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## 左西孟旦对脓毒症休克患者心肌损伤的保护作用探讨\*

王 艳 卢晓娥 董道然 马 欣 宗 媛<sup>△</sup>

(陕西省人民医院重症医学科 陕西 西安 710068)

**摘要 目的:**探讨左西孟旦对脓毒症休克患者心肌损伤的保护作用。**方法:**选择我院 2013 年 1 月至 2017 年 12 月收治的 149 例脓毒症休克患者,根据随机数字表法分为观察组(73 例)及对照组(76 例),对照组给予常规治疗及静脉注射多巴酚丁胺 48 h,观察组在常规治疗基础上给予静脉注射多巴酚丁胺 24h 后再静脉注射左西孟旦 24 h。观察和比较两组的心脏功能参数、血流动力学指数、肌钙蛋白、乳酸、去甲肾上腺素、机械通气例数及 ICU 病死率。**结果:**治疗前,两组的左室射血分数、左室舒张期末容积指数及左室收缩期末容积指数对比差异无统计学意义( $P>0.05$ );治疗后,观察组的心排量、每搏量指数、左室每搏做功指数均明显高于对照组,中心静脉压低于对照组( $P<0.05$ )。对比治疗前,治疗后观察组的心脏功能参数有明显改善( $P<0.05$ ),而对照组无明显差别( $P>0.05$ )。此外,两组治疗后肌钙蛋白及乳酸水平均低于治疗前,且观察组明显低于对照组( $P<0.05$ )。两组的去甲肾上腺素总用量、机械通气例数及 ICU 病死率对比差异均无统计学意义( $P>0.05$ )。**结论:**左西孟旦对脓毒症休克患者具有心肌保护作用,可以改善患者心脏功能,优化血流动力学,但不能降低患者 ICU 病死率。

**关键词:**左西孟旦;脓毒症休克;心肌损伤;保护

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## Protective Effect of Leosimendan on the Myocardial Injury in Patients with Septic Shock\*

WANG Yan, LU Xiao-e, DONG Dao-ran, MA Xin, ZONG Yuan<sup>△</sup>

(Critical Care Medicine Department, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, 710068, China)

**ABSTRACT Objective:** To investigate protective effect of leosimendan on the myocardial injury in patients with septic shock. **Methods:** 149 cases with septic shock from Jan. 2013 to Dec. 2017 in our hospital were chosen, who were divided into the observation group (73 cases) and control group (76 cases), the control group were given routine treatment and intravenous administration of dobutamine for 48 h, the observation group were given routine treatment, intravenous injection of dobutamine for 24 h and intravenous injection of leosimendan for 24 h. The cardiac function parameters, hemodynamic index, troponin, lactate, norepinephrine, mechanical ventilation and ICU mortality of two groups were compared. **Results:** Before treatment, the left ventricular ejection fraction, left ventricular diastolic final volume index and left ventricular systolic final volume index of two groups had no significant different ( $P>0.05$ ). After treatment, the cardiac function parameters were got improved in the observation group ( $P<0.05$ ), while there was no difference in the control group ( $P>0.05$ ). The cardiac output, each stroke index, left ventricle per beat index in observation group were all higher than control group, while the central venous pressure were lower than control group ( $P<0.05$ ). The troponin and lactate levels after treatment were all lower than before treatment, while the observation group was obvious lower than control group ( $P<0.05$ ), the total amount of norepinephrine, mechanical ventilation and ICU mortality between groups had no significant difference ( $P>0.05$ ). **Conclusion:** Leosimendan had myocardial protective effect on patients with septic shock, which could improve the heart function, optimize hemodynamics, while have could not decrease the ICU mortality.

**Key words:** Leosimendan; Septic shock; Myocardial damage; Protection

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### 前言

脓毒症是由于感染引起的宿主反应失调,导致危及生命的器官功能障碍,是重症监护室住院患者最常见的死亡原因,常

继发于严重感染、烧/创伤、休克等急危重症,严重威胁患者生命健康及生活质量<sup>[1]</sup>。脓毒症休克是脓毒症合并出现的全身细胞代谢紊乱、循环障碍的严重情况,病死率高<sup>[2]</sup>。脓毒症休克期间,患者会出现心肌抑制及心肌损伤,导致左心室射血分数、右

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作者简介:王艳(1981-),女,硕士研究生,主治医师,研究方向:危重症患者心脏保护研究,E-mail: wangyan201803@163.com

<sup>△</sup> 通讯作者:宗媛(1973-),女,学士,副主任医师,研究方向:危重症患者器官保护,E-mail: annie9500@21cn.com

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心室射血分数及舒张功能下降,而脓毒症休克后若合并心脏功能损伤会大大提高患者的死亡率<sup>[3]</sup>。

左西孟旦是一种心肌内钙离子增敏剂,多用于急性冠脉综合征及急性心力衰竭的治疗,且不会加大心率失常的风险、不增加心肌耗氧量及钙超载,同时可以改善患者的血液动力学,安全性较高<sup>[4]</sup>。目前,已有动物实验表明左西孟旦可改善脓毒症休克导致的心肌抑制状态<sup>[5]</sup>,但其药物循证研究目前仍相对缺乏<sup>[6]</sup>。因此,本研究主要探讨了左西孟旦对脓毒症休克患者心肌损伤的保护作用,以期临床左西孟旦治疗脓毒症休克提供参考依据。

## 1 资料与方法

### 1.1 一般资料

选择 2013 年 1 月至 2017 年 12 月我院收治的脓毒症休克患者 149 例,所有患者根据随机数字表法,分为观察组(73 例)及对照组(76 例)。纳入标准:经心脏超声、影像学检查及临床诊

断确诊,符合 2012 年脓毒症诊治指南中关于脓毒症休克的诊断标准<sup>[7]</sup>;患者有急性循环衰竭状态,且以低血压为主,收缩压低于基础血压水平超过 40 mmHg 或收缩压低于 90 mmHg,且持续时间超过 1 h,平均动脉压 <60 mmHg;尿量减少明显且存在高乳酸血症;毛细血管再充盈时间 >3 s,四肢皮肤有厥冷、花斑等症状;需机械通气及入重症监护室治疗。排除标准:胸腔积液/气胸等可影响监测疾病、严重心律失常者,入组前合并心脏瓣膜疾病、急性心肌梗死及心内解剖分流等会引起心肌抑制疾病者,合并股动脉置管、深静脉置管禁忌症者,处于妊娠期者,病情进展迅速无法完成本次研究者,左室射血分数 >45%者。

本研究中,男 79 例,女 70 例,年龄 25~69 岁,平均年龄  $46.1 \pm 8.6$  岁。患者的原发病为:肺部感染共 54 例,化脓性胆系感染共 32 例,腹腔感染共 22 例,肠穿孔共 25 例,血流感染共 16 例。两组患者的一般资料对比差异无统计学意义( $P>0.05$ ),具有可比性。本文患者知情同意,并经医院伦理委员会批准。

表 1 两组一般资料对比

Table 1 Comparison of the general Data between two groups

| Groups      | Index                      | Observation group | Control group | P     |
|-------------|----------------------------|-------------------|---------------|-------|
| n           | -                          | 73                | 76            | -     |
| Sex         | Male                       | 39                | 40            | 0.923 |
|             | Female                     | 34                | 36            |       |
| Average age | Age(year)                  | 46.8± 9.5         | 44.7± 9.2     | 0.172 |
|             | Plumunary infection        | 28                | 26            | 0.847 |
|             | Enterobrosis               | 13                | 12            |       |
|             | Abdominal infection        | 10                | 12            |       |
|             | Suppurative bile infection | 15                | 17            |       |
|             | Bloodstream infection      | 7                 | 9             |       |

### 1.2 治疗方法

两组均维持体内水电解质平衡、酸碱平衡,依据脓毒症休克指南共识给予常规补液、抗生素、血管活性药物治疗,同时行机械通气。对照组在常规治疗基础上静脉注射  $5 \mu\text{g/kg} \cdot \text{min}$  多巴酚丁胺治疗 48 h。观察组先以  $5 \mu\text{g/kg} \cdot \text{min}$  的速度静脉注射多巴酚丁胺 24 h,之后 24 h 改用左西孟旦  $0.2 \mu\text{g/kg} \cdot \text{min}$  静脉注射。

### 1.3 观察指标

(1)应用床旁超声检测两组治疗前后的心脏功能参数,包括左室射血分数、左室舒张期末容积指数、左室收缩期末容积指数;(2)对比两组的血流动力学指数,应用脉搏指示连续心排血量技术及无创心排仪监测患者的心排血量、心率、每搏量指数、左室每搏做功指数、外周血管阻力指数、平均动脉压及中心静脉压;(3)采用多功能免疫分析仪检查两组的肌钙蛋白、血气分析仪监测乳酸水平;(4)记录两组的去甲肾上腺素总用量、机械通气例数、ICU 病死率。

### 1.4 统计学方法

采用 SPSS19.0 软件对比分析本文数据,计量资料用均数±标准差表示,组间用 t 检验比较,计数资料用百分比或例数表示,组间用卡方检验比较, $P<0.05$  为差异有统计学意义。

## 2 结果

### 2.1 两组治疗前后的心脏功能参数对比

治疗前,两组的左室射血分数、左室舒张期末容积指数及左室收缩期末容积指数对比差异无统计学意义( $P>0.05$ )。与治疗前相比,治疗后对照组与治疗前对比无统计学意义( $P>0.05$ ),观察组左室射血分数明显高于对照组( $P<0.05$ ),而左室舒张期末容积指数及左室收缩期末容积指数明显低于对照组( $P<0.05$ )。

### 2.2 两组治疗前后血流动力学指数对比

治疗前,两组心排血量、每搏量指数、左室每搏做功指数、中心静脉压、心率、外周血管阻力指数及平均动脉压对比差异无统计学意义( $P>0.05$ );治疗后,对照组的中心静脉压明显高于治疗前,其他指标前后对比差异无统计学意义( $P>0.05$ );与对照组相比,观察组心排血量、每搏量指数、左室每搏做功指数明显较高( $P<0.05$ ),而中心静脉压明显较低( $P<0.05$ )。

### 2.3 两组治疗前后的肌钙蛋白、乳酸水平的对比

治疗前,两组的肌钙蛋白、乳酸水平对比差异无统计学意义( $P>0.05$ )。治疗后,两组肌钙蛋白及乳酸水平均低于治疗前,且观察组明显低于对照组( $P<0.05$ )。

表 2 两组治疗前后的心脏功能参数对比

Table 2 Comparison of the cardiac function parameters between two groups before and after treatment

| Groups            | N  | Left ventricular ejection fraction |                 | Left ventricular diastolic final volume index |                 | Left ventricular contraction final volume index |                 |
|-------------------|----|------------------------------------|-----------------|-----------------------------------------------|-----------------|-------------------------------------------------|-----------------|
|                   |    | Before treatment                   | After treatment | Before treatment                              | After treatment | Before treatment                                | After treatment |
|                   |    |                                    |                 |                                               |                 |                                                 |                 |
| Control group     | 73 | 0.4± 0.1                           | 0.4± 0.1        | 79.5± 12.3                                    | 78.6± 13.6      | 49.5± 14.6                                      | 48.3± 13.4      |
| Observation group | 76 | 0.4± 0.1                           | 0.5± 0.1*       | 78.4± 12.5                                    | 61.7± 11.4*     | 48.8± 13.4                                      | 32.7± 9.5*      |
| P                 | -  | 1.000                              | <0.001          | 0.589                                         | <0.001          | 0.761                                           | <0.001          |

Note: Compared with before treatment, \*P&lt;0.05.

表 3 两组治疗前后血流动力学指数对比

Table 3 Comparison of the haemodynamics index between two groups before and after treatment

| Groups                                                      | Control group    |                 | Observation group |                 |
|-------------------------------------------------------------|------------------|-----------------|-------------------|-----------------|
|                                                             | Before treatment | After treatment | Before treatment  | After treatment |
| Cardiac output(L/min·m <sup>2</sup> )                       | 3.4± 0.5         | 3.6± 0.7        | 3.3± 0.6          | 4.6± 0.7**      |
| Heart rate(times/min)                                       | 116.5± 12.1      | 116.2± 12.9     | 117.4± 14.1       | 117.8± 15.1     |
| Stoke index(mL/m <sup>2</sup> )                             | 37.3± 5.1        | 37.5± 4.5       | 36.4± 4.8         | 39.8± 5.1**     |
| Left ventricular stroke work index(kg/min·m <sup>2</sup> )  | 28.8± 1.5        | 28.1± 1.2       | 29.1± 3.1         | 33.7± 2.4**     |
| Systemic vascular resistance index(kpa/s·L·m <sup>2</sup> ) | 118.5± 10.5      | 120.5± 12.4     | 117.3± 9.1        | 119.8± 12.4     |
| Mean arterial pressure (mmhg)                               | 67.61± 11.6      | 68.3± 9.2       | 67.3± 12.6        | 66.1± 9.4       |
| Central venous pressure (mmhg)                              | 10.41± 2.5       | 12.4± 3.0*      | 10.9± 3.1         | 8.0± 2.1**      |

Note: Compared with before treatment, \*P&lt;0.05; compared with control group, \*\*P&lt;0.05.

表 4 两组治疗前后的肌钙蛋白及乳酸对比

Table 4 Comparison of the troponin and lactic acid level between two groups before and after treatment

| Groups            | n  | Troponin (ng/L)  |                 | Lactic acid (mmol/L) |                 |
|-------------------|----|------------------|-----------------|----------------------|-----------------|
|                   |    | Before treatment | After treatment | Before treatment     | After treatment |
| Control group     | 73 | 2.8± 0.5         | 2.2± 0.6*       | 12.1± 3.0            | 3.2± 0.8*       |
| Observation group | 76 | 2.9± 0.7         | 3.4± 0.8**      | 11.9± 2.8            | 4.7± 1.2**      |
| P                 | -  | 0.316            | <0.001          | 0.674                | <0.001          |

Note: Compared with before treatment, \*P&lt;0.05; compared with control group, \*\*P&lt;0.05.

## 2.4 两组的去甲肾上腺素总用量、机械通气例数、ICU 病死率对比

两组的去甲肾上腺素总用量、机械通气例数及 ICU 病死率对比差异均无统计学意义(P>0.05)。

表 5 两组的去甲肾上腺素总用量、机械通气例数、ICU 病死率对比

Table 5 Comparison of the total amount of norepinephrine, mechanical ventilation and ICU mortality between two groups

| Groups            | n  | Total amount of norepinephrine (μg/kg·min) | Mechanical ventilation | ICU mortality |
|-------------------|----|--------------------------------------------|------------------------|---------------|
|                   |    |                                            |                        |               |
| Control group     | 73 | 0.4± 0.1                                   | 61(83.6)               | 32(43.8)      |
| Observation group | 76 | 0.4± 0.1                                   | 59(77.6)               | 29(38.2)      |
| P                 | -  | 1.000                                      | 0.361                  | 0.481         |

## 3 讨论

脓毒症休克患者会出现有效血液容量短缺,导致心脏功能

受到抑制,且患者易出现代谢功能障碍、组织缺氧及心肌抑制<sup>[8]</sup>。脓症患者发生心肌抑制的作用机制常被认为有以下几点:短暂缺血导致心肌灌注损伤<sup>[9]</sup>;脓毒症抢救过程中使用较多药

物,某些药物对心肌有损害作用<sup>[10]</sup>;心肌抑制因子存在于血液循环中,会损害心肌<sup>[11]</sup>;脓毒症存在高心排量,升高心室壁张力压力,损伤心肌细胞<sup>[12]</sup>。脓毒症休克合并心肌抑制是导致患者出现器官功能障碍及死亡的主要原因<sup>[13]</sup>,因此需要引起充分重视。心脏是脓毒症损伤机体的一个主要靶器官<sup>[14]</sup>,脓毒症休克患者中超过 50%存在心肌抑制等左室收缩障碍等现象<sup>[15]</sup>,患者常伴心肌损伤,增加了患者的死亡率<sup>[16]</sup>。

脓毒症发生时,患者的细胞亚微结构会发生变化,会损伤心肌细胞,裂解心肌内肌钙蛋白,从而导致肌钙蛋白水平上升<sup>[17]</sup>,因此,脓毒症休克者心肌功能障碍的直接因素是心肌细胞内钙离子失衡<sup>[18]</sup>,其钙离子敏感性降低,会改变信息细胞内钙离子动态平衡<sup>[19]</sup>,而肌钙蛋白与心肌抑制程度明显相关<sup>[20]</sup>。本研究中,两组治疗后的肌钙蛋白水平均显著降低,且观察组明显低于对照组,表明左西孟旦对脓毒症休克患者的肌钙蛋白改善能力较强。主要是由于左西孟旦对患者心肌细胞上的肌钙蛋白可进行选择性结合,从而提高肌钙蛋白与钙离子复合物构象的稳定性,增加患者机体内肌钙蛋白的含量<sup>[21]</sup>。观察组心排量、每搏量指数、左室每搏做功指数明显高于对照组,而中心静脉压明显低于对照组,表明左西孟旦可显著降低患者的乳酸水平,具有改善患者心脏收缩功能,优化血流动力学的作用。

左西孟旦在改善患者肌钙蛋白的同时<sup>[22]</sup>不增加心律失常的发生,且不增加心肌耗氧量<sup>[23]</sup>,对患者高动力代谢状态的脓毒性休克心肌抑制有重要作用<sup>[24]</sup>,既可以改善患者全身组织氧代谢,又可改善线粒体钙超载,调节线粒体数量,从而起到心肌保护的作用<sup>[25-27]</sup>;同时,其会激活血管平滑肌上的钾离子通道,促进血管扩张,改善患者的血流动力学<sup>[28,29]</sup>;且具有抑制心肌细胞凋亡及抗氧化作用,可共同改善脓毒症休克的心肌抑制状态<sup>[30,31]</sup>。本研究中,两组的去甲肾上腺素总用量、机械通气例数及 ICU 病死率对比差异无统计学意义,提示与常规治疗相比,左西孟旦治疗脓毒症休克疗效相当,但也可能与本研究样本量较少有关,有待进一步扩大样本量深入研究。

综上所述,左西孟旦对脓毒症休克患者具有心肌保护作用,可以改善患者心脏功能,优化血流动力学,但不能降低患者 ICU 病死率。

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