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右美托咪定联合丙泊酚对体外循环下心脏瓣膜置换术患者心肌损伤、肾功能和细胞免疫功能的影响*

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摘要 目的:观察右美托咪定联合丙泊酚对体外循环(CPB)下心脏瓣膜置换术患者心肌损伤、肾功能和细胞免疫功能的影响。方法:回顾性分析2020年1月~2020年12月期间新疆医科大学第一附属医院收治的120例CPB下心脏瓣膜置换术患者的临床资料,根据麻醉方案的不同将患者分为对照组和研究组,各为60例,对照组患者接受丙泊酚麻醉,研究组患者接受右美托咪定联合丙泊酚麻醉。观察两组患者围术期指标、血流动力学、心肌损伤、肾功能和细胞免疫功能变化情况,记录两组围术期不良反应发生情况。结果:研究组患者的心脏复跳时间、术后苏醒时间、术后拔管时间、ICU滞留时间、术后住院时间均短于对照组患者($P<0.05$)。术前(T0)~术毕(T3)时间点,两组患者的平均动脉压(MAP)、心率(HR)先下降后升高,肌酸激酶同工酶(CK-MB)和肌钙蛋白I(cTnI)水平则持续升高($P<0.05$),但CPB开始后30 min(T1)~T3时间点,研究组患者的MAP、HR高于对照组患者,CK-MB、cTnI水平则低于对照组患者($P<0.05$)。两组患者T0、术中、术后24 h的尿素氮(BUN)、血清胱抑素C(CysC)水平呈升高趋势($P<0.05$)。术中、术后24 h两组患者的CD4⁺、CD4⁺/CD8⁺均较T0下降,但研究组高于对照组($P<0.05$);术中、术后24 h两组患者的CD8⁺较T0升高,但研究组低于对照组($P<0.05$)。两组不良反应发生率对比无统计学差异($P>0.05$)。结论:右美托咪定联合丙泊酚应用于CPB下心脏瓣膜置换术患者,可减轻心肌损伤和细胞免疫功能抑制,维持血流动力学稳定,且不增加肾功能损伤和不良反应发生率。

关键词:右美托咪定;丙泊酚;体外循环;心脏瓣膜置换术;心肌损伤;肾功能;细胞免疫功能

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Effects of Dexmedetomidine Combined with Propofol on Myocardial Injury, Renal Function and Cellular Immune Function in Patients Undergoing Heart Valve Replacement under Cardiopulmonary Bypass*

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ABSTRACT Objective: To observe the effects of dexmedetomidine combined with propofol on myocardial injury, renal function and cellular immune function in patients undergoing cardiac valve replacement under cardiopulmonary bypass (CPB). **Methods:** The clinical data of 120 patients with cardiac valve replacement under CPB who were treated in the First Affiliated Hospital of Xinjiang Medical University from January 2020 to December 2020 were analyzed retrospectively, they were randomly divided into control group and study group according to different anesthesia schemes, with 60 cases in each group. Patients in the control group received propofol anesthesia, and patients in the study group received dexmedetomidine combined with propofol anesthesia. The perioperative indexes, hemodynamics, myocardial injury, renal function and cellular immune function in the two groups were observed, and the perioperative adverse reactions in the two groups were recorded. **Results:** The cardiac repulse time, postoperative recovery time, postoperative extubation time, ICU stay time and postoperative hospitalization time in the study group were shorter than those in the control group ($P<0.05$). The mean arterial pressure (MAP) and heart rate (HR) decreased first and then increased in two groups from pre-operation (T0) to post-operation (T3) time point, while the levels of creatine kinase isoenzyme (CK-MB) and troponin I (cTnI) continued to increase ($P<0.05$), but 30min after CPB (T1) to T3 time point, MAP and HR in the study group were higher than those in the control group, while the levels of CK-MB and cTnI were lower than those in the control group ($P<0.05$). The levels of brea nitrogen (BUN), serum cystatin C(CysC) showed an upward trend at T0, intraoperative and postoperative 24 hours in two groups ($P<0.05$). CD4⁺ and CD4⁺/CD8⁺ at intraoperative and postoperative 24

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hours in two groups decreased compared with T0, but the study group was higher than the control group ($P<0.05$), CD8⁺ at intraoperative and postoperative 24 hours in two groups increased compared with T0, but the study group was lower than the control group ($P<0.05$). There was no statistical difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Dexmedetomidine combined with propofol in patients undergoing cardiac valve replacement under CPB can reduce myocardial injury and inhibition of cellular immune function, maintain hemodynamic stability, and do not increase the incidence of renal function injury and adverse reactions.

Key words: Dexmedetomidine; Propofol; Cardiopulmonary bypass; Heart valve replacement; Myocardial injury; Renal function; Cellular immune function

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前言

体外循环(CPB)下心脏瓣膜置换术是目前临床中广泛应用的重要手术方式,其属有创术式,加之CPB下血液和人工管道接触、血液稀释、缺血再灌注等因素,可导致机体产生应激反应,产生血流波动,造成多脏器功能及免疫功能损伤^[1-3]。安全有效的麻醉方案对于CPB下心脏瓣膜置换术的顺利进行至关重要。丙泊酚是临床中广泛应用的强效、快速的全身麻醉剂,具有起效快、进入麻醉平稳、苏醒迅速以及术后恶心、呕吐发生率低等优点,但其心肌保护作用效果稍弱^[4]。右美托咪定属新型α2肾上腺素受体激动剂,具有抗焦虑、镇痛/镇静、抗交感等多种作用,被广泛应用于麻醉时辅助镇静^[5]。鉴于此,本文回顾性分析120例CPB下心脏瓣膜置换术患者的临床资料,旨在观察右美托咪定联合丙泊酚的应用价值,以期为此类患者临床麻醉方案的选择提供依据。

1 资料与方法

1.1 一般资料

回顾性分析2020年1月~2020年12月期间新疆医科大学第一附属医院收治的120例CPB下心脏瓣膜置换术患者的临床资料,纳入标准:(1)均符合手术指征,成功完成手术;(2)均为初次换瓣,左室射血分数(LVEF)>40%;(3)美国麻醉协会(ASA)分级II~III级,纽约心功能分级(NYHA)II~III级;(4)术前简易智力状态检查量表(MMSE)^[6]评分≥26分;(5)实施手术操作及麻醉管理均为同一组人员;(6)对本研究所用麻醉药物无禁忌症。排除标准:(1)合并恶性肿瘤、急慢性感染;(2)存在肝、肺、肾等脏器严重功能障碍;(3)长期使用镇静与抗抑郁药物;(4)合并呼吸循环系统、免疫系统疾病;(5)存在凝血功能障碍者;(6)合并严重高血压、糖尿病等合并症。临床病例及分组:120例CPB下心脏瓣膜置换术患者根据麻醉方案的不同分为对照组(n=60)和研究组(n=60),对照组女28例,男32例,平均年龄(59.86±4.73)岁;ASA分级:II级32例,III级28例;行单纯主动脉瓣置换术6例、单纯二尖瓣置换术43例、主动脉瓣与二尖瓣双瓣置换术11例;NYHA分级:II级34例,III级26例;平均体质量指数(23.82±2.41)kg/m²。研究组女26例,男34例,平均年龄(59.15±5.14)岁;ASA分级:II级33例,III级27例;行单纯主动脉瓣置换术5例、单纯二尖瓣置换术46例、主动脉瓣与二尖瓣双瓣置换术9例;NYHA分级:II级36例,III级24例;平均体质量指数(24.07±2.38)kg/m²。两组患者一般资料对比无统计学差异($P>0.05$),具有可比性。

1.2 方法

患者入手术室后开放外周静脉通道,行生命体征监护。麻醉诱导:依次静脉注射2.00mg咪达唑仑注射液[国药准字H20067040,规格:2mL:2mg(以咪达唑仑计),宜昌人福药业有限责任公司]、0.20mg/kg依托咪酯注射液(国药准字H32022992,规格:10mL:20mg,江苏恩华药业股份有限公司)、2~3μg/kg枸橼酸舒芬太尼注射液(国药准字H20203712,规格:按C22H30N2O2S计1mL:50μg,国药集团工业有限公司廊坊分公司)、0.6~1mg/kg罗库溴铵注射液(国药准字H20183106,规格:5mL:50mg,福安药业集团庆余堂制药有限公司)。气管插管后,对照组患者以恒速泵注5.00mg/(kg·h)丙泊酚乳状注射液(国药准字H20143369,规格:50mL:1g,广东嘉博制药有限公司);研究组患者则在恒速泵注5.00mg/(kg·h)丙泊酚的基础上加用4μg/(kg·h)的盐酸右美托咪定注射液[国药准字H20163388,规格:2mL:0.2mg(按右美托咪定计),辰欣药业股份有限公司]干预。达深度麻醉后,以4.00~6.00mg/(kg·h)丙泊酚、0.6~1mg/(kg·h)罗库溴铵进行麻醉维持,间断追加1~2μg/kg枸橼酸舒芬太尼注射液。采用浅低温30℃对患者进行CPB,保持活化凝血时间>480s,红细胞比容25%~30%,维持灌注量在2.0~2.4L/(m²·min),心脏复跳后辅助循环约为主动脉阻断时间的30%,在患者电解质及酸碱平衡等指标稳定后平稳停机。送ICU后,待患者自主呼吸恢复,意识恢复,血流动力学稳定,查血气分析无明显异常,即可以拔除气管导管。

1.3 观察指标

(1)观察两组患者的心脏复跳时间、术后苏醒时间、术后拔管时间、ICU滞留时间、术后住院时间。(2)记录两组患者术前(T0)、CPB开始后30 min(T1)、CPB结束(T2)、术毕(T3)时的平均动脉压(MAP)、心率(HR)。采集所有患者上述各时间点的中心静脉血2mL,离心处理后取血清以免疫抑制速率法检测血清肌酸激酶同工酶(CK-MB)和肌钙蛋白I(cTnI)水平,试剂盒购自武汉博士德生物工程有限公司。(3)采集所有患者T0、术中、术后24 h的外周静脉血标本6mL,取3mL应用美国库尔特(COULTER)公司生产的EPICSXL流式细胞仪测定血清CD4⁺、CD8⁺T淋巴细胞比例,并计算CD4⁺/CD8⁺。另3mL离心处理后取血清采用手工酶法检测尿素氮(BUN)水平,以免免疫比浊法检测两组患者血清胱抑素C(CysC)水平。(4)记录两组患者围术期不良反应发生情况。

1.4 统计学方法

以SPSS23.0软件进行数据分析。计量资料以MEAN±SD表示,组间比较采用t检验。计数资料以n(%)表示,组间比较

采用卡方检验。使用 Bonferroni 校正法对时间维度多次比较的检验水准进行调整。检验水准为 $\alpha=0.05$ 。

2 结果

2.1 两组患者围术期指标对比

研究组患者的心脏复跳时间、术后苏醒时间、术后拔管时间、ICU 滞留时间、术后住院时间均短于对照组患者($P<0.05$)，见表 1。

2.2 两组患者血流动力学、心肌损伤指标对比

T0 时间点，两组患者的 MAP、HR、CK-MB、cTnI 水平对比差异无统计学意义 ($P>0.05$)。T1~T3 时间点，两组患者的 MAP、HR 先下降后升高，CK-MB、cTnI 水平则持续升高 ($P<0.05$)。T1~T3 时间点，研究组患者的 MAP、HR 高于对照组患者，CK-MB、cTnI 水平则低于对照组患者 ($P<0.05$)。见表 2。

2.3 两组患者肾功能指标对比

两组患者 T0、术中、术后 24 h 的 BUN、CysC 水平呈升高趋势，组内不同时间点对比差异有统计学意义 ($P<0.05$)，但两组患者 T0、术中、术后 24 h 的 BUN、CysC 水平组间对比无统计学差异 ($P>0.05$)，见表 3。

2.4 两组患者细胞免疫功能指标对比

T0 时间点，两组患者的 CD4⁺、CD8⁺、CD4⁺/CD8⁺ 对比差异无统计学意义 ($P>0.05$)。术中、术后 24 h 两组患者的 CD8⁺ 升高，但研究组低于对照组 ($P<0.05$)。术中、术后 24 h 两组患者的 CD4⁺、CD4⁺/CD8⁺ 下降，但研究组高于对照组 ($P<0.05$)。见表 4。

2.5 两组不良反应发生率对比

研究组发生恶心 1 例，呕吐 2 例，低血压 1 例，心搏徐缓 1 例。对照组出现恶心 2 例，呕吐 1 例。对照组 5.00%(3/60) 与研究组 8.33%(5/60) 不良反应发生率组间对比无统计学差异 ($\chi^2=0.536, P=0.464$)。

表 1 两组患者围术期指标对比($\bar{x}\pm s$)

Table 1 Comparison of perioperative indexes between the two groups($\bar{x}\pm s$)

Groups	Cardiac repulse time (s)	Postoperative recovery time(h)	Postoperative extubation time(h)	ICU stay time(h)	Postoperative hospitalization time(d)
Control group(n=60)	103.54± 9.63	7.15± 0.71	16.28± 2.31	29.64± 2.57*	18.32± 1.41
Study group(n=60)	96.03± 8.54	6.02± 0.55	13.12± 2.24	26.17± 2.61	15.08± 1.53
t	4.520	9.746	7.607	7.388	12.062
P	0.000	0.000	0.000	0.000	0.000

表 2 两组患者血流动力学、心肌损伤指标对比($\bar{x}\pm s$)

Table 2 Comparison of hemodynamics and myocardial injury indexes between the two groups($\bar{x}\pm s$)

Groups	Time points	MAP(mmHg)	HR(beats/min)	CK-MB(μ/ml)	cTnI(ng/ml)
Control group(n=60)	T0	95.11± 5.28	84.97± 6.34	23.95± 2.24	0.29± 0.06
	T1	82.29± 5.13 ^a	69.02± 5.33 ^a	51.97± 6.28 ^a	0.78± 0.09 ^a
	T2	85.14± 4.26 ^{ab}	73.04± 5.29 ^{ab}	89.91± 5.13 ^{ab}	0.92± 0.14 ^{ab}
	T3	88.25± 4.24 ^{abc}	77.26± 6.22 ^{abc}	118.31± 6.24 ^{abc}	1.27± 0.18 ^{abc}
Study group(n=60)	T0	94.96± 5.27	85.76± 7.31	23.49± 2.73	0.29± 0.04
	T1	85.16± 4.22 ^{ad}	73.17± 5.23 ^{ad}	34.56± 2.48 ^{ad}	0.44± 0.06 ^{ad}
	T2	88.04± 3.28 ^{abd}	77.76± 5.87 ^{abd}	67.04± 5.34 ^{abd}	0.73± 0.09 ^{abd}
	T3	91.38± 4.22 ^{abcd}	81.98± 6.74 ^{abcd}	95.93± 6.32 ^{abcd}	0.92± 0.13 ^{abcd}

Note: compared with T0 in the same group, ^a $P<0.05$. Compared with T1 in the same group, ^b $P<0.05$. Compared with T2 in the same group, ^c $P<0.05$. Compared with the control group, ^d $P<0.05$.

表 3 两组患者肾功能指标对比($\bar{x}\pm s$)

Table 3 Comparison of renal function indexes between the two groups($\bar{x}\pm s$)

Groups	Time points	BUN(mmol/L)	CysC(mg/L)
Control group(n=60)	T0	6.38± 0.69	0.81± 0.7
	Intraoperative	7.92± 0.74 ^a	0.94± 0.08 ^a
	Postoperative 24 hours	10.26± 0.83 ^{ab}	1.08± 0.09 ^{ab}
Study group(n=60)	T0	6.43± 0.72	0.82± 0.09
	Intraoperative	7.84± 0.68 ^a	0.93± 0.10 ^a
	Postoperative 24 hours	10.21± 0.66 ^{ab}	1.08± 0.12 ^{ab}

Note: compared with T0 in the same group, ^a $P<0.05$. Compared with intraoperative in the same group, ^b $P<0.05$.

表 4 两组患者细胞免疫功能指标对比($\bar{x} \pm s$)Table 4 Comparison of cellular immune function indexes between the two groups($\bar{x} \pm s$)

Groups	Time points	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺
Control group(n=60)	T0	36.19± 5.35	23.02± 1.37	1.57± 0.22
	Intraoperative	26.27± 4.34 ^a	29.16± 1.52 ^a	0.90± 0.15 ^a
	Postoperative 24 hours	21.22± 3.29 ^{ab}	33.07± 2.26 ^{ab}	0.64± 0.11 ^{ab}
Study group(n=60)	T0	36.25± 4.26	23.09± 1.45	1.57± 0.28
	Intraoperative	31.37± 4.72 ^{ac}	26.22± 2.61 ^{ac}	1.20± 0.13 ^{ac}
	Postoperative 24 hours	27.11± 4.63 ^{abc}	29.86± 2.54 ^{abc}	0.91± 0.12 ^{abc}

Note: compared with T0 in the same group, ^aP<0.05. Compared with intraoperative in the same group, ^bP<0.05.

Compared with the control group, ^cP<0.05.

3 讨论

CPB 下心脏瓣膜置换术是指在手术过程中采用 CPB 相关仪器装置将静脉血引流至体外及调节温度后回输动脉系统的操作,可保证在心脏停跳的情况下,体内脏器仍能获得充足的血流灌注,同时也有利于获得清晰的心脏手术视野,顺利完成心脏瓣膜置换操作^[7,8]。CPB 过程中需要阻断主动脉,而在 CPB 使用结束后主动脉的再开放会造成心肌发生缺血再灌注,诱发心肌损伤^[9]。此外,行此类手术时整个机体处于控制性休克状态,通常伴有强烈应激反应,除了会引起血流波动外,还伴有不同程度的免疫抑制^[10,11]。因此,CPB 下心脏瓣膜置换术中采取多种的综合措施减轻心肌损伤、维持血流稳定、保护脏器、减轻免疫抑制尤为重要。丙泊酚是麻醉镇静、镇痛的常用药物,应用广泛^[12]。以往的研究证实^[13],丙泊酚也可在一定程度上保护心脏,但具有剂量依赖性。而丙泊酚的大量使用又易导致血流波动明显,增加不良反应发生风险^[14]。右美托咪定能产生近似自然睡眠的镇静及镇痛作用,已被证实动物心脏手术方面具有一定度的心肌保护作用^[15],既往临床实践也报道过右美托咪定对心脏手术的预后具有积极作用^[16]。

CPB 所提供的血流灌注为非生理性灌注,可造成内环境发生紊乱^[17]。本次研究结果显示,右美托咪定联合丙泊酚应用于 CPB 下心脏瓣膜置换术患者,可维持血流动力学稳定,减轻心肌损伤。右美托咪定可作用于中枢神经系统蓝斑核的突触后 α 受体产生睡眠、镇静及抗焦虑等作用^[18]。同时右美托咪定可结合神经元突触前后的 α 2A 受体,进而降低去甲肾上腺素的表达,减轻机体应激,从而维持血流稳定^[19]。而右美托咪定的心肌保护作用也得到了丁晶晶等^[20]学者的认同。CK-MB 和 CTnI 是心肌损伤的敏感指标,其水平可作为判断心脏复苏预后的指标^[21]。分析右美托咪定心肌保护效应的机制可能为右美托咪定能间接提升心脏迷走神经张力,降低心肌耗氧量,提升心肌储备能力^[22];同时右美托咪定可激活胆碱能抗炎通路,减少炎症细胞因子释放量,缓解心肌炎症反应^[23]。本次研究结果发现,右美托咪定联合丙泊酚应用于 CPB 下心脏瓣膜置换术患者可减轻免疫抑制。以往的研究证实右美托咪定可促使巨噬细胞激活,诱导细胞免疫反应,从而减轻免疫抑制^[24]。CPB 下心脏瓣膜置换术患者在手术期间处于控制性休克状态,一定程度上存在肾组织低灌注,加上血流通过非生物界面时容易造成患者应激

反应,这些均可导致肾损伤^[25-27]。BUN 是国内外广泛使用的筛查肾损伤的生物学指标^[28],CysC 是可反映早期肾小球滤过功能受损的有效指标^[29],结合本次研究结果发现,两种麻醉方案均不可避免的产生肾损伤,但右美托咪定联合丙泊酚不会增加肾功能损害。可能是因为右美托咪定通过激动外周、中枢交感神经突触前和肾脏局部的 α 受体,从而避免了肾血管的剧烈收缩^[30,31]。观察两组麻醉安全性可知,两组不良反应发生率,统计学方面对比差异不显著,说明右美托咪定联合丙泊酚治疗较为安全。

综上所述,丙泊酚联合右美托咪定应用于 CPB 下心脏瓣膜置换术患者,可减轻心肌损伤和细胞免疫功能抑制,维持血流动力学稳定,且不增加肾功能损伤和不良反应发生率,促进患者术后恢复,效果可靠。

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