

参附注射液对小儿先天性心脏病术后急性肾损伤的影响

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【摘要】 目的 观察参附注射液对小儿先天性心脏病术后急性肾损伤(AKI)的影响。**方法** 选择2016年8月至2018年12月西南医科大学附属医院收治的62例心房或心室间隔缺损修补术患儿,按治疗方法不同分为西医对照组和参附注射液组,每组31例。参附注射液组患儿从麻醉诱导开始至体外循环结束给予20 mL参附注射液;西医对照组患儿泵入相同体积的生理盐水。观察两组麻醉时间、手术总时间、体外循环时间、主动脉夹闭时间和米力农、多巴胺、肾上腺素、硝普钠等药物使用情况;于术前(T0)、手术开始(T1)、体外循环开始(T2)、体外循环结束(T3)、手术结束(T4)采用化学发光法测定血清肌酐(SCr)水平,计算肾小球滤过率(eGFR);同时记录两组各时间点平均动脉压(MAP)、心率(HR)、中心静脉压(CVP)和肾上腺素、去甲肾上腺素水平。**结果** 参附注射液组和西医对照组患儿麻醉时间、手术总时间、体外循环时间、主动脉夹闭时间和米力农、多巴胺、肾上腺素、硝普钠等药物的使用情况比较差异均无统计学意义(均 $P>0.05$)。两组患者T0~T4时各时间点HR、CVP比较差异均无统计学意义(均 $P>0.05$);两组MAP水平T0和T1时比较差异均无统计学意义(均 $P>0.05$);随时间延长,西医对照组MAP较T0时明显降低,而参附注射液组MAP水平较T0时则明显升高,至T2时参附注射液组MAP已明显高于西医对照组[mmHg(1 mmHg=0.133 kPa): 66.6 ± 6.5 比 53.1 ± 6.7 , $P<0.05$]。两组患儿T0~T1时肾上腺素及去甲肾上腺素比较差异无统计学意义($P>0.05$),随时间延长,均较T0时明显降低,但同一时间点两组比较差异无统计学意义(均 $P>0.05$)。T0时两组SCr和eGFR比较差异无统计学意义(均 $P>0.05$),T1时两组SCr均较T0时明显增高,但参附注射液组SCr水平却明显低于西医对照组($\mu\text{mol/L}$: 42.43 ± 15.91 比 56.58 ± 16.80 , 均 $P<0.05$),T2开始两组SCr逐渐降低,但仍明显高于T0,两组均于T4达到最低水平,且参附注射液组T4时SCr水平明显低于西医对照组($\mu\text{mol/L}$: 36.24 ± 9.72 比 46.85 ± 15.91 , $P<0.05$)。两组T1~T4时eGFR均较T0明显降低,但随着时间延长均逐渐升高,T4时达到最高水平,且参附注射液组明显高于西医对照组($\text{mL}\cdot\text{min}^{-1}\cdot1.73\text{ m}^{-2}$: 113.7 ± 12.1 比 79.6 ± 12.5 , $P<0.05$)。参附注射液组术后AKI发生率显著低于西医对照组[22.58%(7/31)比64.52%(20/31), $P<0.05$]。**结论** 参附注射液可减少小儿先天性心脏病术后AKI的发生。

【关键词】 参附注射液; 小儿; 先天性心脏病; 术后; 急性肾损伤

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【Abstract】 Objective To investigate the effect of Shenfu Injection on acute renal injury (AKI) in children with congenital heart disease after operation. **Methods** Sixty-two children with atrial or ventricular septal defect, treated in Affiliated Hospital of Southwest Medical University from August 2016 to December 2018, were divided into two groups according to different treatment methods, such as conventional Western medicine treatment group and Shenfu Injection group, with 31 cases in each group. The children in Shenfu Injection group were given 20 mL Shenfu Injection from the beginning of anesthesia induction to the end of cardiopulmonary bypass, the children in Western medicine conventional treatment group were pumped with the same volume of normal saline. The anesthesia time, total operation time, cardiopulmonary bypass time, aortic clamping time, and the use of milrinone, dopamine, epinephrine, sodium nitroprusside and other drugs in the two groups were observed. The serum creatinine (SCr) level was measured by chemiluminescence method before operation (T0), at the beginning of operation (T1), at the beginning of cardiopulmonary bypass (T2), at the end of cardiopulmonary bypass (T3) and at the end of operation (T4), and the glomerular filtration rate (eGFR) was calculated. The mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), adrenaline (E) and noradrenaline (NE) in two groups were recorded at each time point. **Results** There was no significant difference in anesthesia time, total operation time, cardiopulmonary bypass time, aortic clamping time and the use of milrinone, dopamine, E and sodium nitroprusside between the Shenfu Injection group and Western medicine conventional treatment group (all $P>0.05$). There was no significant difference in HR and CVP between the two groups at T0-T4 (all $P>0.05$). There was no significant difference in MAP level between the two groups at T0 and T1 (both $P>0.05$), with the time prolonging, the MAP level of Western medicine conventional treatment group was significantly lower than that of T0, while MAP level of Shenfu Injection group was significantly higher than that of T0. At T2, the MAP level of Shenfu Injection group was significantly higher than that of the Western medicine conventional treatment group [mmHg

(1 mmHg = 0.133 kPa): 66.6 ± 6.5 vs. 53.1 ± 6.7 , $P < 0.05$]. There was no significant difference in E and NE between the two groups at T0 and T1 ($P > 0.05$), with the time prolonging, both E and NE decreased compared with those at T0 (both $P < 0.05$), but there was no significant difference at the same time point (all $P > 0.05$). At T0, there was no significant difference in SCr and eGFRs between the two groups (both $P > 0.05$), at T1, the SCr levels of two groups were significantly higher than those at T0, but the SCr level of Shenfu Injection group was significantly lower than that of Western medicine conventional treatment group ($\mu\text{mol/L}$: 42.43 ± 15.91 vs. 56.58 ± 16.80 , all $P < 0.05$). From T2, the SCr levels of two groups began to gradually reduce, but it was still significantly higher than those at T0, the two groups reached the lowest level at T4, and the level of SCr in Shenfu Injection group was significantly lower than that of Western medicine conventional treatment group ($\mu\text{mol/L}$: 36.24 ± 9.72 vs. 46.85 ± 15.91 , $P < 0.05$). Compared with T0, the eGFRs levels of the two groups were significantly lower at T1–T4, but gradually increased with time, reached the highest level at T4, and the eGFRs level of Shenfu Injection group was significantly higher than that of Western medicine conventional treatment group ($\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$: 113.7 ± 12.1 vs. 79.6 ± 12.5 , $P < 0.05$). The incidence of AKI in Shenfu Injection group was significantly lower than that in Western medicine conventional treatment group [22.58% (7/31) vs. 64.52% (20/31), $P < 0.05$]. **Conclusion** Shenfu Injection can reduce the incidence of AKI in children with congenital heart disease after operation.

【Key words】 Shenfu Injection; Children; Congenital heart disease; After operation; Acute kidney injury

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急性肾损伤 (AKI) 是先天性心脏病术后患儿常见的并发症。虽然肾功能恶化是先天性心脏病术后患儿一种常见现象,但如果不能进行有效治疗,最终将发展成为肾衰竭或终末期肾脏病,严重影响患儿术后恢复,甚至导致患儿死亡^[1]。相关研究显示,参附注射液对急性冠脉综合征 (ASC) 患者冠状动脉 (冠脉) 介入术后及脓毒症合并 AKI 肾功能有良好的保护作用^[2-3]。但参附注射液是否能预防先天性心脏病患儿术后 AKI 的发生尚未明确。因此,本研究观察参附注射液对先天性心脏病术后患儿肾功能的影响,为临床预防先天性心脏病术后患儿 AKI 的发生提供一定依据。

1 资料与方法

1.1 病例选择: 选择 2016 年 8 月至 2018 年 12 月入住本院进行心房或心室间隔缺损修补术的患儿 62 例。

1.1.1 纳入标准: ① 年龄 1~14 岁; ② 行心房或心室间隔缺损修补术。

1.1.2 排除标准: 术前肌酐 (Cr) $\geq 61.88 \mu\text{mol/L}$ 、紫绀型心脏病、各种心律失常、动脉导管未闭、主动脉狭窄、严重左心室功能障碍〔经胸超声心动图检查显示射血分数 (EF) < 0.05 〕、右心衰竭等。

1.1.3 伦理学: 本研究符合医学伦理学标准并获得医院伦理委员会的批准 (审批号: K2018-11-13), 对患儿采取的治疗和检测均得到过患儿监护人的知情同意,并签署知情同意书。

1.2 研究分组: 将患儿按治疗方法不同分为西医对照组和参附注射液组,每组 31 例。

1.3 治疗方法: 患儿入院后,快速建立外周静脉通道,静脉注射氯胺酮 $1 \sim 2 \text{ mg/kg}$,待患儿安静后,连接相关监护设备。麻醉诱导: 咪达唑仑 0.2 mg/kg 、

丙泊酚 2 mg/kg 、舒芬太尼 $1 \sim 2 \mu\text{g/kg}$ 、维库溴铵 $0.1 \sim 0.2 \text{ mg/kg}$, 3 min 后行气管插管,麻醉维持: 七氟醚 $2\% \sim 3\%$ 、丙泊酚 $1 \sim 5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ 、舒芬太尼 $1 \sim 2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, 间断推注维库溴铵 $0.1 \sim 0.2 \text{ mg/kg}$, 整个麻醉期间脑电双频指数 (BIS) 维持在 $40 \sim 60$ 。麻醉诱导后,分别行桡动脉、颈内静脉穿刺置管测定动脉压和中心静脉压。从麻醉诱导至体外循环结束参附注射液组患儿给予 20 mL 参附注射液; 西医对照组患儿给予相同体积的生理盐水。整个麻醉及手术过程中根据患儿病情静脉泵注米力农、多巴胺、肾上腺素、硝普钠等。麻醉及手术操作均由同一组医生完成。

1.4 指标收集

1.4.1 不同治疗方法两组先天性心脏病术后 AKI 患儿基本情况: 收集两组患者性别、年龄、身高、手术类型、麻醉时间、手术总时间、主动脉夹闭时间和米力农、多巴胺、肾上腺素、硝普钠等使用情况。

1.4.2 不同治疗方法两组先天性心脏病术后 AKI 患儿术中观察指标: 于术前 (T0)、手术开始 (T1)、体外循环开始 (T2)、体外循环结束 (T3)、手术结束 (T4) 5 个时间点,取患儿肘静脉血 3 mL,低温离心 5 min,取上清液,置于 -80°C 深低温冰箱待检。采用化学发光法测定血清肌酐 (SCr) 水平,并计算肾小球滤过率 (eGFR)。根据 AKI 诊断标准,AKI 定义为术后 3 d 内 SCr 绝对增加 $\geq 22.89 \mu\text{mol/L}$ 或 SCr 增加百分比 $\geq 50\%$; 并收集两组患儿平均动脉压 (MAP)、心率 (HR)、中心静脉压 (CVP)、肾上腺素和去甲肾上腺素等资料。术后患儿均由同一组 ICU 医生及手术医生进行管理。

1.5 统计学方法: 使用 SPSS 19.0 统计分析数据,符合正态分布的计量资料以均数 $\pm$ 标准差

表 1 不同治疗方法两组先天性心脏病患儿一般资料比较

组别	例数 (例)	性别(例)		年龄 (岁, $\bar{x} \pm s$)	体质量 (kg, $\bar{x} \pm s$)	身高 (cm, $\bar{x} \pm s$)	手术类型(例)	
		男性	女性				房间隔缺损	室间隔缺损
西医对照组	31	18	13	3.2 ± 1.0	11.3 ± 2.3	86.2 ± 11.2	5	26
参附注射液组	31	20	11	3.4 ± 1.1	12.1 ± 2.2	87.4 ± 12.1	6	25
组别	麻醉时间 (min, $\bar{x} \pm s$)	手术总时间 (min, $\bar{x} \pm s$)	体外循环时间 (min, $\bar{x} \pm s$)	主动脉夹闭时间 (min, $\bar{x} \pm s$)	药物使用情况(例)			
					米力农	多巴胺	肾上腺素	硝普钠
西医对照组	253.2 ± 56.1	192.8 ± 45.4	92.2 ± 28.1	65.4 ± 22.6	20	25	6	10
参附注射液组	248.3 ± 52.4	185.2 ± 42.3	93.1 ± 29.3	68.2 ± 23.8	18	26	5	12

($\bar{x} \pm s$)表示,采用独立样本 t 检验;计数资料以例表示,采用 χ^2 检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 不同治疗方法两组先天性心脏病患儿基本情况比较(表 1):两组患儿性别、年龄、体质量、身高、手术类型、麻醉时间、手术总时间、体外循环时间、主动脉夹闭时间和米力农、多巴胺、肾上腺素、硝普钠等药物使用情况比较差异均无统计学意义

(均 $P > 0.05$),说明两组资料均衡,有可比性。

2.2 不同治疗方法两组先天性心脏病患儿术中 MAP、HR、CVP、肾上腺素、去甲肾上腺素水平的比较(表 2):两组患儿 T0 ~ T4 时 HR、CVP 比较差异无统计学意义($P > 0.05$)。随时间延长西医对照组 MAP 均较 T0 时降低;参附注射液组除 T1 时外其余各时间点均较 T0 时明显升高;且参附注射液组 T2 ~ T4 时 MAP 明显高于西医对照组(均 $P < 0.05$)。

两组患儿 T0 ~ T1 时肾上腺素及去甲肾上腺素水平比较差异无统计学意义($P > 0.05$),随时间延长均较 T0 时降低(均 $P < 0.05$),但同一时间点两组比较差异无统计学意义(均 $P > 0.05$)。

2.3 不同治疗方法两组先天性心脏病患儿术后 SCr、eGFR 水平比较(表 3):两组患儿 T0 时 SCr 和 eGFR 比较差异无统计学意义($P > 0.05$);T1 ~ T4 时两组 SCr、eGFR 均较 T0 时明显降低;参附注射液组 T1 ~ T4 各时间点 SCr 均明显低于西医对照组,eGFR 均明显高于西医对照组(均 $P < 0.05$)。

2.4 不同治疗方法两组先天性心脏病患儿术后 AKI 发生率比较:参附注射液组术后 AKI 发生率较西医对照组明显降低[22.58%(7/31)比 64.52%(20/31), $P < 0.05$]。

3 讨论

本研究结果显示,参附注射液可降低小儿先天性心脏病术后 SCr 水平,增加 eGFR,

表 2 不同治疗方法两组先天性心脏病患儿 MAP、HR、CVP、肾上腺素、去甲肾上腺素比较($\bar{x} \pm s$)

组别	例数 (例)	MAP(mmHg)				
		T0	T1	T2	T3	T4
西医对照组	31	64.2 ± 5.1	62.4 ± 4.5	53.1 ± 6.7 ^a	55.2 ± 6.6 ^a	53.5 ± 5.7 ^a
参附注射液组	31	63.3 ± 5.2	61.2 ± 4.8	66.6 ± 6.5 ^{ab}	65.8 ± 6.8 ^{ab}	64.6 ± 5.6 ^{ab}
组别	例数 (例)	HR(次/min)				
		T0	T1	T2	T3	T4
西医对照组	31	113.4 ± 17.3	123.5 ± 17.6	125.3 ± 17.2	117.6 ± 15.6	112.7 ± 16.3
参附注射液组	31	116.2 ± 18.1	121.5 ± 18.3	113.6 ± 16.9	112.4 ± 14.5	108.2 ± 14.6
组别	例数 (例)	CVP(mmHg)				
		T0	T1	T2	T3	T4
西医对照组	31	6.2 ± 2.1	8.3 ± 2.5	7.2 ± 2.3	7.1 ± 2.6	7.5 ± 2.8
参附注射液组	31	6.3 ± 2.2	8.1 ± 2.2	7.0 ± 2.1	7.1 ± 2.5	7.3 ± 2.6
组别	例数 (例)	肾上腺素(mg/L)				
		T0	T1	T2	T3	T4
西医对照组	31	142.3 ± 5.2	145.5 ± 6.1	132.4 ± 5.3 ^a	128.6 ± 4.8 ^a	125.6 ± 4.5 ^a
参附注射液组	31	145.6 ± 5.5	146.4 ± 5.9	132.5 ± 6.1 ^a	131.5 ± 5.5 ^a	129.6 ± 5.8 ^a
组别	例数 (例)	去甲肾上腺素(mg/L)				
		T0	T1	T2	T3	T4
西医对照组	31	132.1 ± 8.6	131.4 ± 8.2	121.3 ± 7.5 ^a	118.5 ± 7.2 ^a	116.3 ± 6.8 ^a
参附注射液组	31	133.2 ± 8.1	133.0 ± 8.5	120.2 ± 7.9 ^a	118.4 ± 8.4 ^a	115.3 ± 6.5 ^a

注:与本组 T0 时比较,^a $P < 0.05$;与西医对照组比较,^b $P < 0.05$;1 mmHg=0.133 kPa

表 3 不同治疗方法两组先天性心脏病患儿血 SCr 和 eGFR 水平比较($\bar{x} \pm s$)

组别	例数 (例)	SCr($\mu\text{mol/L}$)				
		T0	T1	T2	T3	T4
西医对照组	31	28.29 ± 2.00	56.58 ± 16.80 ^a	51.27 ± 15.03 ^a	48.62 ± 14.14 ^a	46.85 ± 15.91 ^a
参附注射液组	31	29.17 ± 14.14	42.43 ± 15.91 ^{ab}	39.78 ± 14.14 ^{ab}	37.13 ± 13.26 ^{ab}	36.24 ± 9.72 ^{ab}
组别	例数 (例)	eGFR($\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)				
		T0	T1	T2	T3	T4
西医对照组	31	123.6 ± 16.3	72.3 ± 11.5 ^a	73.6 ± 11.9 ^a	75.8 ± 12.8 ^a	79.6 ± 12.5 ^a
参附注射液组	31	125.6 ± 15.6	105.3 ± 12.8 ^{ab}	108.3 ± 12.5 ^{ab}	112.3 ± 12.6 ^{ab}	113.7 ± 12.1 ^{ab}

注:与本组 T0 时比较,^a $P < 0.05$;与西医对照组比较,^b $P < 0.05$

最终降低术后 AKI 的发生。

小儿先天性心脏病术后发生 AKI 的机制包括心脏手术引发的全身炎症反应增加了炎症细胞因子、内毒素和代谢产物的释放^[4]；其次，心脏手术也可导致缺血/再灌注(I/R)损伤、氧化应激和神经内分泌激活^[5]；再者，I/R 过程中产生的大量氧自由基促进了肾小管上皮细胞凋亡，使抗氧化酶和过氧化物活化酶的活性降低，脂质过氧化反应显著增加，进一步造成肾小管损伤^[6]。

参附注射液是中药复方制剂参附汤提取物，其有效成分为人参皂苷、附子和乌头类生物碱，具有较强的拟交感神经作用，可同时兴奋 α 、 β 受体，从而起到减轻心肌缺血性损伤，增强心肌收缩力，增加心排血量，改善微循环的作用，近来其在感染性疾病、心血管疾病和心肺复苏等急危重症的治疗方面中起到了积极作用^[7]。参附注射液可通过增加一氧化氮(NO)水平舒张血管^[8-9]。同时参附注射液对肾脏 I/R 损伤有明显的保护作用，可直接灭活黄嘌呤氧化酶，清除氧自由基，降低脂质过氧化水平，其中人参皂苷有增加谷胱甘肽过氧化物酶(GSH-Px)活性，减轻线粒体肿胀，降低肾血管阻力，增加肾血流量，有效纠正低氧血症，保护肾功能^[10]。此外，乌头类生物碱是 β 受体激动剂，能显著增加心肌收缩力和心排血量，升高血压；人参皂苷有与强心苷相似的作用，能改善微循环，降低左室舒张期末内径(LVEDD)和 B 型钠尿肽(BNP)水平，升高左室射血分数(LVEF)、增强机体的适应性，达到升压稳压的作用^[11]。相关研究显示，参附注射液也可降低血黏度，改善微循环，延长动物耐缺氧时间，抗休克和脂质氧化，调节免疫功能，改善血液流变学等^[12-13]。本研究显示，西医对照组 T1 后 MAP 降低，而参附注射液组 T1 后 MAP 无明显变化，参附注射液组 MAP 较西医对照组相对更稳定。两组肾上腺素和去甲肾上腺素水平比较差异均无统计学意义。因此，在行小儿先天性心脏病手术后，给予参附注射液可稳定血流动力学，这可能成为肾功能保护的因素之一。

本研究使用参附注射液的 31 例患儿中，仍有 7 例患儿发生 AKI，可能与 AKI 发生的复杂病理机制有关，仍需进一步研究。

综上所述，参附注射液可减少小儿先天性心脏病术后 AKI 的发生，其发挥肾功能保护作用机制可能与其提供了更为稳定的血流动力学有关。

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