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·基础研究·

一种新型复苏液对脓毒症大鼠凝血功能障碍的影响研究

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[摘 要] **目的** 探究一种由腺苷、利多卡因及硫酸镁(ALM)组成的新型复苏液对脓毒症大鼠凝血功能障碍的影响。**方法** 将48只雄性SD大鼠随机分成ALM治疗组、脓毒症组和假手术组,每组16只。假手术组大鼠在开腹检查盲肠后直接缝合;ALM治疗组和脓毒症组大鼠均通过盲肠结扎穿刺建立脓毒症模型。造模后2 h,ALM治疗组大鼠通过尾静脉注入0.3 mL的ALM复苏液,随后以0.5 mL·kg^{-1}·h^{-1}的速度持续输注4 h;脓毒症组和假手术组大鼠在相同时间注入等量的0.9%氯化钠注射液。测定各组大鼠造模后6、12 h血浆凝血功能指标凝血酶原时间(PT)、活化部分凝血酶原时间(APTT),组织因子(TF)及血管内皮损伤指标内皮多糖包被核心蛋白Syndecan-1、细胞间黏附分子-1(ICAM-1)的浓度。**结果** 与假手术组比较,ALM治疗组及脓毒症组大鼠造模后12 h的PT延长,造模后6 h和12 h的APTT及TF、ICAM-1、Syndecan-1水平延长/升高($P<0.01$)。与脓毒血症组比较,ALM治疗组大鼠造模后12 h的PT显著缩短,造模后6 h和12 h的APTT及TF、ICAM-1、Syndecan-1水平显著缩短/降低($P<0.01$)。**结论** ALM复苏液能够减少内皮多糖包被的降解,抑制血管内皮细胞与炎症细胞黏附,减少TF释放,从而改善脓毒症大鼠的凝血功能。

[关键词] 脓毒症;液体复苏;凝血功能障碍;内皮糖萼

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Effect of a novel resuscitation fluid on coagulation dysfunction in septic rats

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Abstract: Objective To explore the impact of a novel resuscitation fluid comprising adenosine, lidocaine and magnesium (ALM) on the coagulation dysfunction in septic rats. **Methods** A total of 48 male Sprague-Dawley rats were randomly assigned to the ALM treatment

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group, sepsis group, and sham surgery group, with 16 rats in each group. Rats in the sham surgery group had their cecum directly sutured after laparotomy examination, and rats both in the ALM treatment group and the sepsis group were established septic models by cecal ligation and puncture. Two hours after modeling, rats in the ALM treatment group were administrated 0.3 mL of ALM resuscitation fluid via tail vein injection, followed by continuous infusion of ALM resuscitation fluid at a rate of 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$; rats in the sepsis group and the sham surgery group were injected with the same amount of 0.9% sodium chloride solution at the same time. The prothrombin time (PT), activated partial thromboplastin time (APTT), and concentrations of tissue factor (TF), endothelial injury marker of endothelial glycocalyx core protein Syndecan-1, and intercellular adhesion molecule-1 (ICAM-1) of rats in each group were detected. **Results** Compared with the sham surgery group, the PT 12 hours after modeling of rats in the ALM treatment group and the sepsis group prolonged, and the APTT as well as the levels of TF, ICAM-1, and Syndecan-1 6 hours and 12 hours after modeling prolonged/elevated ($P<0.01$). Compared with the sepsis group, the PT 12 hours after modeling of rats in the ALM treatment group significantly shortened, and the APTT as well as levels of TF, ICAM-1, and Syndecan-1 6 hours and 12 hours after modeling significantly shortened/reduced ($P<0.01$). **Conclusion** ALM resuscitation fluid attenuates coagulation dysfunction in septic rats through reducing the degradation of endothelial glycocalyx, inhibiting the adhesion between endothelial cells and inflammatory cells, as well as decreasing the release of TF.

Keywords: sepsis; fluid resuscitation; coagulation dysfunction; endothelial glycocalyx

脓毒症是指因感染引起的宿主反应失调导致的危及生命的器官功能障碍，据估计，全球每年大约有500万人死于脓毒症[1-2]。脓毒症患者的血管内皮细胞损伤、促凝血途径和抗凝血途径之间的平衡被破坏，导致全身凝血酶生成、抗凝血酶活性和纤维蛋白溶解受抑制，这种情况称为脓毒症性凝血病，通常与不良临床结局和高病死率有关[3-5]。脓毒症时，机体免疫系统启动，分泌白细胞介素-6、肿瘤坏死因子α等大量炎症因子，能够促进单核细胞和血管内皮细胞中组织因子（tissue factor, TF）的表达和活化，增加血管内皮细胞黏附，促进凝血酶产生，启动凝血过程。若脓毒症持续进展，促凝机制被过度激活，组织因子途径抑制因子、活化蛋白C和抗凝血酶被抑制，纤维蛋白溶解功能异常，导致凝血与炎症反应失衡，甚至发展为弥散性血管内凝血[6-7]。血管内皮细胞是保持体内凝血与抗凝血平衡的重要组成部分，作为血管内膜的屏障，可通过阻止白细胞、血小板与其黏附，抑制凝血启动和血小板聚集；此外，血管内皮细胞能够阻止炎症因子与其受体结合。一旦血管内皮细胞受损或降解，将引发并加剧炎症反应，进而影响凝血过程的启动[8-9]。

以腺苷（adenosine）、利多卡因（lidocaine）、硫酸镁（magnesium）为主要成分的ALM复苏液，具有一定的心肌保护作用，可作为一种新型的心脏停搏液应用于心脏外科手术中[10-11]。随后的研究发现，在失血性休克、心脏搏动骤停以及脓毒症等动物模型中，稀释的ALM复苏液较腺苷、利多卡因、硫酸镁单药使用效果更优，不仅能保护心肌、抗心律失常，还具有抗炎、改善凝血功能和血小板功能的作用，但具体机制尚未明确[11-12]。目前，国内已有研究显示，利多卡因能够缓解炎症反应并发挥器官保护的作用[13]，但尚无ALM复苏液的研究。鉴于脓毒症中炎症、凝血功能紊乱与内皮功能密切相关，本研究拟在脓毒症并凝血功能障碍的大鼠模型中探究ALM复苏液对脓毒症凝血功能障碍的影响及其可能机制。

1 材料与方法

1.1 实验材料

1.1.1 ALM复苏液的制备 将50 mg腺苷加入到5 mL的氯化钠溶液中，充分摇至溶解，再加入100 mg利多卡因注射液，混匀后加入50 mg硫酸镁溶液，检测溶液的pH值并调整至7.2~7.5，当液体完全溶解后，加入0.9%氯化钠溶液配至10 mL，并置于4 ℃冰箱中保存，使用前复温，整个过程在无菌操作台完成。

1.1.2 实验动物 48只7~12周龄、体质量为（300±50）g的雄性SD大鼠均由贵州医科大学实验动物中心提供（生产许可证号：SCXK[黔]2018-0001），本研究获贵州医科大学伦理委员会审批（批准号：1806108）。

1.1.3 主要试剂和仪器 全自动凝血分析仪（美国沃芬公司），大鼠ELISA检测试剂盒（武汉伊莱瑞特生物科技有限公司），标准规格酶标仪（德国Eppendorf公司），多功能酶标仪（美国BioTek公司）。

1.2 方法

1.2.1 动物分组处理 按照随机数字表法将48只大鼠分为ALM治疗组、脓毒症组和假手术组，每组16只。假手术组大鼠开腹探查盲肠后关腹，不进行盲肠结扎及穿刺。脓毒症组和ALM治疗组大鼠通过盲肠结扎穿刺建立脓毒症模型[14]，在造模2 h后，ALM治疗组大鼠于尾静脉先注射0.3 mL ALM复苏液作为负荷剂量，随后以0.5 $mL \cdot kg^{-1} \cdot h^{-1}$的剂量持续输注

4 h[15];期间假手术组和脓毒症组大鼠输注等体积的0.9%氯化钠注射液。

1.2.2 指标检测 造模后6、12 h,每组每个时间点取8只大鼠进行麻醉后采血,并置入含有抗凝剂的试管中,以3 000 r/min的速度离心15 min,收集上层血浆。在全自动凝血分析仪上检测凝血酶原时间(prothrombin time, PT)和活化部分凝血酶原时间(activated partial thromboplastin time, APTT)。根据试剂盒说明书使用ELISA法检测TF、内皮多糖包被核心蛋白Syndecan-1和细胞间黏附分子1(intercellular adhesion molecule-1, ICAM-1)水平。

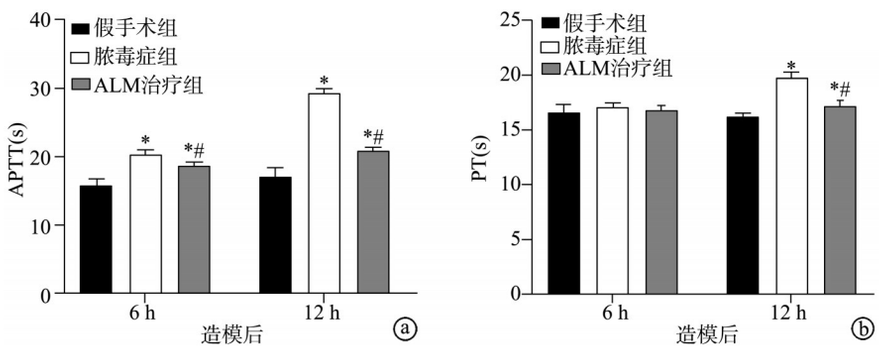
1.3 统计学处理

数据分析使用SPSS 24.0统计学软件完成。采用*Kolmogorov-Smirnow*法评估数据的正态性,符合正态分布的资料以均数±标准差($\bar{x}\pm s$)表示,多组间比较使用单因素方差分析(*ANOVA*),两两比较采用*LSD*检验。$P<0.05$为差异有统计学意义。

2 结果

2.1 凝血功能指标比较

与假手术组比较,脓毒症组和ALM治疗组大鼠造模后12 h的PT,造模后6、12 h的APTT延长,差异均有统计学意义($P<0.01$);与脓毒症组相比,ALM治疗组大鼠造模后12 h的PT及造模后6、12 h的APTT缩短,差异均有统计学意义($P<0.01$),见图1。

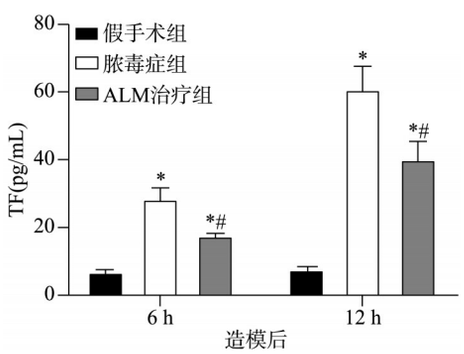


a:APTT;b:PT *:与假手术组同时间点比较,$P<0.01$;#:与脓毒症组同时间点比较,$P<0.01$

图1 不同时间点大鼠APTT、PT的变化

2.2 大鼠血浆中TF浓度变化

与假手术组相比,脓毒症组和ALM治疗组大鼠造模后6、12 h血浆中TF浓度均明显上升($P<0.01$);与脓毒症组相比,ALM治疗组大鼠造模后6、12 h血浆中TF浓度均明显下降($P<0.01$),见图2。



*:假手术组同时间点比较,$P<0.01$;#:与脓毒症组同时间点比较,$P<0.01$

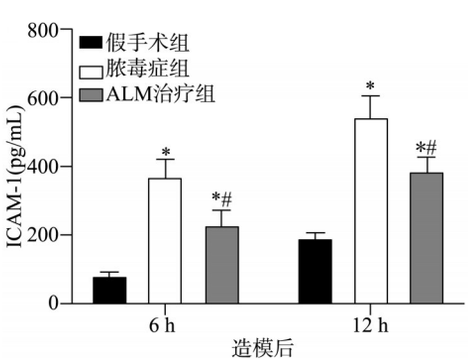
图2 不同时间点大鼠TF浓度变化

2.3 大鼠血浆中ICAM-1水平变化

与假手术组相比,脓毒症组、ALM治疗组大鼠造模后6、12 h血浆中ICAM-1浓度均明显上升($P<0.01$);与脓毒症组相比,ALM治疗组大鼠造模后6、12 h血浆中ICAM-1水平明显下降($P<0.01$),见图3。

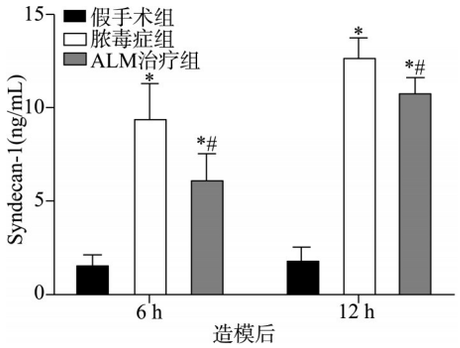
2.4 大鼠血浆中Syndecan-1浓度变化

与假手术组相比,脓毒症组、ALM治疗组大鼠造模后6、12 h血浆中Syndecan-1浓度均显著升高($P<0.01$)。与脓毒症组相比,ALM治疗组大鼠造模后6、12 h血浆中Syndecan-1浓度显著降低($P<0.01$),见图4。



*:与假手术组同时间点比较,$P<0.01$;#:与脓毒症组同时间点比较,$P<0.01$

图3 不同时间点大鼠血浆ICAM-1水平比较



*:与假手术组同时间点比较,$P<0.01$;#:与脓毒症组同时间点比较,$P<0.01$

图4 不同时间点大鼠血浆Syndecan-1浓度比较

3 讨论

脓毒症性凝血病的特征是全身性炎症和凝血系统的过度激活,导致微血管血栓形成、器官灌注减少,进而引起器官功能障碍[7]。据统计,约24%的脓毒症患者会发展为脓毒症性凝血病,且其病死率增加约2倍[5,16]。

体内凝血酶生成的过程分为三个阶段:起始、扩增和增殖。在起始阶段,凝血过程由表达TF的细胞(如单核细胞、内皮细胞或血小板)开始[17]。在脓毒症情况下,促炎细胞因子会激活单核细胞等,从而引起TF的表达增加[18]。同时内皮屏障的破坏也会导致循环中TF的表达增加。TF是一种促凝血糖蛋白,通过结合凝血因子Ⅶ并将其转化为活化的Ⅶ因子,从而启动外源性凝血途径。临床上,炎症引起凝血激活的标志物之一是血浆TF[19]。本研究结果显示,脓毒症组大鼠造模后6、12 h血浆中TF浓度均显著高于假手术组,这与以往研究结果一致[20],提示在脓毒症发展初期,效应细胞释放出大量的TF,随着TF数量的激增,凝血系统被激活。此外,本研究中脓毒血症大鼠的PT、APTT明显延长,提示脓毒症常伴有凝血障碍,与既往研究结果一致[21]。

内皮糖萼由血管内皮细胞合成,是分隔血流和血管壁的屏障,主要成分包括Syndecan-1等蛋白聚糖骨架及硫酸软骨素、硫酸角质素、透明质酸等糖胺聚糖侧链[22]。在正常生理情况下,内皮糖萼具有自我修复功能,发生脓毒症时,内皮糖萼损伤,并从血管内皮上脱落[23]。在脓毒症中,内皮糖萼的降解会导致抗凝血功能减弱,而炎症因子和介质会活化内皮细胞,增加黏附分子的表达,促进白细胞、血小板在内皮表面的滚动和附着。这一系列变化促进了微血管内血栓的形成,最终造成内皮细胞和周围组织的损伤[24]。有研究证实,血浆中ICAM-1、Syndecan-1的含量可作为血管内皮损伤的指标[25]。另有研究显示,相较于实验性内毒素血症志愿者,脓毒症患者血浆中Syndecan-1水平明显增高[26]。因此,在脓毒症初期,内皮糖萼损伤及炎症反应的加剧,可能进一步激活凝血过程。本研究发现,脓毒症组大鼠血浆中ICAM-1及Syndecan-1浓度升高,提示脓毒症大鼠出现血管内皮损伤。

目前脓毒症仍然缺乏特效治疗,寻找有效的药物治疗方案成为现代医学和药理学研究的重点[27]。腺苷是一种内源性嘌呤核苷,通过与四种G蛋白偶联受体A1、A2A、A2B、A3相互作用来传递信号。腺苷可以通过A2A受体抑制炎症细胞的激活及表达,促进内皮细胞功能的恢复[28]。有研究发现,利多卡因可以诱导静息中性粒细胞的早期凋亡[29];且国内一项动物实验表明,利多卡因可以保护脓毒症大鼠的重要器官,显著提高其生存率[30]。镁是多种酶的辅助因子,参与300多种酶促反应[31]。硫酸镁通过抑制NF-κB的活化和Ca^{2+}通道的开放,发挥强效的抗炎作用,并通过抑制各种免疫细胞激活,减少炎症因子释放,改善脓毒症引起的炎症反应[32]。ALM复苏液是含腺苷、利多卡因和硫酸镁的药物组合。已有多项研究证实,低剂量ALM复合液可降低冠状动脉阻力、保护心肌和器官、抑制炎症反应、提高血小板功能,在器官代谢和凝血功能方面起着重要的作用[10-11,33-35]。本研究发现,与脓毒症组相比,ALM治疗组大鼠血浆中PT及APTT缩短,TF、Syndecan-1和ICAM-1水平显著降低,表明ALM复苏液能够减轻凝血障碍,减少血管内皮糖萼脱落,避免凝血系统的过度激活。

综上所述,ALM复苏液可通过减少TF释放、降低内皮多糖包被降解、抑制炎症细胞黏附于血管内皮细胞,从而改善脓毒症大鼠的凝血功能。

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