ^a

注: 与治疗前比较, ^a*P*<0.05; 与对照组比较, ^b*P*<0.05

冰箱中保存备检。采用酶联免疫吸附试验(ELISA)检测两组患者外周血白细胞介素(IL-1β、IL-6)、肿瘤坏死因子-α(TNF-α)水平,用血细胞分析仪检测白细胞计数(WBC),用免疫荧光分析仪检测C-反应蛋白(CRP),用血气分析仪检测动脉血乳酸,操作均严格按试剂盒说明书进行。并统计ICU住院率、ICU住院时间及28d病死率。

1.4 统计学方法:使用SPSS 20.0及Stata 13.0统计软件分析数据,符合正态分布的连续变量资料以均数±标准差($\bar{x} \pm s$)表示,采用Student *t* 检验或Wilcoxon 秩和检验,分类变量资料以百分数表示,采用χ² 检验或Fisher 精确检验。应用Kaplan-Meier 法绘制28d生存曲线,Log-rank 检验比较两组28d病死率的差异。*P*<0.05为差异有统计学意义。

2 结果

2.1 一般资料:中药治疗组2例在试验期间转入其他科室继续治疗,2例自动出院,1例转院;对照组3例转院,1例自动出院,1例入组后7d内死亡,1例在试验期间转入其他科室继续治疗。最终中药治疗组32例、对照组31例患者完成研究。两组患者入组时性别、年龄、急性生理与慢性健康状况评分系统II(APACHE II)评分、SOFA评分、平均动脉压(MAP)、氧合指数(PaO₂/FiO₂)、血肌酐(SCr)及不同感染来源的组成比例等一般资料比较差异均无

统计学意义(均*P*>0.05;表1),说明两组资料均衡,有可比性。

2.2 两组患者治疗前后炎症介质及动脉血气分析指标水平比较(表2):两组治疗后IL-1β、IL-6、TNF-α均呈先升高后降低的趋势,治疗后14d,中药治疗组IL-1β明显低于对照组,IL-6、TNF-α于治疗后7d起明显低于对照组,持续到治疗后14d(均*P*<0.05)。两组间各时间点WBC、CRP比较差异均无统计学意义(均*P*>0.05)。对照组治疗后乳酸均逐渐降低,中药治疗组治疗后呈先降低后升高的趋势,且治疗后3d起中药治疗组即明显低于对照组。

2.3 两组ICU住院率和ICU住院时间比较(表3):中药治疗组ICU住院率和ICU住院时间较对照组明显降低(均*P*<0.05)。

2.4 28d病死率(表3;图1):中药治疗组28d病死率明显低于对照组(*P*<0.05)。生存曲线分析也发现,中药治疗组28d生存率明显高于对照组(*P*=0.045)。

表 3 两组患者 ICU 住院率、ICU 住院时间及 28 d 病死率比较

组别	例数 (例)	ICU 住院率 [% (例)]	ICU 住院时间 (d, $\bar{x} \pm s$)	28 d 病死率 [% (例)]
对照组	31	83.87(26)	13.5 ± 5.8	29.03(9)
中药治疗组	32	56.25(18) ^a	10.2 ± 5.4 ^a	9.37(3) ^a

注: 与对照组比较, ^a*P*<0.05

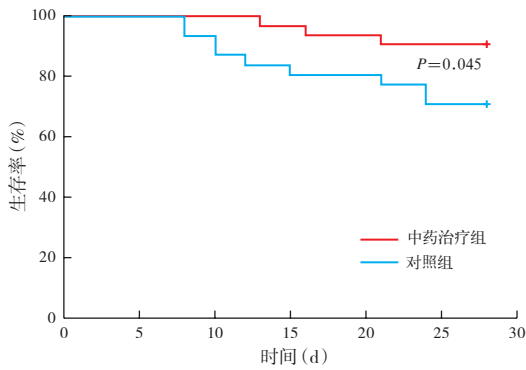


图 1 两组脓毒症患者 28 d Kaplan-Meier 生存曲线

3 讨论

脓毒症是临床常见的急危重症,病死率高。急性期过度的炎症反应和后期免疫麻痹,是脓毒症患者预后差的主要原因^[4],而巨噬细胞过度活化在脓毒症免疫调控中发挥核心作用^[5]。研究表明,脓毒症时,巨噬细胞的葡萄糖代谢方式从氧化磷酸化向有氧糖酵解转变,后者是介导巨噬细胞免疫功能过度激活的关键机制,直接推动脓毒症病情进展^[4, 6-7]。生理状态下,巨噬细胞主要通过葡萄糖三羧酸循环、氧化磷酸化产生三磷酸腺苷(ATP)获能。脓毒症时线粒体功能障碍,三羧酸循环产能明显降低,不能满足细胞的代谢需要,此时巨噬细胞在有氧环境下,改变葡萄糖代谢方式,即通过有氧糖酵解快速产生ATP,为其释放大量炎症介质提供必需的能量^[8-9]。在此代谢改变的基础上,IL-1β、IL-6、TNF-α等巨噬细胞相关促炎介质过度释放,全身炎症反应显著增强^[10-11]。

除了为巨噬细胞释放炎症介质提供所需的能量,有氧糖酵解还会导致乳酸大量积聚,增加脓毒症治疗的难度。研究表明,脓毒症患者血清乳酸水平>4 mmol/L时,病死率明显增加^[12],有氧糖酵解代谢产生的乳酸是脓毒症时高乳酸血症的重要来源^[13]。因此,降低巨噬细胞有氧糖酵解代谢水平,减少巨噬细胞过度释放炎症介质的能量供应,减轻全身炎症反应,减少乳酸积聚,是治疗脓毒症的新思路。

脓毒症以发热、神昏为主症,中医将其归属于“伤寒”“外感热病”“厥证”“温病”等范畴。从脓毒症发生发展的过程来看,“邪毒炽盛”是其关键,“热”“瘀”“毒”三者密切相关、相互转化、相互孳生而阻滞脉络为患^[14]。有氧糖酵解的代谢方式也与“热”“瘀”“毒”有密切联系。有氧糖酵解可快速产能,增加代谢,性质属“阳”属“热”。国医大师周仲瑛教授将“瘀热”理论应用于“外感热病”

“厥证”等疑难重症,并认为其常与“毒”复合为患,应用凉血散瘀法为基础辨治瘀热相搏证,与清热解毒法相并行,疗效满意^[15]。在周仲瑛教授瘀热理论指引下,用具有清热解毒、凉血散瘀作用的经典方剂犀角地黄汤治疗脓毒症,效果显著。方中水牛角为君,清心火而解毒,心火得清,则诸火皆平;生地黄的臣,滋阴凉血清热,协助水牛角解血分之热毒;牡丹皮清热凉血散瘀;赤芍和营泻热祛瘀共为佐使,全方共奏清热解毒、凉血散瘀之功效。本课题组前期的研究表明,犀角地黄汤可显著降低脓毒症患者的APACHE II评分及SOFA评分^[16],其机制可能与犀角地黄汤可下调血清TNF-α、IL-6等巨噬细胞相关炎症介质水平有关^[17]。

本研究选择老年脓毒症患者这一免疫功能失调的特殊群体,观察犀角地黄汤对其炎症介质和预后的影响。结果表明,犀角地黄汤可显著降低脓毒症患者IL-1β、IL-6及TNF-α水平,减少血清乳酸聚集,降低转入ICU治疗的患者比例,缩短ICU住院时间,并降低脓毒症患者的28 d病死率。其具体作用机制可能与犀角地黄汤能下调脓毒症时巨噬细胞有氧糖酵解代谢,减少炎症介质过度释放所需的能量,并降低血清乳酸水平有关,这还有待后期进一步的实验和临床研究加以证实。

本研究尚存在一些限制。第一,未获取脓毒症患者的巨噬细胞,并检测与有氧糖酵解代谢相关的关键酶,因此未获得犀角地黄汤改善预后的机制与抑制巨噬细胞有氧糖酵解相关的直接证据。第二,因中药的特殊颜色和口感,即使试验中对治疗药物和生理盐水不透光密封保存,依然无法做到双盲。第三,本随机对照研究样本量较小,且有可能产生选择偏倚,对研究结果造成影响。

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