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## 瑞马唑仑对老年患者气管插管时依托咪酯半数有效血浆浓度的影响\*

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**摘要:**目的 探讨瑞马唑仑对老年患者气管插管时依托咪酯半数有效血浆浓度( $C_{p50}$ )的影响。方法 选取医院2021年8月至2022年1月收治的行单腔导管气管插管全身麻醉手术的老年患者60例,随机分为对照组和观察组,各30例,按剔除标准最终分别纳入24例、26例。对照组患者静脉缓慢推注舒芬太尼和依托咪酯麻醉诱导,观察组患者在此基础上预先静脉注射0.1 mg/kg 甲苯磺酸瑞马唑仑。两组患者均遵循Dixon改良序贯法原则设定依托咪酯的血浆靶浓度,依据预试验,首例患者依托咪酯血浆靶浓度对照组设为0.99  $\mu\text{g}/\text{mL}$ ,观察组设为0.58  $\mu\text{g}/\text{mL}$ ;视气管插管反应,阳性则上调一例患者的依托咪酯血浆靶浓度,阴性则下调。采用Probit回归分析计算两组的依托咪酯 $C_{p50}$ 及95%置信区间(95%CI);观察两组患者的依托咪酯用量、麻醉诱导期间去甲肾上腺素用量、气管导管拔除时间,以及不良反应发生情况。结果 观察组依托咪酯 $C_{p50}$ 为0.62  $\mu\text{g}/\text{mL}$ [95%CI(0.54, 0.70)],显著低于对照组的0.97  $\mu\text{g}/\text{mL}$ [95%CI(0.88, 1.06)]。观察组患者依托咪酯给药量为(0.32  $\pm$  0.07)mg/kg,显著低于对照组的(0.46  $\pm$  0.08)mg/kg( $P < 0.05$ );麻醉诱导期间,两组患者的去甲肾上腺素用量及气管导管拔除时间比较,差异无统计学意义( $P > 0.05$ );观察组患者肌阵挛发生率为7.69%,显著低于对照组的37.50%( $P < 0.05$ )。结论 0.1 mg/kg 瑞马唑仑可降低老年患者气管插管时依托咪酯的 $C_{p50}$ ,对拔除气管导管时间无影响,且安全性良好。

**关键词:**瑞马唑仑;依托咪酯;半数有效血浆浓度;气管插管

### Effect of Remimazolam on the Median Effective Plasma Concentration of Etomidate During Tracheal Intubation in Elderly Patients

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**Abstract: Objective** To investigate the effect of remimazolam on the median effective plasma concentration ( $C_{p50}$ ) of etomidate during tracheal intubation in elderly patients. **Methods** A total of 60 elderly patients who underwent general anesthesia with elective single-lumen catheter tracheal intubation in the hospital were selected and randomly divided into the control group and the observation group, with 30 cases in each group. According to the exclusion criteria, 24 cases and 26 cases were included in the control group and the observation group, respectively. The patients in the control group received slow intravenous infusion of sufentanil and etomidate for anesthesia induction, and on this basis, the patients in the observation group were pre-injected with 0.1 mg/kg of remimazolam toluenesulfonate. The plasma target concentration of etomidate was set according to the principle of the Dixon modified sequential method, and the plasma target concentration of etomidate of the first patient was set at 0.99  $\mu\text{g}/\text{mL}$  in the control group and 0.58  $\mu\text{g}/\text{mL}$  in the observation group according to the pre-test. According to the endotracheal intubation response, positive cases upregulated while the negative cases downregulated the plasma target concentration of etomidate in the next case, with an adjacent ratio of 1:1.2. The  $C_{p50}$  and 95% confidence interval (CI) of etomidate in the two groups were calculated by the Probit regression analysis. The dose of etomidate and norepinephrine during anesthesia induction, the time of tracheal extubation, and the incidence of adverse reactions were observed. **Results** The  $C_{p50}$  of etomidate in the observation group was 0.62  $\mu\text{g}/\text{mL}$  [95%CI (0.54, 0.70)], which was significantly lower than 0.97  $\mu\text{g}/\text{mL}$  [95%CI (0.88, 1.06)] in the control group. The dose of etomidate in the observation group was (0.32  $\pm$  0.07) mg/kg, which was significantly lower than (0.46  $\pm$

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0.08) mg/kg in the control group ( $P < 0.05$ ). The difference in the dose of norepinephrine and the time of tracheal extubation between the two groups during the induction of anesthesia was not statistically significant ( $P > 0.05$ ). The incidence of myoclonus in the observation group was 7.69%, which was significantly lower than 37.50% in the control group ( $P < 0.05$ ). **Conclusion** Remimazolam 0.1 mg/kg can reduce the  $C_{p50}$  of etomidate during tracheal intubation in elderly patients, with no effect on the time of tracheal extubation, and it is safe.

**Key words:** remimazolam; etomidate; median effective plasma concentration; tracheal intubation

老年患者器官功能储备和代偿功能下降,对麻醉药物的敏感性增加<sup>[1-2]</sup>。气管插管操作刺激性大,麻醉诱导期间循环系统功能不稳定,易导致心脑血管意外发生<sup>[3]</sup>。故维持老年患者循环系统功能稳定十分必要,以减少围术期并发症的发生。联合用药是目前麻醉诱导常采取的用药方式,既可减少单一药物的用量和不良反应,又能提高麻醉诱导的安全性。瑞马唑仑是一种超短效苯二氮革类镇静/麻醉药物<sup>[4]</sup>,具有镇静、遗忘等作用,起效快,对循环、呼吸系统影响较小,可用于麻醉诱导<sup>[5]</sup>。依托咪酯对呼吸、循环系统影响小,可轻微扩张冠状动脉,增加心肌细胞氧输送<sup>[6]</sup>,对颅内压影响小,适用于脏器储备功能下降的老年患者。但麻醉诱导时依托咪酯不能完全阻断喉镜进入和气管插管引起的交感反应,循环表现为血压、心率骤升等心血管反应<sup>[7-8]</sup>。如需完全抑制气管插管反应,需加大依托咪酯的剂量或联合其他药物,但大剂量依托咪酯会抑制肾上腺皮质功能,导致血浆皮质类固醇激素水平下降<sup>[9]</sup>,同时可引起肌颤、术后恶心呕吐等不良反应。本研究中遵循Dixon改良序贯法设定老年患者气管插管时依托咪酯的血浆浓度,探讨预先静脉注射0.1 mg/kg 甲苯磺酸瑞马唑仑对患者半数有效血浆浓度( $C_{p50}$ )的影响。现报道如下。

## 1 资料与方法

### 1.1 一般资料

**纳入标准:**择期行单腔导管经口气管插管全身麻醉手术;年龄65~80岁;美国麻醉医师协会(ASA)分级为I-III级;体质指数(BMI)18~30 kg/m<sup>2</sup>;手术时间2~4 h。本研究方案经医院医学伦理委员会批准[批件号为NO. 伦审2021(KY-E-279)号],患者签署知情同意书。

**排除标准:**对脂类物质、瑞马唑仑过敏;术前合并肾上腺皮质功能不全;预计困难气道(Mallampati气道分级为III-IV级,张口度受限等);长期服用苯二氮革类及阿片类药物史,酒精依赖史;合并颅脑损伤、脑电图异常。

**剔除标准:**一次插管不成功;插管超过30 s;插管前1 min使用血管活性药物。

**病例选择与分组:**选取我院2021年8月至2022年1月收治的行单腔导管经口气管插管全身麻醉手术患者60例,随机分为观察组和对照组,各30例。最终纳入50例,观察组26例,对照组24例。两组患者一般资料比

较,差异无统计学意义( $P > 0.05$ ),具有可比性。详见表1。

表1 两组患者一般资料比较

Tab. 1 Comparison of patients' general data between the two groups

组别	性别	年龄	ASA分级(I级/	BMI	Mallampati气道分级
	(男/女,例)	( $\bar{X} \pm s$ ,岁)	II级/III级,例)	( $\bar{X} \pm s$ ,kg/m <sup>2</sup> )	(I级/II级,例)
观察组(n=26)	16/10	70.20±4.50	1/18/7	24.01±2.80	17/9
对照组(n=24)	14/10	70.80±4.30	1/15/8	24.03±2.50	16/8
$\chi^2/t$ 值	0.053	-0.511	0.260	-0.032	0.009
P值	0.817	0.612	0.878	0.975	0.924

### 1.2 方法

两组患者送达手术室后予20G留置针开通静脉通道,给予8 mL/(kg·h)乳酸林格注射液(中国大冢制药有限公司,国药准字H12020009,规格为每袋500 mL)静脉滴注,面罩吸氧流量设为4 L/min,监测心电图(ECG)、心率(HR)、脉搏血氧饱和度(SpO<sub>2</sub>)、无创血压(NBP)、脑电双频指数(BIS)及有创动脉压。对照组患者缓慢静脉推注0.4 μg/kg 枸橼酸舒芬太尼注射液[宜昌人福药业有限责任公司,国药准字H20054171,规格为每支1 mL:50 μg(按C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S计)]1 min,再经血浆靶控模式(TCI)输注依托咪酯乳状注射液(江苏恩华药业股份有限公司,国药准字H20020511,规格为每支10 mL:20 mg)。观察组患者在对照组治疗基础上预先静脉注射0.1 mg/kg 注射用甲苯磺酸瑞马唑仑(江苏恒瑞医药股份有限公司,国药准字H20190034,规格为每瓶36 mg(按C<sub>21</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>2</sub>计)]1 min。依据预试验,首例患者依托咪酯血浆靶浓度对照组设为0.99 μg/mL,观察组设为0.58 μg/mL。警觉/镇静观察(OAA/S)评分≤1分时,两组患者均静脉注射0.3 mg/kg 苯磺顺阿曲库铵注射液(杭州澳亚生物技术股份有限公司,国药准字H20213438,规格为每支5 mL:10 mg)。两组患者BIS低于60且依托咪酯效应室浓度与设定的血浆浓度平衡后,由同一高年资主治医师在可视喉镜下行单腔导管气管插管并机械通气。麻醉诱导过程中出现收缩压低于30%基础值或平均动脉压(MAP)低于50 mmHg(1 mmHg=0.133 kPa),静脉注射重酒石酸去甲肾上腺素注射液(远大医药<中国>有限公司,国药准字H42021301,规格为每支1 mL:2 mg),每次4 μg,必要时

重复追加;若患者HR低于50次/分,则给予硫酸阿托品注射液(遂成药业股份有限公司,国药准字H41021257,规格为每支1 mL:0.5 mg)0.3 mg,对症治疗。

遵循Dixon改良序贯法原则,设定靶控输注依托咪酯的血浆浓度,相邻血浆浓度比值定为1:1.2,如果气管插管反应判定为阳性,即气管插管后2 min内MAP超过插管前即刻MAP的20%或HR高于90次/分,气管插管后出现流泪或任何体动反应,则上调下一例患者1个浓度阶梯的依托咪酯血浆浓度;反之,则下调。出现7个阳/阴折点的试验例数为每组的最终试验例数且结束试验。

### 1.3 观察指标

记录两组患者的依托咪酯用量、麻醉诱导期间去甲肾上腺素用量、气管导管拔除时间,以及不良反应(恶心呕吐、肌阵挛)发生情况。

### 1.4 统计学处理

采用SPSS 23.0统计学软件分析。计量资料以 $\bar{x} \pm s$ 表示,行*t*检验;计数资料以率(%)表示,行 $\chi^2$ 检验;采用概率单位回归分析法(Probit回归分析)计算 $C_{P50}$ 及95%置信区间(95%CI)。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

两组患者序贯试验结果见图1和图2。Probit回归分析计算得观察组依托咪酯 $C_{P50}$ 为0.62  $\mu\text{g}/\text{mL}$  [95%CI (0.54, 0.70)],显著低于对照组的0.97  $\mu\text{g}/\text{mL}$  [95%CI (0.88, 1.06)]。其余结果见表2和表3。

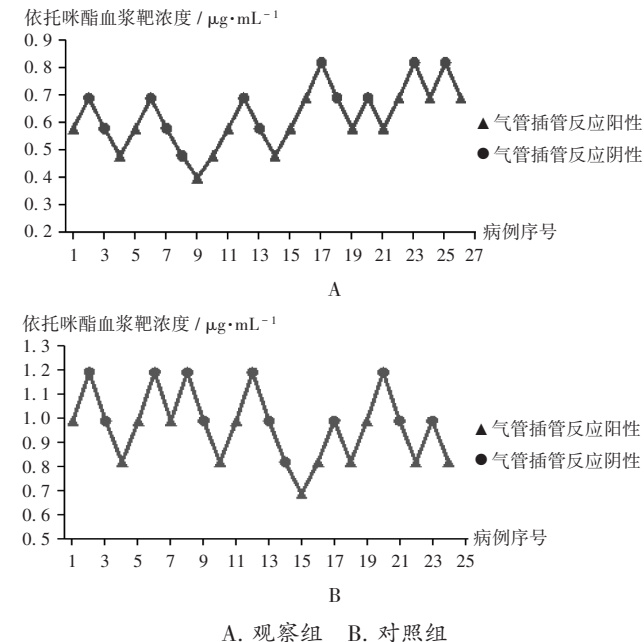


图1 依托咪酯抑制气管插管反应患者阴性/阳性反应序贯图  
A. Observation group B. Control group

Fig.1 Sequential diagram of negative/positive responses in patients with etomidate inhibition of tracheal intubation

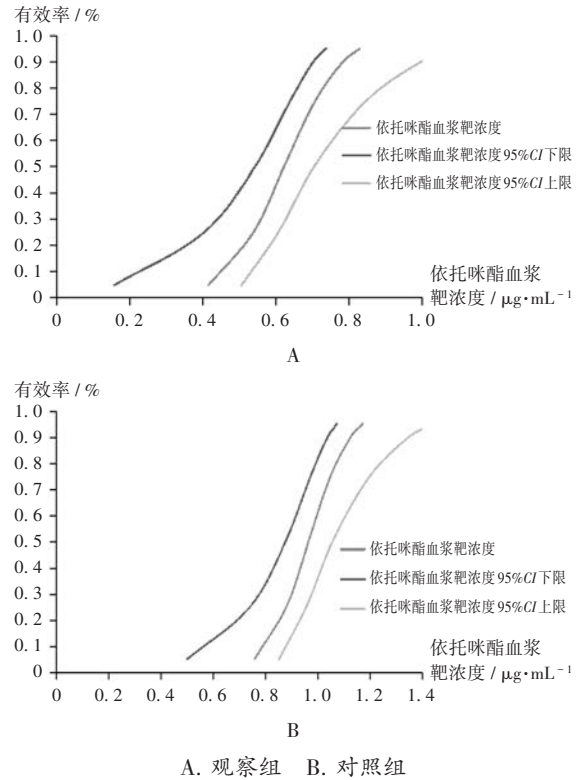


图2 依托咪酯抑制气管插管反应量效曲线

A. Observation group B. Control group

Fig.2 Dose-response curve of etomidate inhibition of tracheal intubation

表2 两组患者依托咪酯、去甲肾上腺素用量及气管导管拔除时间比较( $\bar{X} \pm s$ )

Tab.2 Comparison of etomidate and norepinephrine dose and time of tracheal extubation between the two groups ( $\bar{X} \pm s$ )

组别	依托咪酯用量(mg)	依托咪酯给药量(mg/kg)	去甲肾上腺素用量( $\mu\text{g}$ )	气管导管拔除时间(min)
观察组( $n=26$ )	19.94 $\pm$ 4.71	0.32 $\pm$ 0.07	2.92 $\pm$ 5.13	37.15 $\pm$ 15.59
对照组( $n=24$ )	29.18 $\pm$ 6.31	0.46 $\pm$ 0.08	4.83 $\pm$ 9.44	39.96 $\pm$ 15.03
<i>t</i> 值	-5.893	-7.004	-0.879	-0.646
<i>P</i> 值	0.000	0.000	0.385	0.521

表3 两组患者不良反应发生情况比较[例(%)]

Tab.3 Comparison of the incidence of adverse reactions between the two groups [case (%)]

组别	肌阵挛	恶心呕吐
观察组( $n=26$ )	2(7.69)	2(7.69)
对照组( $n=24$ )	9(37.50)	5(20.83)
$\chi^2$ 值	6.462	1.790
<i>P</i> 值	0.011	0.239

## 3 讨论

全身麻醉诱导行气管插管操作需置入喉镜,插入气管导管时舌、咽喉、气管等感受器受到机械性压迫、牵拉等刺激,冲动信号通过蓝斑-交感-肾上腺髓质系统、下丘脑-垂体-肾上腺皮质轴系快速上传激活

应激系统,引起患者神经-体液改变,造成血清儿茶酚胺类物质含量成倍上升<sup>[10]</sup>,循环表现为血压及心率骤升,可能导致患者尤其是老年患者严重的心脑血管意外。

本研究中经依托咪酯麻醉诱导时联用镇静药物瑞马唑仑。陈瑜等<sup>[11]</sup>研究认为,0.3 mg/kg瑞马唑仑可保证老年患者麻醉诱导安全、有效。乔迎帅等<sup>[12]</sup>的研究显示,联合0.25 μg/kg舒芬太尼时,瑞马唑仑抑制18~64岁患者气管插管反应的有效中量( $ED_{50}$ )为0.190 mg/kg。故本研究中选择预先静脉注射0.1 mg/kg瑞马唑仑联合依托咪酯进行麻醉诱导。与弹丸式静脉推注法比较,麻醉药物以TCI方式给药虽会延长麻醉诱导时程,但血流动力学相对平稳,易于调整麻醉深度,还可预估患者苏醒和恢复的时间,适用于老年患者的麻醉诱导<sup>[13-14]</sup>。故依托咪酯经TCI输注。

本研究结果显示,观察组患者依托咪酯  $C_{p50}$  为0.62 μg/mL[95%CI(0.54,0.70)],显著低于对照组的0.97 μg/mL[95%CI(0.88,1.06)],表明在老年患者全身麻醉诱导期间联用瑞马唑仑时依托咪酯抑制气管插管反应的  $C_{p50}$  明显下降。气管插管反应的  $C_{p50}$  受多种因素影响,如实施的靶控方案、有无术前用药及个体差异、统计学方法、性别、年龄及TCI平衡时间等<sup>[15]</sup>。本研究结果显示,观察组患者依托咪酯用量显著低于对照组( $P < 0.05$ ),但均在推荐剂量范围内(0.2~0.6 mg/kg);观察组患者肌阵挛发生率显著低于对照组( $P < 0.05$ )。这是由于瑞马唑仑与依托咪酯均作用于中枢抑制性γ-氨基丁酸A(GABA<sub>A</sub>)受体而发挥镇静、催眠作用,理论上瑞马唑仑联合依托咪酯表现为叠加效应,可达到加深麻醉抑制气管插管反应的效果,减少依托咪酯的用量,从而降低剂量相关性的不良反应。观察组患者手术结束到气管导管拔除的时间短于对照组,但差异无统计学意义( $P > 0.05$ )。可能由于瑞马唑仑是一种超短效镇静药物,蓄积少,作用时间短,剂量小,且单次使用,对术后拔管时间影响不大。

综上所述,0.1 mg/kg瑞马唑仑可降低老年患者气管插管时依托咪酯的  $C_{p50}$ ,对拔除气管导管时间无影响,且安全性良好。

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