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体外循环心脏手术患者肝功能的表达水平及腺苷蛋氨酸的干预机制研究*

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摘要 目的:探讨体外循环心脏手术患者肝功能的表达水平及腺苷蛋氨酸的干预机制。**方法:**选取2017年5月至2018年6月在海南医学院第二附属医院接受体外循环心脏手术的患者184例,根据随机数字表法分为观察组及对照组各92例,分别比较术前、术后所有患者肝功能指标水平。术后对照组患者给予生理盐水干预7d,观察组患者给予腺苷蛋氨酸干预7d,比较两组患者干预7d后肝功能指标、炎症反应指标以及心肌损伤指标水平。**结果:**术前患者的总胆红素(TBI)、直接胆红素(DBI)、丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)水平均显著低于术后,差异均有统计学意义($P<0.05$)。干预7d后观察组患者的TBI、DBI、ALT、AST、血清肿瘤坏死因子- α (TNF- α)、白细胞介素-8(IL-8)、肌酸激酶同工酶(CK-MB)、肌钙蛋白(cTnT)水平均显著低于对照组,而白细胞介素-10(IL-10)水平显著高于对照组,差异均有统计学意义($P<0.05$)。观察组不良反应发生率为7.61%(7/92),与对照组的2.17%(2/92)相比,差异无统计学意义($P>0.05$)。**结论:**体外循环心脏手术会对患者肝功能造成一定程度的损害,而腺苷蛋氨酸对患者的肝功能以及心肌组织均有一定的保护作用,同时能减轻炎症反应程度,无严重药物不良反应发生。

关键词:体外循环;心脏手术;腺苷蛋氨酸;肝功能;炎症反应;心肌损伤

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Expression Level of Liver Function in Patients of Cardiac Surgery with Cardiopulmonary Bypass and Intervention Mechanism of Ademetionine*

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ABSTRACT Objective: To study the expression level of liver function in patients of cardiac surgery with cardiopulmonary bypass and the intervention mechanism of ademetionine. **Methods:** A total of 184 patients underwent cardiopulmonary bypass surgery in the Second Affiliated Hospital of Hainan Medical University from May 2017 to June 2018 were selected, and were divided into observation group and the control group according to random number table method, with 92 cases in each group. The liver function indexes levels of all the patients before and after operation were compared respectively. After surgery, the patients in the control group were given saline intervention for 7d, and the patients in the observation group were given ademetionine intervention for 7d. The liver function indexes, inflammatory response indexes and myocardial injury indexes between the two groups were compared after seven days of intervention. **Results:** The total bilirubin (TBI), direct bilirubin (DBI), alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels before surgery were significantly lower than those after surgery, the differences were statistically significant ($P<0.05$). After seven days of intervention, the TBI, DBI, ALT, AST, serum tumor necrosis factor- α (TNF- α) and interleukin-8 (IL-8), creatine kinase isoenzyme (CK-MB), cardiac troponin T (cTnT) levels of observation group were significantly lower than those of the control group, and the interleukin-10 (IL-10) level of observation group was significantly higher than that of the control group, the differences were statistically significant ($P<0.05$). The incidence of adverse reactions in the observation group was 7.61% (7/92), and there was no significant difference compared with 2.17% (2/92) in the control group ($P>0.05$). **Conclusion:** Cardiopulmonary bypass surgery can cause some damage to liver function, but ademetionine has certain protective effect in the patients' liver function and myocardial tissue and can reduce the degree of inflammatory reaction at the same time, without serious adverse drug reaction.

Key words: Cardiopulmonary bypass; Cardiac surgery; Ademetionine; Liver function; Inflammatory reaction; Myocardial injury

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前言

心脏手术由于受体外循环这个无法避免的因素影响,会对患者的肝、心、肺等脏器以及凝血机制造成不同程度的损害^[1-3]。

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有研究报道显示,部分患者在术后均会出现肝功能异常情况,如不给予及时有效的干预,甚至会导致肝功能衰竭,严重影响患者的生活质量^[4,5]。因此,寻找一种有效的干预手段,对改善患者术后的肝功能以及预后均有极其重要的意义。总胆红素(total bilirubin, TBI)、直接胆红素(direct bilirubin, DBI)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)及天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)均为临床常用的肝功能检测指标,已被广泛地应用于对患者肝功能情况的评价^[6,7]。腺苷蛋氨酸是在人体组织及体液内普遍存在的一类生理活性分子,额外补充能够防止腺苷蛋氨酸合成酶的缺乏,对患者的肝功能具有较好的调节作用^[8,9]。鉴于此,本文通过研究体外循环心脏手术患者肝功能的表达水平及腺苷蛋氨酸的干预机制,旨在为体外循环心脏手术患者肝功能的改善提供数据支持,现将结果进行如下报道。

1 资料和方法

1.1 临床资料

选取2017年5月至2018年6月在海南医学院第二附属医院接受体外循环心脏手术的患者184例。纳入标准^[10]:(1)年龄 ≥ 18 岁;(2)术前肝功能正常;(3)无长期服用影响肝功能药物史。排除标准:(1)严重的心肾肺功能不全者;(2)入院前接受过激素或免疫调节剂治疗者;(3)对腺苷蛋氨酸药物过敏者;(4)精神失常者。根据随机数字表法分为观察组及对照组各92例。其中观察组男52例,女40例,年龄25-78岁,平均 (52.39 ± 11.32) 岁;体外循环时间50-95 min,平均 (71.38 ± 12.34) min;手术类型:二尖瓣置换术37例,二尖瓣成形术7例,先天性心脏病畸形矫正术4例,主动脉瓣置换术30例,二尖瓣+主动脉瓣置换术14例。对照组男49例,女43例,年龄27-75岁,平均 (50.57 ± 11.49) 岁;体外循环时间51-93 min,平均 (70.18 ± 21.24) min;手术类型:二尖瓣置换术36例,二尖瓣成形术6例,先天性心脏病畸形矫正术5例,主动脉瓣置换术30例,二

尖瓣+主动脉瓣置换术15例。两组患者在年龄、性别、体外循环时间、手术类型等方面对比无统计学差异($P>0.05$),具有可比性。所有患者均已对本次研究知情同意,且签署了同意书。海南医学院第二附属医院的伦理委员会已评审通过。

1.2 研究方法

术后对照组患者给予生理盐水干预,剂量为3 mg/kg,每日2次,连续干预7d。观察组患者术后给予腺苷蛋氨酸(浙江震元制药有限公司,国药准字:H20140078)干预,具体方法、剂量均与对照组相同。

1.3 观察指标

分别比较术前、术后所有患者肝功能指标TBI、DBI、ALT、AST水平,干预7d后对比观察组及对照组肝功能指标水平以及血清肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-8(interleukin-8, IL-8)、白细胞介素-10(interleukin-10, IL-10)、肌酸激酶同工酶(creatine kinase isoenzyme, CK-MB)、肌钙蛋白(cardiac troponin T, cTnT)水平。其中肝功能指标、CK-MB、cTnT均采用日立公司的7180型全自动生化分析仪检测。血清TNF- α 、IL-8、IL-10水平均采用酶联免疫吸附法(enzyme-linked immunosorbent assay, ELISA)进行检测,相关试剂盒购自深圳晶美公司。观察两组药物不良反应发生情况。

1.4 统计学方法

数据分析采用SPSS21.0统计软件进行。性别比例、手术类型等计数资料以率的形式表示并采用卡方检验,肝功能指标、炎症因子等计量资料对比予以t检验,以均数 $\pm$ 标准差($\bar{x} \pm s$)表示。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 手术前后所有患者的肝功能指标水平对比

术前患者TBI、DBI、ALT、AST水平均显著低于术后,差异均有统计学意义($P<0.05$),见下表1。

表1 手术前后所有患者的肝功能指标水平对比($\bar{x} \pm s$)

Table 1 Comparison of liver function indexes in all patients before and after operation($\bar{x} \pm s$)

Times	n	TBI($\mu\text{mol/L}$)	DBI($\mu\text{mol/L}$)	ALT(IU/L)	AST(IU/L)
Before surgery	184	25.32 $\pm$ 4.16	4.78 $\pm$ 2.34	33.29 $\pm$ 11.47	32.82 $\pm$ 11.29
After surgery	184	44.27 $\pm$ 5.85	8.76 $\pm$ 4.83	64.41 $\pm$ 18.93	62.94 $\pm$ 17.53
t	-	36.094	10.194	19.174	19.651
P	-	0.000	0.000	0.000	0.000

2.2 干预7d后两组患者肝功能指标水平对比

干预7d后观察组患者的TBI、DBI、ALT、AST水平均显著低于对照组,差异均有统计学意义($P<0.05$),见下表2。

2.3 干预7d后两组患者血清炎症因子、CK-MB、cTnT水平对比

干预7d后观察组血清TNF- α 、IL-8、CK-MB、cTnT水平均显著低于对照组,而IL-10水平显著高于对照组,差异均有统计学意义($P<0.05$),见下表3。

2.4 药物不良反应发生情况比较

观察组输注腺苷蛋氨酸后有5例出现恶心不适,2例出现

低钾血症,均给予相应治疗后有所好转,不良反应发生率为7.61%(7/92),对照组有2例出现呕吐现象,不良反应发生率为2.17%(2/92),两组比较无统计学差异($\chi^2=2.921$, $P=0.087$)。

3 讨论

由于体外循环心脏手术患者在术后需长期服用抗凝药物治疗,因此,如果患者发生肝功能损伤,不但会对抗凝药物的服用以及治疗方案调整造成严重影响,而且一旦发生肝功能衰竭,缺乏有效的处理方式,易导致患者死亡^[11-13]。有研究报道表

表 2 干预 7d 后两组患者肝功能指标水平对比($\bar{x} \pm s$)Table 2 Comparison of liver function indexes between two groups after seven days of intervention($\bar{x} \pm s$)

Groups	n	TBI($\mu\text{mol/L}$)	DBI($\mu\text{mol/L}$)	ALT(IU/L)	AST(IU/L)
Observation group	92	28.76 $\pm$ 4.93	5.39 $\pm$ 2.42	37.84 $\pm$ 12.29	38.15 $\pm$ 11.96
Control group	92	38.24 $\pm$ 5.67	6.68 $\pm$ 3.64	51.63 $\pm$ 15.37	52.31 $\pm$ 13.57
t	-	12.246	2.882	6.764	7.568
P	-	0.000	0.004	0.000	0.000

表 3 干预 7d 后两组患者血清炎症因子、CK-MB、cTnT 水平对比($\bar{x} \pm s$)Table 3 Comparison of serum inflammatory factors,CK-MB and cTnT levels between two groups after seven days of intervention($\bar{x} \pm s$)

Groups	n	TNF- α (ng/mL)	IL-8(ng/mL)	IL-10(ng/mL)	CK-MB($\mu\text{g/L}$)	cTnT($\mu\text{g/L}$)
Observation group	92	1.69 $\pm$ 0.15	0.21 $\pm$ 0.12	50.92 $\pm$ 5.33	40.87 $\pm$ 7.46	0.54 $\pm$ 0.19
Control group	92	2.18 $\pm$ 0.17	0.39 $\pm$ 0.11	38.27 $\pm$ 4.05	48.52 $\pm$ 8.35	1.08 $\pm$ 0.26
t	-	20.730	6.782	18.345	6.642	21.448
P	-	0.000	0.000	0.000	0.000	0.000

明,体外循环心脏手术会对患者肝功能的多个生化指标造成影响,从而对肝脏的合成、代谢以及排泄等一系列功能造成损害,甚至会破坏肝胆管上皮以及肝细胞的完整性,严重影响患者临床治疗效果及预后^[14-16]。其中导致患者发生肝功能损伤的主要原因包括体外循环时间、手术出血量以及术后低心排量等因素^[17,18]。且有研究报道认为,体外循环心脏手术会使得患者血清炎症因子水平增高,从而出现一定程度的炎症反应,对器官组织造成炎症损害^[19,20]。同时也会对患者的心肌组织造成一定损害,影响患者的手术疗效^[21,22]。由此,对患者实施有效的干预措施显得尤为重要。

本研究结果发现手术前患者的 TBI、DBI、ALT、AST 水平均显著低于手术后 ($P < 0.05$)。这与以往的研究报道具有一致性,说明了体外循环心脏手术会对患者的肝功能造成一定损害^[23]。分析原因主要可能与患者在接受体外循环心脏手术过程中产生的低血流灌注、炎症反应以及栓塞等因素有关。其中低血流灌注可通过血液稀释、低温、缩血管物质水平的变化以及缺血再灌注等对患者肝细胞造成的损伤。如体外循环手术结束后,患者的肝血流逐渐恢复,此时氧自由基和花生四烯酸的激活可能导致肝血流减少,严重时致肝细胞坏死^[24]。与此同时,干预后观察组患者的 TBI、DBI、ALT、AST 水平均显著低于对照组 ($P < 0.05$)。这提示了采用腺苷蛋氨酸对体外循环手术患者进行干预,可对患者肝功能提供一定的保护作用。究其原因,我们认为腺苷蛋氨酸的主要活性成分为腺苷蛋氨酸-1,4-二磺酸盐,其可有效恢复患者肝细胞的转甲基以及转流基的作用,进一步促进患者的肝功能恢复,是目前临床上用以治疗体外循环心脏手术后发生肝功能损害的有效药物^[25]。另有研究报道显示^[26,27],腺苷蛋氨酸参与了谷胱甘肽的生成,在一定程度上有利于肝脏内谷胱甘肽的含量增加,从而达到增强肝脏解毒功能的作用,进一步有效促进黄疸的消退,促进患者肝功能恢复。此外,干预后观察组血清 TNF- α 、IL-8 水平均显著低于对照组,而 IL-10 水平显著高于对照组。这表明了腺苷蛋氨酸干预可显著减轻患者炎症反应,从而降低炎症对器官组织所造成的损害。

其中主要作用机制可能是腺苷蛋氨酸可通过对核因子- κ B 介导的炎症信号途径产生抑制作用,从而增强了抗炎因子的基因表达^[28,29]。另外,CK-MB、cTnT 均是临床上用来反映患者心肌损伤的敏感指标^[30]。而本文结果显示,干预后观察组血清 CK-MB、cTnT 水平均显著低于对照组。这提示了腺苷蛋氨酸干预对患者的心肌组织具有一定的保护作用,可显著减轻体外循环引发的心肌损伤。两组不良反应率比较无统计学差异,说明腺苷蛋氨酸的用药安全性较好。

综上所述,体外循环心脏手术会对患者肝功能造成一定程度的损害,而腺苷蛋氨酸可有效促进患者肝功能的恢复,同时对心肌组织具有一定的保护作用,且能减轻体外循环所导致的炎症反应,有助于患者早日康复。

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