

doi: 10.13241/j.cnki.pmb.2021.23.040

右美托咪定复合七氟醚对先天性心脏病介入封堵术患儿血流动力学、氧化应激反应和心肌损伤的影响*

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摘要 目的:观察右美托咪定复合七氟醚对先天性心脏病(CHD)介入封堵术患儿血流动力学、心肌损伤和氧化应激反应的影响。**方法:**选择2016年1月-2020年12月期间在我院择期行介入封堵术的CHD患儿106例。按照住院号奇偶顺序将患儿分为对照组(七氟醚麻醉)和观察组(右美托咪定复合七氟醚麻醉),各53例。观察两组围术期间的血流动力学、氧化应激反应和心肌损伤指标变化情况,记录两组患儿苏醒即刻的躁动评分和镇静评分、苏醒时间和围术期间的不良反应发生率。**结果:**两组T0~T4时间点心率(HR)均呈先升高后降低趋势,平均动脉压(MAP)均呈先降低后升高趋势($P<0.05$)。术后24 h,观察组血清超氧化物歧化酶(SOD)水平高于对照组,丙二醛(MDA)水平低于对照组($P<0.05$)。术后24 h,观察组血清肌酸激酶同工酶(CK-MB)、心肌肌钙蛋白I(cTnI)、心脏型脂肪酸结合蛋白(H-FABP)水平均低于对照组($P<0.05$)。观察组苏醒即刻的躁动评分低于对照组($P<0.05$)。两组患儿不良反应总发生率对比无差异($P>0.05$)。**结论:**右美托咪定复合七氟醚应用于行介入封堵术的CHD患儿,可减少躁动发生情况,同时不影响患儿血流动力学和苏醒情况,在减轻氧化应激、心肌损伤方面亦有一定的积极意义。

关键词:右美托咪定;七氟醚;先天性心脏病;介入封堵术;血流动力学;氧化应激;心肌损伤

中图分类号:R541.1;R614 **文献标识码:**A **文章编号:**1673-6273(2021)23-4588-05

Effects of Dexmedetomidine Combined with Sevoflurane on Hemodynamics, Oxidative Stress Reaction and Myocardial Injury in Children With Congenital Heart Disease Undergoing Transcatheter Closure*

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ABSTRACT Objective: To observe the effects of dexmedetomidine combined with sevoflurane on hemodynamics, myocardial injury and oxidative stress reaction in children with congenital heart disease (CHD) undergoing transcatheter closure. **Methods:** From January 2016 to December 2020, 106 children with CHD undergoing transcatheter closure in our hospital were selected. According to the hospitalization number odd-even order, the children were divided into control group (sevoflurane) and observation group (dexmedetomidine combined with sevoflurane), 53 cases in each group. The hemodynamics, oxidative stress reaction and myocardial injury indexes during the perioperative period of the two groups were observed. The the agitation score immediately after awakening, awakening time, the sedation score immediately after awakening and the incidence of perioperative adverse reactions were recorded in two groups. **Results:** Heart rate (HR) at T0~T4 time points in two groups showed a trend of increasing firstly and then decreasing, mean arterial pressure (MAP) was firstly decreased and then increased ($P<0.05$). 24 h after operation, the serum superoxide dismutase (SOD) level in observation group was higher than that in control group, and the serum malondialdehyde (MDA) level was lower than that of control group ($P<0.05$). 24 h after operation, the serum creatine kinase isoenzyme (CK-MB), cardiac troponin I(cTnI) and cardiac fatty acid binding protein (H-FABP) levels in observation group were lower than those in control group ($P<0.05$). The score of agitation score immediately after awakening in the observation group was lower than that in the control group ($P<0.05$). There was no significant difference in the total incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The application of dexmedetomidine combined with sevoflurane in children with CHD undergoing transcatheter closure can reduce the occurrence of agitation, and does not affect the hemodynamics and recovery of children. It also has certain positive significance in reducing oxidative stress and myocardial injury.

* 基金项目:山东省自然科学基金项目(ZR2013HM012)

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(收稿日期:2021-05-23 接受日期:2021-06-17)

Key words: Dexmedetomidine; Sevoflurane; Congenital heart disease; Transcatheter closure; Hemodynamics; Oxidative stress; Myocardial injury

Chinese Library Classification(CLC): R541.1; R614 **Document code:** A

Article ID: 1673-6273(2021)23-4588-05

前言

先天性心脏病(CHD)是小儿先天性畸形疾病的常见种类,人群发病率约为0.6%~0.8%^[1]。介入封堵术创伤小、术后并发症少、恢复快,在小儿CHD中得到广泛应用^[2],但儿童心理和生理均未发育成熟,多数患儿需在全麻下完成手术^[3]。目前临床针对小儿CHD介入封堵术中多选用七氟醚吸入保留自主呼吸的麻醉方法,但此类麻醉方案患儿术后苏醒慢,且不少患儿术后存在苏醒期躁动^[4]。右美托咪定是镇痛、镇静、抗交感作用较好的 α_2 肾上腺素能受体激动剂^[5]。已有研究证实少量的右美托咪定可预防七氟醚麻醉的术后躁动^[6],但有关右美托咪定复合七氟醚在小儿CHD介入封堵术的应用价值仍需进一步论证,本研究就此展开分析,以期临床介入封堵术中麻醉方案选择提供指导价值。

1 资料与方法

1.1 临床资料

选择2016年1月-2020年12月期间符合标准的106例择期行介入封堵术的CHD患儿。纳入标准:(1)所有患儿经心脏彩超确诊为CHD;(2)入院后经手术医师分析病例资料,符合介入封堵术手术指征者;(3)美国麻醉医师协会(ASA)^[7]分级I~II级者;(4)术前将麻醉风险告知患儿监护人,签署知情同意书;(5)心功能分级^[8]I~II级者。排除标准:(1)存在血液系统疾病;(2)心脏彩超显示患儿肺动脉高压;(3)伴有肺、肝、肾等器官功能障碍;(4)术前1周内肺部感染或发热。按照住院号奇偶顺序将患儿分为对照组和观察组,各53例。对照组男23例,女30例,年龄2~10岁,平均 (5.16 ± 1.38) 岁;ASA分级:I级29例,II级24例;心功能分级:I级27例,II级26例;疾病种类:室间隔缺损16例、房间隔缺损18例、房室间隔缺损12例、肺动脉瓣狭窄7例。观察组男22例,女31例,年龄2~8岁,平均 (5.19 ± 1.46) 岁;ASA分级:I级31例,II级22例;心功能分级:I级29例,II级24例;疾病种类:室间隔缺损15例、房间隔缺损17例、房室间隔缺损13例、肺动脉瓣狭窄8例。两组患儿一般资料对比无差异($P>0.05$),组间具有可比性。

1.2 方法

由监护人陪同患儿完成整次手术,进入手术室后采用Datex-Ohmeda S/5多功能麻醉监测仪(美国GE公司生产)常规监测患儿心电图等生命指征。诱导前予以硫酸阿托品注射液(国药准字H32022466,规格:1 mL:5 mg,江苏悦兴药业有限公司)0.01 mg/kg,丙泊酚乳状注射液(乐维静)(国药准字H20040079,规格:1 mL:0.1 g,四川国瑞药业有限责任公司)2 mg/kg。随后通过德国德尔格公司生产的Fabius plus麻醉机予以8%七氟醚(批准文号H20160431,规格:250 mL,Baxter Healthcare Corporation),限压阀压力0 cm H₂O条件下罩吸

入,氧流量5 L/min。术中持续吸入七氟醚维持麻醉至手术结束,术中根据呼吸末二氧化碳分压调整七氟醚吸入浓度,使呼吸末二氧化碳分压维持 <50 mmHg。观察组则在术中吸入七氟醚的同时予以盐酸右美托咪定注射液[国药准字H20090248,规格:2 mL:200 μ g(按右美托咪定计),江苏恒瑞医药股份有限公司]0.4 μ g/kg,持续泵注30 min。

1.3 观察指标

(1)血流动力学:监测两组患儿进入手术室时(T₀)、置入喉罩后(T₁)、穿刺即刻(T₂)、置封堵器即刻(T₃)和手术结束时(T₄)的平均动脉压(MAP)和心率(HR)。(2)氧化应激、心肌损伤指标:分别抽取两组患儿术前24h、术后24h空腹外周肘静脉血5 mL,置于肝素钠采血管中,标注住院号、时间、组别代码。在我院检测室检测,4℃下,2900 rpm分离血清,离心12分钟。分离待测,标本测定前室温下复融,采用比色法检测超氧化物歧化酶(SOD)水平(北京伊塔生物科技有限公司,货号:SY6460),采用酶联免疫吸附试验检测丙二醛(MDA)水平(北京百奥莱博科技有限公司,货号:ARB12124),采用双抗夹心法检测肌酸激酶同工酶(CK-MB)水平(北京百奥莱博科技有限公司,货号:ARB10700),采用酶联免疫吸附试验检测心肌肌钙蛋白I(cTnI)水平(上海广锐生物科技有限公司,货号:ELISA2362),采用用胶乳免疫比浊法检测心脏型脂肪酸结合蛋白(H-FABP)水平(上海信帆生物科技有限公司,货号:XF124-c)。(3)围术期指标:观察两组患儿苏醒时间、苏醒即刻的镇静评分、苏醒即刻的躁动评分,其中苏醒即刻的镇静评分为Ramsay镇静评分^[9],Ramsay镇静评分1~6分,其中烦躁不安为1分,安静合作为2分,嗜睡为3分,浅睡眠为4分,入睡为5分,深睡为6分。苏醒即刻的躁动评分0~4分,嗜睡记0分,清醒、安静合作记1分,哭闹记2分,烦躁但不需要制动记3分,需要制动记4分。其中2~4分为躁动状态^[10]。(4)不良反应:记录两组不良反应(恶心呕吐、窦性心动过缓、低血压、呼吸抑制等)发生情况。

1.4 统计学方法

采用SPSS 26.0软件分析数据。以[n(%)]表示计数资料,采用 χ^2 或Fisher检验。用Kolmogorov-Smirnov检验数据正态性,均符合正态分布,正态分布的计量资料以均数 $\pm$ 标准差表示,重复观测资料行两因素重复测量方差分析,其组间两两比较采用LSD-t检验,组内两两比较差值t检验。检验标准为 $\alpha=0.05$ 。

2 结果

2.1 不同时间点血流动力学分析

两组T₀时间点HR、MAP比较无差异($P>0.05$)。与T₀时间点对比,两组T₁~T₄时间点HR先升高后降低,MAP先降低后升高($P<0.05$),两组T₁~T₄时间点HR、MAP组间比较无差异($P>0.05$),参见表1。

表 1 不同时间点血流动力学分析 ($\bar{x}\pm s$)
Table 1 Hemodynamics analysis at different time points($\bar{x}\pm s$)

Groups	Time points	HR(beats/min)	MAP(mmHg)
Control group(n=53)	T0	104.31±10.02	71.82±8.90
	T1	127.91±9.66 ^t	68.62±6.58 ^t
	T2	121.61±11.05 ^t	75.66±6.11 ^t
	T3	114.06±8.48 ^t	75.94±7.03 ^t
	T4	111.81±9.21 ^t	78.53±7.09 ^t
Observation group(n=53)	T0	104.41±8.23	73.02±6.87
	T1	128.66±10.52 ^t	69.31±6.57 ^t
	T2	119.24±8.81 ^t	75.24±5.30 ^t
	T3	116.08±12.29 ^t	75.56±6.86 ^t
	T4	100.52±10.00 ^t	76.73±8.45 ^t
Overall analysis	HF coefficient	0.9603	0.9799
Group comparison	F, P	2.103, 0.057	0.047, 0.829
Intra group comparison	F, P	108.259, 0.000	26.185, 0.000
Interaction	F, P	7.801, 0.000	0.765, 0.514

Note: the significant mark t was compared with T0 time point $P<\alpha'$, α' was Bonferroni's corrected test level =0.05/4=0.013.

2.2 手术前后氧化应激指标分析 两组术前 24 h SOD、MDA 比较无差异 ($P>0.05$)。与术前 24 h 对比,两组术后 24 h SOD 降低,MDA 升高 ($P<0.05$),与对照组相比, 观察组 SOD 高于对照组,MDA 低于对照组 ($P<0.05$),参见表 2。

表 2 手术前后氧化应激指标分析 ($\bar{x}\pm s$)
Table 2 Analysis of oxidative stress indexes before and after operation($\bar{x}\pm s$)

Groups	Time points	SOD(U/mL)	MDA(mmol/mL)
Control group(n=53)	24 h before operation	97.63±6.31	2.96±0.54
	24 h after operation	58.93±7.26*	4.83±0.81*
Observation group(n=53)	24 h before operation	98.22±7.29	3.02±0.62
	24 h after operation	71.46±8.16**	3.71±0.75**

Note:Compared with 24h before operation,* $P<0.05$; Compared with control group, ** $P<0.05$.

2.3 手术前后心肌损伤指标分析 两组术前 24 h CK-MB、cTnI、H-FABP 比较无差异 ($P>0.05$)。与术前 24 h 对比, 两组术后 24 h CK-MB、cTnI、H-FABP 升高 ($P<0.05$), 与对照组相比, 观察组 CK-MB、cTnI、H-FABP 低于对照组 ($P<0.05$),参见表 3。

表 3 手术前后心肌损伤指标分析 ($\bar{x}\pm s$)
Table 3 Analysis of myocardial injury indexes before and after operation ($\bar{x}\pm s$)

Groups	Time points	CK-MB(U/L)	cTnI(μ g/mL)	H-FABP(ng/mL)
Control group(n=53)	24 h before operation	19.62±3.02	0.10±0.03	118.52±20.25
	24 h after operation	38.73±5.83*	3.22±0.23*	197.22±21.32*
Observation group(n=53)	24 h before operation	20.03±3.24	0.11±0.03	117.96±18.21
	24 h after operation	29.86±3.94**	2.16±0.38**	159.91±24.13**

Note: Compared with 24h before operation, * $P<0.05$; Compared with control group, ** $P<0.05$.

2.4 围术期指标分析 两组苏醒即刻的镇静评分、苏醒时间组间对比无差异 ($P>0.05$)。观察组的苏醒即刻的躁动评分低于对照组 ($P<0.05$),参见表 4。

2.5 不良反应发生率对比 两组不良反应发生率无差异 ($P>0.05$)。参见表 5。

3 讨论

表 4 围术期指标分析 ($\bar{x} \pm s$)Table 4 Analysis of perioperative indexes ($\bar{x} \pm s$)

Groups	Awakening time(min)	Sedation score immediately after awokenin(scores)	Agitation score immediately after awakening(scores)
Control group(n=53)	13.86±2.11	1.42±0.21	2.64±0.27
Observation group(n=53)	13.74±3.37	1.51±0.26	1.83±0.31
t	0.220	-1.960	14.344
P	0.827	0.053	0.000

表 5 不良反应发生率对比【例(%)】

Table 5 Comparison of the incidence of adverse reactions[n(%)]

Groups	Respiratory depression	Nausea and vomiting	Sinus bradycardia	Hypotension	Total incidence rate
Control group(n=53)	2(3.78)	1(1.89)	2(3.78)	1(1.89)	6(11.32)
Observation group (n=53)	3(5.66)	2(3.78)	3(5.66)	2(3.78)	10(18.87)
χ^2					1.178
P					0.278

介入封堵术是目前治疗小儿 CHD 的首选方法和常用方法^[11]。介入封堵术又属于有创操作,可能引起患儿疼痛、烦躁、血流波动或者不配合手术等,为了介入封堵术操作精细准确,需要患儿安静配合,无随意活动和兴奋挣扎,麻醉过程中保持呼吸道畅通,力求 MAP、HR 平稳^[12,13]。此外,介入封堵术虽然手术时间较短,但需要术后苏醒迅速,要求麻醉药物消除快,而 CHD 患儿普遍年龄较小,故而临床对小儿 CHD 行介入封堵术的麻醉的镇痛、镇静提出了较高要求。

七氟醚具有诱导及苏醒快、对循环呼吸抑制轻等药理学特点^[14],但在临床实践中却发现七氟醚吸入麻醉后会增加小儿苏醒期的躁动发生率^[15]。右美托咪定为高选择性、高效的 α_2 肾上腺素能受体激动剂,与 α_2 、 α_1 的受体结合率为 1620:1^[16]。右美托咪定可通过抑制腺苷酸环化酶,产生突触后抑制,发挥镇静、镇痛效果,同时右美托咪定可作用于蓝斑核前膜 α_2 受体,达到降低突触后膜兴奋性的目的^[17,18]。此外,右美托咪定最显著的特点是对呼吸影响非常轻微,符合介入封堵术的麻醉需求^[19]。本次研究结果显示,两组手术期间 HR、MAP 有一定的波动,但两组患儿组间对比未见明显差异,可见两种麻醉方案均可引起血流波动,且复合麻醉方案不会引起更严重的血流波动,因右美托咪定对 α_2 、 α_1 的高选择特性,很少作用于 α_2B 受体,从而使两组患儿在血流波动的变化上差异性不大^[20,21]。以往的研究报道证实^[22],右美托咪定具有少心肌耗氧量、降低手术难度、促进心脏功能等作用。本次研究中,右美托咪定复合七氟醚应用于行介入封堵术的小儿 CHD 中,可减轻心肌损伤和氧化反应。在 CHD 期间,心肌损伤的主要原因包括氧化应激、心肌缺血再灌注损伤和机械损伤,cTnI 被认为是心肌损伤的金标准标记^[23],CK-MB 是肌酸激酶的一种同工酶,心肌损伤时,CK-MB 可快速释放入血,约 6 h 后即可检测到 CK-MB 抬高^[24]。H-FABP 可介导质膜到脂质合成部位的脂肪酸传递,同时还可与过氧化物酶体增殖物激活受体 α 相互作用,从而诱导氧化应激反应^[25]。氧化应激可导致氧自由基大量生成,氧自由基则是

通过脂质过氧化反应发挥细胞损伤作用。MDA 是脂质过氧化的降解产物,可促使细胞通透性增加而导致细胞变性坏死^[26]。SOD 是清除氧自由基的重要酶类,其水平减少,可导致心肌缺血再灌注损伤更为严重^[27]。以往也有不少研究证实^[28,29],右美托咪定具有心肌保护作用,推测可能是因为右美托咪定可以通过抑制脂质过氧化作用,从而减轻对机体的刺激有关^[30]。两组苏醒时间、苏醒即刻的镇静评分组间对比无差异,而观察组的苏醒即刻的躁动评分低于对照组,主要是由于右美托咪定不依赖 γ -氨基丁酸系统的特殊镇静作用机制,使得苏醒及镇静方面两组比较无差异^[31]。右美托咪定强效的镇静、镇痛、抗交感和抗焦虑作用可有效减少躁动发生情况^[32],同时右美托咪定复合七氟醚并未明显增加不良反应发生率,安全可靠。本研究的局限性在于:样本量偏小,纳入患儿仅为房间隔缺损、室间隔缺损、房室间隔缺损、肺动脉瓣狭窄,未涉及合并肺动脉高压、发绀型患儿,且未研究使用的是常规剂量,在以后的工作中,将就此进行进一步的深入分析。

综上所述,右美托咪定复合七氟醚麻醉应用于介入封堵术中,可维持围手术期血流动力学稳定,减轻机体氧化应激、心肌损伤,并减少躁动发生情况,是安全有效的麻醉方案。

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