

doi: 10.13241/j.cnki.pmb.2020.18.016

氯胺酮复合咪达唑仑全麻在无水乙醇治疗先天性周围血管畸形中的 效果评价*

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摘要 目的:观察氯胺酮复合咪达唑仑在无水乙醇治疗儿童先天性周围血管畸形的应用效果。**方法:**选择择期全麻下行无水乙醇治疗周围血管畸形儿童 50 例,随机分为两组:氯胺酮复合咪达唑仑组(M 组)和丙泊酚持续输注组(P 组),M 组以咪达唑仑和氯胺酮基础下全麻,P 组采用芬太尼镇痛基础下丙泊酚持续静注全麻,观察并记录入室(T_0)、麻醉诱导后 5 min(T_1)、手术开始后 30、60、90 min(分别为 T_2 、 T_3 、 T_4)、拔管后 5 min(T_5)的 MAP 与 HR,监测脑电双频指数(bispectral index, BIS)并记录 BIS<40 次数、平均注射无水乙醇量、术中输液量、苏醒时间及苏醒后 5 min 视觉模拟评分(Visual analog scales, VAS)、Ramsay 镇静评分结果。**结果:**(1)与 M 组相比,P 组 MAP($T_2 \sim T_5$ 4 个时间点)、HR($T_1 \sim T_5$ 5 个时间点)和 BIS 值(T_3 和 T_4 2 个时间点)均显著降低,差异有统计学意义($P<0.05$);三个指标其余时间点两组患儿相比,差异均无统计学意义($P>0.05$);(2)与 M 组患儿相比,P 组 BIS 值<40 的患儿例数以及应用阿托品和麻黄碱例数均显著增加,差异具有统计学差异($P<0.05$);两组患儿平均无水乙醇注射量比较显著差异无统计学意义($P>0.05$);(3)与 M 组相比,P 组患儿全麻苏醒拔管后 5 min VAS 评分显著降低,Ramsay 评分显著升高($P<0.05$);两组患儿不良事件发生率均无统计学差异($P>0.05$)。**结论:**氯胺酮复合咪达唑仑全麻应用于无水乙醇注射治疗儿童周围血管畸形,能维持术中血流动力学平稳,且缩短苏醒时间。

关键词:咪达唑仑;氯胺酮;丙泊酚;无水乙醇;周围血管畸形

中图分类号:R654.4;R969 **文献标识码:**A **文章编号:**1673-6273(2020)18-3474-04

The Effect of Ketamine Combined with Midazolam in the Treatment of Vascular Malformations with Ethanol Under General Anesthesia*

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ABSTRACT Objective: To evaluate the effect of ketamine combined with midazolam for ethanol treatment in congenital vascular malformations under general anesthesia. **Methods:** Fifty pediatric patients scheduled for ethanol treatment in congenital vascular malformations under general anesthesia were randomly divided into ketamine combined with midazolam group (M group) and propofol group (P group), with 25 cases in each group. Children in group M was treated with midazolam and ketamine, and group P with continuous infusion of propofol on the basis of sufentanil. During the procedure, MAP and HR were recorded at baseline (T_0), 5 min after induction (T_1), 30, 60, 90min (T_2 , T_3 , T_4) after beginning of the operation, and 5 min after extubation (T_5). BIS index and the number of BIS<40, the average ethanol consumption, operation time, infusion volume, recover time, VAS and Ramsay score after extubation were recorded. **Results:** (1) Compared with the M group, the MAP ($T_2 \sim T_5$ 4 time points), HR ($T_1 \sim T_5$ 5 time points) and BIS values (T_3 and T_4 2 time points) of P group were significantly reduced($P<0.05$). there were no significant difference in the three indicators between the two groups ($P>0.05$). (2) Compared with the group M, the cases of children with BIS value <40 and with atropine and ephedrine in group P were both increased significantly, the difference was statistically significant ($P<0.05$). There was no significant difference in the amount of absolute ethanol injection ($P>0.05$). (3) Compared with the M group, the VAS score was significantly lower at 5 min after general anesthesia in the P group, and the Ramsay score was significantly increased ($P<0.05$). There was no significant difference in adverse event rate between the two groups ($P>0.05$). **Conclusions:** Midazolam combined with ketamine in the treatment of congenital vascular malformation with ethanol could stabilize hemodynamic parameters in the operation and shorten the awakening time in pediatric patients.

Key words: Midazolam; Ketamine; Propofol; Ethanol; Vascular malformation

Chinese Library Classification(CLC): R654.4; R969 **Document code:** A

Article ID:1673-6273(2020)18-3474-04

* 基金项目:陕西省重点研发项目(2018SF-125)

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(收稿日期:2019-12-07 接受日期:2019-12-30)

前言

周围血管畸形是先天性动静脉发育异常引起的疾病,也称动静脉畸形(arteriovenous malformations,AVMs)。通常其发病机制是由于富含内皮细胞的基因内皮糖蛋白的功能丧失突变引起人类疾病遗传性出血性毛细血管扩张,从而促使血管内皮生长因子 A(Vascular endothelial growth factor A,VEGFA)引起血管畸形^[1]。目前相关报道指出,血管畸形可能与巨大先天性黑色素细胞痣^[2]、蓝色橡胶泡痣综合征^[3]以及口腔颌面部血管瘤^[4,5]等疾病密切相关,通常可通过内窥镜检查、磁共振血管造影等技术对该病进行诊断^[6],病理检查可观察到血管畸形通常伴有血栓^[7]。目前研究较多的为血管畸形和口腔颌面部动静脉畸形^[8,9],血管介入下行无水乙醇注射是治疗 AVMs 有效的栓塞硬化疗法^[10],但无水乙醇作用于迂曲的畸形血管后会随着病变血管团溢出进入血液循环^[11],而少量的乙醇入血液会对儿童中枢神经系统产生多重作用^[12],尤其对 γ -氨基丁酸、谷氨酸及内源性阿片系统产生多重影响,而全麻下镇痛镇静药效与之有着叠加效应。由于 AVMs 发病率低,且长需反复多次治疗,关于麻醉方法的研究鲜有报道,本研究以不同作用机制的镇静镇痛药物为基础,观察血管介入下无水乙醇注射治疗四肢 AVMs 患儿 50 例,探讨氯胺酮复合咪达唑仑在无水乙醇治疗儿童先天性周围血管畸形的应用效果,报道如下。

1 资料与方法

1.1 一般资料及分组

选择 2017 年 8 月-2018 年 3 月择期行血管介入治疗 AVMs 患儿 50 例,病变部位局限于单侧上肢或下肢,处于 Schobinger 临床分期的 II(静止)或 III(扩张)期^[13],约为单侧肢体面积的 1/8~1/6,无关节活动受限。ASAI~II 级,年龄 6~14 岁,体重 17~51 kg,其中男 21 例,女 29 例。本研究经本院医学伦理会批准,患儿家长均签署麻醉知情同意书。排除标准:肝肾功能、凝血功能异常,心力衰竭,对酒精及麻醉药物过敏,中枢神经系统疾病史及术中改用其它栓塞剂,手术时间小于 90 min 大于 120 min 予以剔除。采用随机的原则,按随机数字系统奇偶数的方法随机分为氯胺酮复合咪达唑仑组(M 组)和丙泊酚持续输注组(P 组),剔除 4 例不符合研究方案的患儿后,每组 23 例。

1.2 药品、试剂与仪器

麻醉机(德国 Dräger Primus,型号:Fabius2000)心电监护仪(飞利浦,型号:MP20)。氯胺酮注射液(江苏恒瑞医药,批号:H35020148,规格:2 mL:100 mg)。咪达唑仑注射液(江苏恩华药业,批号:H20153019,规格:2 mL:10 mg)。右美托咪定注射液(江苏恒瑞医药,批号:H20090248,规格:2 mL:200 μ g)。丙泊酚(北京费森尤斯卡比医药,批号:J20070007,规格:20 mL:200 mg)。芬太尼(宜昌人福药业,批号:H42022076,规格:1 mL:100 μ g)。

1.3 麻醉方法

麻醉前 30 min 肌注阿托品 0.01~0.02 mg/kg,入室后开放静脉通路,监测无创血压、脉搏氧饱和度(SpO_2)、心电图及脑电双频指数(bispectral index,BIS)。两组患儿术前均禁食 4-6h,禁饮 2h,术中输液方案相同(根据小儿补液的 4:2:1 法则)。M 组

患儿麻醉依次静注咪达唑仑 0.5 mg/kg,氯胺酮 0.3 mg/kg,顺阿曲库铵 0.15 mg/kg 和依托咪酯 2 mg/kg;P 组患儿依次静注丙泊酚 3~5 mg/(kg·h),芬太尼 2~3 μ g/kg,顺阿曲库铵 0.15 mg/kg。诱导后 4min 行气管插管,M 组在 BIS 指导下间断静注咪达唑仑 0.02~0.05 mg/kg 和氯胺酮 0.05~0.1 mg/kg,咪达唑仑和氯胺酮总量分别不超过 1 mg/kg 和 2 mg/kg。T 组术中泵注丙泊酚 4~6 mg/(kg·h)及瑞芬太尼 0.1 μ g/(kg·min)维持麻醉。麻醉诱导后 10 min 静注地塞米松 0.1 mg/kg,术中间断静注顺阿曲库铵 0.1 mg/kg 维持肌松。麻醉成功后,X 线下造影确定栓塞血管部位,确定栓塞剂种类,注射无水乙醇每 10 min 不超过 0.1 mL/kg,总量不超过 1 mL/kg,最大剂量不超过 50 mL,每次注射后观察 10~15 min,所有手术均由同 2 名医生共同完成,所有病人麻醉均由 2 位工作 5 年以上麻醉医生完成。术毕前约 30 min 不再追加肌松药,两组均采用滴定纳美芬进行阿片类药物拮抗。所有病人采用容量控制呼吸模式,采用 60%氧浓度,手术结束前约 10 min 静注酮咯酸氨丁三醇 0.5 mg/kg 衔接镇痛。麻醉医师根据经验调整血压、心率等生命体征变化,血压低可以静注麻黄碱 3~5 mg,心动过缓静注阿托品 0.1 mg,必要时重复给药。

1.4 观察指标

观察并记录入室(T_0)、麻醉诱导后 5 min(T_1)、手术开始后 30、60、90(分别为 T_2 、 T_3 、 T_4)、拔管后 5 min(T_5)的 MAP、HR 与 BIS 值,BIS<40 下降次数、平均无水乙醇注射量、术中输血量、苏醒后 5 min 视觉模拟评分(Visual analog scales,VAS)结果、Ramsay 镇静评分结果及苏醒期躁动情况。

1.5 统计学处理

采用 SPSS22.0 统计软件进行分析,计量资料以 $\bar{x} \pm s$ 表示,组间比较以单因素方差分析和 t 检验,计数资料比较采用 χ^2 检验,定义 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 一般情况比较

本研究中共筛选下肢 AVMs 患儿 50 例,其中共有 4 例患儿不符合研究方案,3 例患儿改用其它栓塞剂,其中 M 组 2 例,P 组 1 例;另外 P 组有 1 例患儿对麻醉药物过敏。患儿两组患儿的年龄、性别、体重、手术时间、麻醉时间及术中输血量比较差异无统计学意义($P>0.05$),见表 1。

2.2 不同时间点 MAP、HR 和 BIS 值比较

两组患儿 T_0 时三个指标比较差异均无统计学意义($P>0.05$);与 M 组相比,P 组 MAP($T_2 \sim T_4$ 4 个时间点)、HR($T_1 \sim T_5$ 5 个时间点)和 BIS 值(T_3 和 T_4 2 个时间点)均显著降低,差异有统计学意义($P<0.05$);其余时间点两组患儿三个指标相比差异无统计学意义($P>0.05$),见表 2。

2.3 两组患儿 BIS<40 次数及平均无水乙醇注射量比较

与 M 组患儿相比,P 组 BIS 值<40 的患儿所占比例显著增加,差异具有统计学差异($P<0.05$);两组患儿平均无水乙醇注射量比较差异无统计学意义($P>0.05$);P 组患儿应用阿托品和麻黄碱例数较 M 组显著增加,差异具有统计学差异($P<0.05$),见表 3。

表 1 手术治疗相关指标对比结果($\bar{x} \pm s$)

Table 1 Comparison results of operation treatment related indexes($\bar{x} \pm s$)

Groups	Age(year)	Male/Female	Weight(kg)	Infusion volume (mL/kg)	Operation time (min)	Anesthesia time (min)
Group M	10.7±2.6	9/14	34.2±4.7	10.1±2.9	96.4±8.3	105.3±11.9
Group P	10.4±2.3	10/13	33.7±5.2	10.6±3.3	93.1±9.5	104.7±9.2

Note: Compared with Group M, * $P < 0.05$.

表 2 两组患者不同时间点的 MAP、HR 和 BIS 值比较(n=23)

Table 2 Comparison of MAP, HR and BIS values at different time points between the two groups (n=23)

Indicator	Group	T ₀	T ₁	T ₂	T ₃	T ₄	T ₅
MAP(mmHg)	Group M	96.3±11.4	94.6±10.6	91.8±8.8	90.6±8.4	91.4±10.5	90.2±10.74
	Group P	97.4±10.7	92.7±9.8	83.1±9.1*	73.4±8.3*	70.3±9.6*	81.7±11.4*
HR(times/min)	Group M	101.6±11.5	112.4±13.8	109.5±11.5	103.4±10.4	98.6±7.9	109.6±9.9
	Group P	104.3±9.3	94.3±8.6*	86.3±7.3*	82.7±8.1*	80.8±9.5*	85.4±10.3*
BIS value	Group M	99.7±10.1	58.4±4.7	55.2±3.9	50.0±4.2	53.6±4.7	89.1±7.6
	Group P	99.8±10.9	56.9±3.8	54.8±3.9	42.3±6.0*	41.6±3.9*	85.3±8.4

Note: compared with Group M, * $P < 0.05$.

表 3 两组患儿 BIS<40 例数及平均无水乙醇注射量比较(n=23)

Table 3 Comparison of BIS<40 times and average absolute ethanol injection in two groups (n=23)

Groups	BIS<40[n(%)]	Average absolute ethanol injection(mL/kg)	Atropine[n(%)]	Ephedrine[n(%)]
Group M	0(0)	0.67±0.08	2(8.7)	3(13.0)
Group P	8(34.8)*	0.65±0.07	9(36.0)*	13(56.5)*

Note: compared with Group M, * $P < 0.05$.

表 4 两组苏醒期 VAS、Ramsay 评分比较(n=23)

Table 4 Comparison of VAS and Ramsay scores between the two groups in the recovery period (n=23)

Indicator	VAS scores	RAMSAY scores
Group M	0.4±0.06	2.15±0.61
Group P	0.3±0.07*	3.4±0.76*

Note: compared with Group M, * $P < 0.05$.

2.4 苏醒期 VAS、Ramsay 评分及不良反应比较

与 M 组相比, P 组患儿全麻苏醒拔管后 5 min VAS 评分显著降低, Ramsay 评分显著升高($P < 0.05$)。两组患儿苏醒期平稳, 无躁动发生, 其中 M 组患儿 8 例, P 组 9 例出现面部潮红, 观察期间无恶心、呕吐及不良事件发生。

3 讨论

既往关于 AVMs 治疗的研究表明, 乙醇栓塞术是治疗是治疗 AVM 有效方法^[14,15]。高浓度(>98%)的无水乙醇与目标血管壁接触后, 刺激静脉伤害感受器, 导致严重的疼痛, 此类介入手术需在全麻下进行^[16]。咪达唑仑或氯胺酮的组合通常用于诱导麻醉和镇静^[17,18], 相关研究表明: 两者联合使用在缓解患者术前焦虑、抑郁等不良情绪方面具有显著效果^[19]。在本研究中, 氯胺酮复合咪达唑仑组血流动力学波动较小且恢复迅速, 考虑随着乙醇注射量的增多, 乙醇可通过增加 GABA 能的抑制性反应产生催眠作用, 并调节 NMDA 受体的兴奋性^[27], 本组应用

NMDA 受体拮抗剂氯胺酮, 可以安全有效的增强已知的对 NMDA 受体神经兴奋性刺激, 减少对过多的 GABA 激动, 调节镇静; 而且, 乙醇可以加速氯胺酮在体内的消除, 促进氯胺酮转换为去甲氯胺酮, 促进在体内的代谢^[28]。

本研究发现, 随着麻醉及手术进程的延长, 无水乙醇注射量的增加, 与氯胺酮复合咪达唑仑组相比, 丙泊酚组 BIS 指数下降次数明显增多, 出现的血压和心率的下降幅度更大, 且不容易由血管活性药物麻黄碱纠正, 有研究报道, 在治疗 AVMs 中血浆乙醇浓度可达到 4.3-21.5 mmol/L^[20], 乙醇与丙泊酚共同激活 γ -氨基丁酸(-aminobutyric acid, GABA), 促进氯离子内流, 产生突触后抑制, 降低中枢兴奋性^[21]; 而且, 乙醇也作用于 N-甲基-D 天冬氨酸(N-methyl-D-aspartate, NMDA)受体, 抑制谷氨酸活性, 导致记忆丧失, 与丙泊酚发挥双重协同作用, 对大脑产生明显的神经抑制作用^[22]。与此同时, 乙醇刺激内源性阿片系统-内啡肽和脑啡肽释放^[23], 与芬太尼产生了协同镇静作用。由于丙泊酚镇静起效快且代谢时间短, 我们在本研究过程

中,根据 BIS 及时调整丙泊酚泵注速度,苏醒时间与氯胺酮复合咪达唑仑组相比有所延长。

氯胺酮可以通过谷氨酰胺能,单胺能和 GABA 能发挥活性作用,有着复杂多重的药理学效应,可以通过调控神经元活性以及不同种类的焦虑抑郁状态^[24],在长时间的 ICU 镇静中,氯胺酮静注可以降低 GABA 激动剂的用量,减少插管发生率,缩短 ICU 停留时间^[25];氯胺酮也可以减轻酒精戒断时神经过度兴奋对 NMDA 受体的刺激,降低过多的 GABA 激动剂介导的镇静作用^[26]。

最近研究发现,氯胺酮可通过增加侧前额叶皮质,尾状核和岛叶的活性,改变前脑皮质到边缘区域的兴奋性,进而影响认知和精神状况^[29]。在 AVMs 治疗儿童镇静策略上,不同镇静药物对中枢神经系统的镇静水平以及与乙醇的产生的效应不同,其机制间相互作用还未明确。而根据血中乙醇浓度调整用药方案或持续稳定的丙泊酚靶控输注系统在小儿 AVMs 麻醉中的效果,以及吸入麻醉药在此类病例中的应用,还有待进一步观察研究。而且,随着瑞马唑仑和依托咪酯衍生物的发展可能为 AVMs 治疗提供更优良的麻醉方案^[30]。

综上所述,在无乙醇治疗 AVMs 患儿全麻中,氯胺酮与咪达唑仑合用保证了充分的麻醉镇静深度的同时,对血流动力学影响较小,而且苏醒迅速,有一定的临床参考价值。

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