

doi: 10.13241/j.cnki.pmb.2021.24.005

脓毒症大鼠肝肾功能、凝血功能和炎症指标的变化及意义*

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摘要 目的:研究脓毒症大鼠肝肾功能、凝血功能和炎症指标的变化及意义。**方法:**选取 SPF 级雄性 SD 大鼠 20 只,以随机数字表法将其分成实验组与假手术组,每组各 10 只。其中实验组通过盲肠穿刺结扎制备脓毒症大鼠模型,假手术组大鼠仅翻动盲肠,不作结扎处理。分别采集所有大鼠术后 0 h、6 h、12 h、24 h 时的尾静脉血 3 mL,检测并比较上述时间点两组大鼠的肝肾功能、凝血功能和炎症指标水平的差异。**结果:**实验组术后 6 h、12 h、24 h 的谷丙转氨酶(ALT)、尿素氮(BUN)以及肌酐(Cr)水平均高于假手术组($P<0.05$)。实验组术后 24 h 的活化部分凝血活酶时间(APTT)、凝血酶原时间(PT)、纤维蛋白原(FIB)水平均高于假手术组($P<0.05$)。实验组大鼠术后 6 h、12 h、24 h 的血清白细胞计数(WBC)、白细胞介素-6(IL-6)、降钙素原(PCT)水平均高于假手术组($P<0.05$)。**结论:**脓毒症大鼠肝肾功能存在明显的受损,凝血功能障碍明显,且机体内会释放大量的炎症因子。

关键词:脓毒症;肝肾功能;凝血功能;炎症指标

中图分类号:R-33;R631.2 **文献标识码:**A **文章编号:**1673-6273(2021)24-4628-04

Changes and Significance of Liver and Kidney Function, Coagulation Function and Inflammation Indexes in Sepsis Rats*

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ABSTRACT Objective: To study the changes and significance of liver and kidney function, coagulation function and inflammation indexes in sepsis rats. **Methods:** 20 male SPF grade SD rats were selected, and they were randomly divided into experimental group and sham operation group by random number table method, with 10 rats in each group. Sepsis rats in the experimental group were made by cecal puncture and ligation, while rats in the sham operation group were only turned over the cecum without ligation. 3 mL of tail venous blood of all rats at 0 h, 6 h, 12 h and 24 h after surgery was collected respectively, the differences in liver and kidney function, blood coagulation function and inflammation index levels between the two groups at the above time points were detected and compared. **Results:** The levels of alanine aminotransferase (ALT), urea nitrogen (BUN) and creatinine (Cr) in experimental group at 6 h, 12 h and 24 h after surgery were higher than those in sham operation group($P<0.05$). The levels of activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen (FIB) in experimental group at 24 h after surgery were higher than those in sham operation group ($P<0.05$). The levels of serum white blood cell count (WBC), interleukin-6 (IL-6) and procalcitonin (PCT) in the experimental group at 6 h, 12 h and 24 h after surgery were higher than those in the sham operation group($P<0.05$). **Conclusion:** The liver and kidney functions of sepsis rats are obviously impaired, and the coagulation dysfunction is obvious, and a large amount of inflammatory transmitters are released in the body.

Key words: Sepsis; Liver and kidney function; Coagulation function; Inflammation index

Chinese Library Classification(CLC): R-33; R631.2 **Document code:** A

Article ID: 1673-6273(2021)24-4628-04

前言

脓毒症主要是指宿主对感染的反应失调而致的危及生命的器官功能障碍,属于外科手术以及严重烧伤/创伤等常见的一种严重并发症^[1-3]。如未给予及时有效的处理,随着病情的不断进展极易诱发弥散性凝血功能障碍,继而引发多脏器功能损

伤,并增加患者死亡的风险^[4-6]。迄今为止,关于脓毒症的具体发病机制以及病理生理过程尚且存在一定的争议,患者临床表现以及体征并不典型,从而可能导致医生对患者的病情判断出现偏颇,继而延误患者的治疗,对预后产生不利影响^[7-9]。随着近年来相关研究的不断深入,越来越多的学者发现炎症反应以及凝血系统改变均和该疾病的发生、发展密切相关,甚至会影响患

* 基金项目:上海市第六人民医院东院院级科学研究基金(DY2018011);上海市卫生健康委员会科研项目计划(202040341)

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(收稿日期:2021-04-28 接受日期:2021-05-23)

者预后^[10-12]。且有研究报道证实,凝血功能紊乱贯穿脓毒症整个病理过程,亦是脓毒症发生、发展以及预后的关键性因素^[13-15]。鉴于此,本文通过研究脓毒症大鼠肝肾功能、凝血功能和炎症指标的变化及意义,本研究通过观察脓毒症大鼠肝肾功能、凝血功能和炎症指标水平随时间的变化特点,以期临床脓毒症患者肝肾损伤、凝血功能障碍、炎症的治疗提供病理生理学依据,现作以下报道。

1 材料与方法

1.1 实验动物

选取 SPF 级雄性 SD 大鼠 20 只, 周龄 7-8 周, 体重 200-220 g 左右,以随机数字表法将其分成实验组与假手术组, 每组各 10 只。大鼠均由上海杰思捷实验动物有限公司提供[许可证号:SCXK(沪)2018-0004],合格证编号:20180004030943。购买后运抵实验室,于动物房进行为期 7 d 的适应性饲养,动物房温度 24℃,相对湿度 50%,光照为 12 h 光 - 暗循环(AM8:00-PM8:00),不限制活动,不限制饮水、饮食。体重增至 250-300 g。

1.2 仪器及试剂

AU5800 型全自动生化仪(购自美国贝克曼库尔特有限公司),Multifuge X3R 型冷冻离心机(购自赛默飞世尔科技公司),CytoFLEX 流式细胞仪(购自美国贝克曼库尔特有限公司),CS2000i 型凝血测试仪(购自日本 SYSMAX 株式会社),IMS-20 型全自动雪花制冰机(购自常熟市雪科电器有限公司),DW-HL528S 型超低温冷冻储存箱(购自长虹美菱股份有限公司)。谷丙转氨酶(ALT)、尿素氮(BUN)、肌酐(Cr)、纤维蛋白原(FIB)检测试剂盒均购自宁波瑞源生物科技有限公司。白细胞介素-6(IL-6)、降钙素原(PCT)试剂盒均购自江苏酶免实业有限公司。

1.3 研究方法

(1)造模:实验组实验前 12 h 予以禁食处理,不限制饮水,采用盲肠穿刺结扎制备脓毒症大鼠模型。首先对大鼠进行 40

mg/kg 剂量的戊巴比妥钠腹腔注射麻醉处理。取仰卧位,妥善固定四肢,采用碘伏对腹部皮肤进行重复 2 次消毒,铺无菌巾。于下腹部腹正中中线作一长度为 1.5 cm 的切口,明确盲肠部位并进行肠系膜的游离。以 4-0 号丝线于盲肠远端完成盲肠侧壁的结扎处理,借助 16 号针头重复 2 次贯穿盲肠,保证两个穿刺点间距为 1 cm,稍稍挤压可见盲肠有少量粪渣溢出。之后将盲肠放回腹腔,最后逐层缝合腹壁切口。假手术组则在开腹后仅反动盲肠,术后通过腹部皮下注射无菌生理盐水,作为术中丢失体液的补充。术后将两组大鼠均饲养于 25℃ 环境中,予以大鼠饲料以及饮水。(2)标本采集:分别于术后 0 h、6 h、12 h、24 h 时采集两组大鼠的尾静脉血 4 mL,均分装为两管。其中一管以 8 cm 为离心半径,开展时长为 10 min 的 3000 r/min 离心处理,取血清保存在冰箱(-80℃)中备用;另一管装入抗凝试管保存备用。(3)肝肾功能指标检测:相关指标包括 ALT、BUN 以及 Cr,以酶联免疫吸附试验检测。(4)凝血功能指标检测:相关指标包括活化部分凝血活酶时间(APTT)、凝血酶原时间(PT)以及 FIB。上述指标水平的检测均通过 CS2000i 型凝血测试仪实现。(5)炎症指标检测:相关指标包括白细胞计数(WBC)、IL-6 以及 PCT,其中 WBC 以 CytoFLEX 流式细胞仪完成检测,IL-6 以及 PCT 经酶联免疫吸附法检测。

1.4 统计学处理

所得数据采用 SPSS26.0 进行分析。计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间不同时间点的比较采用重复测量方差分析,组间两两比较采用 LSD-t 检验,组内时间前后比较采用差值 t 检验。计数资料以%表示,比较采用 χ^2 检验。统计推断的检验水准 $\alpha=0.05$ (双侧检验)。组内时间前后比较进行检验水准的调整。

2 结果

2.1 两组大鼠肝肾功能指标评价

实验组术后 6 h、12 h、24 h 的 ALT、BUN 及 Cr 水平均高于假手术组($P<0.05$)及同组术后 0 h($P<0.017$)。见表 1。

表 1 两组大鼠肝肾功能指标评价($\bar{x} \pm s$)

Table 1 Evaluation of liver and kidney function indexes of rats in the two groups($\bar{x} \pm s$)

Groups	Time	ALT(U/L)	BUN(mmol/L)	Cr(μ mol/L)
Sham operation group (n=10)	0 h after surgery	54.32 $\pm$ 10.02	8.75 $\pm$ 1.09	26.03 $\pm$ 2.28
	6 h after surgery	55.62 $\pm$ 10.74	9.04 $\pm$ 0.99	26.33 $\pm$ 2.35
	12 h after surgery	55.07 $\pm$ 11.70	8.95 $\pm$ 1.03	27.19 $\pm$ 2.33
	24 h after surgery	53.67 $\pm$ 11.25	8.99 $\pm$ 1.13	27.71 $\pm$ 2.38 ^t
Experimental group(n=10)	0 h after surgery	54.97 $\pm$ 10.81	8.69 $\pm$ 0.99	26.53 $\pm$ 2.10
	6 h after surgery	75.72 $\pm$ 10.96 ^a	9.94 $\pm$ 1.59 ^a	31.29 $\pm$ 3.17 ^a
	12 h after surgery	201.28 $\pm$ 18.43 ^a	16.13 $\pm$ 1.72 ^a	53.66 $\pm$ 6.33 ^a
	24h after surgery	126.42 $\pm$ 13.65 ^a	12.54 $\pm$ 1.72 ^a	32.42 $\pm$ 4.25 ^a
Overall analysis	HF coefficient	0.3989	0.5784	0.4307
Group comparison	F, P	1,178.814, 0.000	178.676, 0.000	329.553, 0.000
Intra group comparison	F, P	255.099, 0.000	65.572, 0.000	125.543, 0.000
Interaction	F, P	254.577, 0.000	61.781, 0.000	111.398, 0.000

Note: significant marker a was the comparison of two groups at the same time point, $P<0.05$. The fine comparison within the group (time dimension) was the difference t test, and the significant marker t was the comparison with the first time point within the group $P<\alpha'$, α' was Bonferroni's corrected test level = $0.05/3=0.017$, and 3 was the number of fine comparison in time dimension.

2.2 两组大鼠凝血功能指标评价

($P<0.05$)及同组术后 0 h($P<0.017$)。见表 2。

实验组术后 24 h 的 APTT、PT、FIB 水平均高于假手术组

表 2 两组大鼠凝血功能指标评价($\bar{x}\pm s$)

Table 2 Evaluation of coagulation function indexes of rats in the two groups($\bar{x}\pm s$)

Groups	Time	APTT(s)	PT(s)	FIB(g/L)
Sham operation group (n=10)	0 h after surgery	20.10± 3.36	14.29± 2.00	3.69± 1.04
	6 h after surgery	20.35± 3.41	14.51± 2.03	3.75± 1.08
	12 h after surgery	21.05± 3.57	14.29± 2.17	3.88± 1.13
	24 h after surgery	20.21± 3.64	14.51± 2.33	3.83± 1.09
Experimental group(n=10)	0 h after surgery	20.29± 3.50	14.32± 2.26	3.74± 1.02
	6 h after surgery	21.28± 3.48	14.82± 2.29	3.77± 1.08
	12 h after surgery	21.69± 3.69	14.84± 2.24	3.74± 1.11
	24 h after surgery	30.71± 4.19 ^{at}	16.14± 2.83 ^{at}	5.20± 1.21 ^{at}
Overall analysis	HF coefficient	0.8375	1.0345	1.0482
Group comparison	F, P	38.113, 0.000	2.994, 0.092	3.911, 0.045
Intra group comparison	F, P	16.056, 0.000	1.454, 0.231	4.753, 0.004
Interaction	F, P	17.459, 0.000	0.951, 0.419	4.013, 0.009

Note: Same as table 1.

2.3 两组大鼠血清炎症因子水平对比

术组大鼠术后 6 h、12 h、24 h 的血清 WBC、IL-6、PCT 水平均高

实验组大鼠术后 6 h、12 h、24 h 的血清 WBC、IL-6、PCT 水平均高于假手术组($P<0.05$)及同组术后 0 h($P<0.017$);假手

于同组术后 0 h($P<0.05$)。见表 3。

表 3 两组大鼠血清炎症因子水平对比($\bar{x}\pm s$)

Table 3 Comparison of serum inflammatory cytokines between the two groups($\bar{x}\pm s$)

Groups	Time	WBC($\times 10^9/L$)	IL-6(pg/mL)	PCT(ng/mL)
Sham operation group (n=10)	0 h after surgery	305.29± 31.12	83.62± 7.46	48.60± 4.56
	6 h after surgery	506.37± 42.26	177.70± 11.54 ⁱ	100.36± 14.95 ⁱ
	12 h after surgery	598.95± 57.79	205.79± 20.60 ⁱ	149.18± 19.75 ⁱ
	24 h after surgery	421.54± 35.20 ⁱ	105.54± 8.27 ⁱ	55.39± 5.14 ⁱ
Experimental group(n=10)	0 h after surgery	309.35± 47.06 ^{at}	84.29± 7.59	49.70± 4.60
	6 h after surgery	597.08± 52.83 ^{at}	2,704.11± 192.36 ^{at}	202.65± 20.65 ^{at}
	12 h after surgery	625.37± 53.29 ^{at}	3,024.45± 221.74 ^{at}	272.61± 24.90 ^{at}
	24 h after surgery	591.55± 49.02 ^{at}	2,740.47± 199.12 ^{at}	412.84± 49.29 ^{at}
Overall analysis	HF coefficient	0.5492	0.3568	0.3642
Group comparison	F, P	250.260, 0.000	12,300.001, 0.000	1,913.641, 0.000
Intra group comparison	F, P	91.188, 0.000	1,201.285, 0.000	500.460, 0.000
Interaction	F, P	68.111, 0.000	1,062.454, 0.000	417.133, 0.000

Note: Same as table 1.

3 讨论

相关研究报道表明^[16-18],脓毒症的发病机制可能和炎症反应失衡、免疫功能紊乱、凝血功能异常以及线粒体损伤等多种因素有关。其中脓毒症按照病情严重程度的差异可分作脓毒症及脓毒性休克,其中脓毒性休克极易引发多脏器功能损伤,亦是导致脓症患者死亡的主要原因^[19-21]。因此,针对脓症患者而言,密切检测各器官功能状态显得尤为重要,可为临床干预以及预后评估提供可靠依据。凝血系统激活属于脓毒症的关键

发病环节,且其可与炎症反应相互作用,在脓毒症的病理生理过程中发挥着至关重要的作用^[22-24]。另有研究报道表明,脓毒症发生的根本原因是机体过度释放细胞因子以及炎症递质,继而引起炎症反应的失控以及免疫功能紊乱,最终进展为多器官功能障碍综合征,增加死亡的风险^[25,26]。

本研究结果发现,实验组术后 6 h、12 h、24 h 的 ALT、BUN 以及 Cr 水平均高于假手术组及同组术后 0 h。提示脓毒症大鼠肝肾功能存在明显的受损。究其原因,ALT 可反映机体肝细胞损害以及坏死的情况,其水平的异常升高和肝功能损害呈正相

关关系,是目前临床上用以衡量肝功能的重要指标之一,其主要存在于肝细胞的线粒体内,在机体出现脓毒症时,大量内毒素的产生会引起肝细胞线粒体超微结构发生损伤,继而发生功能障碍,导致肝细胞受损凋亡,引起 ALT 水平的异常升高,并形成恶性循环^[27]。BUN 以及 Cr 则是目前临床上广泛用以反映机体肾功能的可靠指标,其表达水平的异常升高反映了肾实质的受损,且受损程度和上述两项指标水平呈正相关。在脓毒症发生之时,机体血压会有不同程度的下降,加之肾动脉灌注缺乏和炎症因子的作用,极易引起急性肾损伤,最终导致上述指标的异常表达^[28]。此外,实验组术后 24 h 的 APTT、PT、FIB 水平均高于假手术组及同组术后 0 h。这提示了凝血系统的异常激活参与了脓毒症发生、发展过程。这可能与以下几点有关^[29,30]:(1)凝血系统的异常激活会促进大量组织因子诱导凝血酶的产生,继而引起血小板活化聚集。(2)抗凝血酶系统、组织因子途径抑制物系统以及蛋白 C 系统等生理性抗凝机制受损。(3)纤溶系统遭受抑制,从而导致纤维蛋白微栓的清除异常。且有研究报道显示,脓毒症发生后机体存在严重炎症,且机体抗炎动态平衡被打破,继而引起多种机体阳性物质以及细胞因子的"瀑布样"释放,从而可能引起凝血功能的紊乱^[31,32]。另外,实验组大鼠术后 6 h、12 h、24 h 的各项血清炎症因子水平均高于假手术组。提示机体内存在大量的炎症因子释放。脓毒症会产生大量的细菌内毒素,从而促进单核细胞、巨噬细胞以及其它炎症细胞产生大量的炎症因子,进一步促进疾病进展。此外,假手术组大鼠术后 6 h、12 h、24 h 的血清 WBC、IL-6、PCT 水平均高于同组术后 0 h。分析原因,手术会对大鼠造成一定程度的创伤,继而引起机体炎症应激反应,导致上述指标发生变化。但上述炎症因子水平会随着时间的推移而逐渐恢复正常。

综上所述,脓毒症大鼠肝肾功能存在一定程度的损伤,且凝血功能障碍明显,炎症反应在脓毒症的发生、发展过程中起着至关重要的作用。

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