

临床研究

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靶控输注瑞芬太尼用于老年患者全麻苏醒期平稳拔管的半数有效剂量

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【摘要】目的:确定靶控输注瑞芬太尼用于老年患者全凭静脉麻醉(total intravenous anaesthesia, TIVA)后苏醒期安全平稳拔管的半数有效剂量。**方法:**择期全麻下行颌骨囊肿手术的老年女性患者 24 例, ASA I~II 级, 采用 Dixon 序贯法进行试验, 开始缝合伤口时第 1 例患者以效应室靶浓度 1 ng/ml 输注瑞芬太尼, 若拔管不平稳, 则下一位预设靶浓度增加 0.5 ng/ml。若拔管平稳, 下一位预设靶浓度减少 0.5 ng/ml。通过 Dixon 法计算瑞芬太尼用于平稳拔管的半数有效剂量(median effective concentration, EC50), 利用 logistic 回归模型进行概率单位转换, 分析瑞芬太尼 EC50 及其 95%可信区间。比较平稳拔管组与不平稳拔管组平均动脉压和心率。**结果:**采用 Dixon 序贯法算出瑞芬太尼用于老年患者术后平稳拔管的 EC50 0.94 ng/ml, 概率单位换算法计算 EC50 0.99 ng/ml (95%CI=0.52~1.51 ng/ml)。拔管期间, 平稳拔管组平均动脉压、心率明显低于不平稳拔管组 ($P<0.05$)。**结论:**靶控输注 0.94 ng/ml 瑞芬太尼可以减少 50% 的老年患者拔管相关的咳嗽反应, 抑制苏醒期心血管反应, 不导致全麻苏醒延迟, 确保了苏醒期的平稳拔管。

【关键词】阿片类镇痛药; 瑞芬太尼; 老年患者; 剂量; 并发症; 气管拔管

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途径。由于前期临床研究病例数的限制, 未设置对照组的比较, 观察时间较短, 超声剂量学和中远期疗效评估等问题都需要在下一步的临床研究中进行进一步探讨和解决, 同时对于不同程度及类型的增生及相关肿瘤基因、分子转归等问题需要进一步研究。

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Median effective concentration of remifentanyl on target-controlled infusion for smooth emergence from anaesthesia and tracheal extubation in elderly patients

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[Abstract] **Objective:** To determine the median effective concentration of remifentanyl on targeted-controlled infusion (TCI) for smooth emergency from total intravenous anaesthesia and tracheal intubation in elderly patients. **Methods:** Twenty-four ASA I – II grade female elderly patients undergoing elective jaw cyst surgery were enrolled in this study. Median effective concentration (EC_{50}) was determined by Dixon's up-and-down method. During skin suture, effect-site TCI of remifentanyl was titrated to initial concentration of 1 ng/ml for the first patient. If the extubation was defined as smooth extubation, the predetermined concentration for the subsequent patient was decreased by 0.5 ng/ml. If it was considered failed smooth extubation, the predetermined concentration was increased by 0.5 ng/ml for the next patient time. The EC_{50} of remifentanyl was calculated by the Dixon's up-and-down method and the EC_{50} and 95% confidence interval (CI) were analyzed using the probit test in a logistic regression model. Mean arterial pressure (MAP) and heart rate (HR) were compared in patients with smooth extubation and without smooth extubation. **Results:** The EC_{50} of remifentanyl for smooth emergency from anaesthesia and tracheal intubation in elderly patients was 0.94 ng/ml by the Dixon's up-and-down method, the EC_{50} and 95% CI of remifentanyl was 0.99 ng/ml (95% CI 0.52 ng/ml–1.51 ng/ml) by probit analysis respectively. MAP and HR were lower in patients with smooth extubation than in those with failed smooth extubation during tracheal extubation ($P < 0.05$). **Conclusion:** Maintaining a remifentanyl infusion at the optimal concentration of 0.94 ng/ml can suppress coughing associated with tracheal extubation and haemodynamic changes, almost without significantly delaying recovery from anaesthesia and thereby targeting smooth extubation for 50% of the elderly patients.

[Key words] analgesics opioid; remifentanyl; elderly patients; dose; complication, tracheal extubation

老年患者一般应激能力较差,自主神经系统的自控能力不强,麻醉苏醒期拔管反应强烈,尤其是口腔颌骨囊肿手术后,气道解剖结构的改变、伤口辅料、出血、分泌物等影响,易导致心脑血管意外或诱发并存症突然恶化^[1],因此确保苏醒期安全平稳拔管尤为重要。瑞芬太尼具有良好的药理学特性,在镇痛、镇静和镇咳方面优势突出^[2],可用于减轻患者麻醉苏醒期的拔管反应^[3],但目前用于老年患者的量效关系尚不清楚。为此本研究将明确靶控输注瑞芬太尼用于老年患者全凭静脉麻醉 (total intravenous anaesthesia, TIVA) 术后安全平稳拔管的半数有效剂量,供临床参考。

1 资料与方法

1.1 临床资料

选择本院择期全麻下行颌骨囊肿手术的老年女性患者 24 例,年龄 65~78 岁,ASA I ~ II 级,体质量 40~70 kg,身高

150~170 cm。排除有严重的心肺疾病,NYNH 心功能分级 $\geq$ III 级,未经控制的高血压和糖尿病,困难气道史,长期接受镇痛、镇静药物治疗史及阿片类药物成瘾史。

1.2 麻醉方法与过程

入室后开放上肢静脉,30 min 内输注复方电解质注射液 5 ml/kg。面罩给氧,常规监测心电图,血压,氧饱和度,脑电双频指数监测 (bispectral index, BIS)。术前 0.5 h 给予咪唑安定 0.05 mg/kg,阿托品 0.5 mg 肌肉注射。麻醉诱导使用靶控输注泵 (CP-600TCI, minto 模型,北京思路高) 以效应室靶浓度 3 ng/ml 靶控输注 (targeted-controlled infusion, TCI) 瑞芬太尼,以效应室靶浓度 2.5 μ g/ml (CP-600TCI, marsh 模型,北京思路高) TCI 丙泊酚,待患者完全无意识后,静推顺式阿曲库铵 0.15 mg/kg,随后经鼻行气管插管,并连接 Drager Fabius 麻醉机控制呼吸,维持术中 $PetCO_2$ 35~40 mmHg。术中调节丙泊酚效应室靶浓度 (1.5~3.5 μ g/ml) 及瑞芬太尼效应室靶浓度 (1.5~4.0 ng/ml),以维持术中血压心率波动在术前 (基础值) 的 10%~20% 左右及 BIS 值 40~60 之间。开始缝合伤口时,将瑞芬太尼效应室靶浓度调定到预设值 (第 1 例患者设为 1.0 ng/ml),维持该浓度至到拔管,尽可能满足该过程在 15 min 以

上,以确保效应室浓度及血浆浓度的稳定。手术结束时,停用丙泊酚,静推曲马多 2 mg/kg 以替代性镇痛,并常规给予新斯的明 0.02 mg/kg 联合阿托品 0.005 mg/kg 拮抗肌松。同时将机械通气转换为手动通气,待患者自主睁眼,恢复足够的自主呼吸频率及潮气量以维持 $\text{SpO}_2 \geq 95\%$ 及 PetCO_2 35~45 mmHg 后,拔除气管插管,观察 5 min 后送入恢复室。

1.3 评价指标

评判苏醒期拔管是否平稳,基于患者拔管即刻的咳嗽反应,以 5 分量表法来评分:1 分代表拔管时无咳嗽和肌肉强直,2 分代表轻咳(1、2 次)但拔管容易,3 分代表拔管时中度咳嗽(3、4 次),4 分代表拔管时剧烈咳嗽(5~10 次)或伴有肌肉强直,5 分代表烦躁不安以致不能拔管(呛咳>10 次或伴支气管痉挛)^[4]。采用 Dixon 序贯实验法^[5],若当前患者拔管评分 ≥ 3 分,定义为拔管不平稳,则下一位患者瑞芬太尼预设效应室靶浓度增加 0.5 ng/ml。反之若拔管评分 < 3 分,则定义为拔管平稳,下一位瑞芬太尼预设靶浓度减少 0.5 ng/ml。以此类推。记录患者麻醉前(基础值)、瑞芬太尼靶浓度达到预设值时(T0)、拔管时(T1)、拔管后 1 min(T2)和拔管后 5 min(T3)的平均动脉压(mean arterial pressure, MAP)、心率(heart rate, HR)和氧饱和度(pulse oxygen saturation, SpO_2),拔管时呼末二氧化碳分压(end tidal carbon dioxide tension, PetCO_2),手术结束至睁眼时间和拔管时间。送入恢复室后 15 min,记录麻醉恢复评分(post-anesthetic recovery scores, PARS)^[6],疼痛程度的视觉模拟评分(visual analogue scale, VAS; 1 分为无痛,10 分为剧烈疼痛)及不良反应。

1.4 统计学方法

采用 SPSS 17.0 软件包分析,以均数 $\pm$ 标准差($\bar{x} \pm s$)表示。采用 Dixon 序贯法计算瑞芬太尼用于平稳拔管的半数有效量(median effect concentration, EC_{50});利用 logistic 回归模型进行概率单位转换,分析瑞芬太尼 EC_{50} 及其 95% 可信区间;重复测量数据采用重复测量多因素方差分析;其余计量资料采用 t 检验,计数资料采用卡方检验。检验水准 $\alpha=0.05$ 。

2 结果

患者年龄(68.3 ± 4.2)岁,体质量(55.3 ± 5.4) kg,身高(159.5 ± 4.4) cm,麻醉时间(84 ± 20) min。如图 1,靶控输注瑞芬太尼效应浓度(effect concentration, Ce) 1.0 ng/ml 时 10 例患者中有 5 例平稳拔管,输注 Ce 1.5 ng/ml 时 7 例中有 5 例平稳拔管。其余有 2 例输注 Ce 2.0 ng/ml 时均平稳拔管,5 例输注 Ce 0.5 ng/ml 时拔管不平稳。采用 Dixon 序贯法,选出其中 8 对平稳拔管-不平稳拔管的数据计算出瑞芬太尼用于老年患者术后平稳拔管的 EC_{50} (0.94 ± 0.38) ng/ml,概率单位换算法计算 EC_{50} 0.99 ng/ml(95%CI=0.52~1.51 ng/ml)。

麻醉苏醒期间,平稳拔管患者 12 例,不平稳拔管患者 12

例。比较 2 组睁眼时间、拔管时间、拔管时 PetCO_2 、 SpO_2 、PARS 评分、术后镇痛 VAS 评分,差别无统计学意义。2 组未发生严重的呼吸抑制、气管痉挛、误吸等不良反应。见表 1。

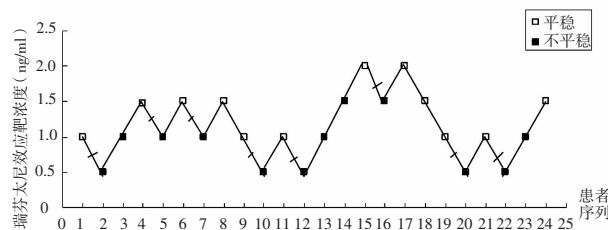


图 1 瑞芬太尼预设浓度下的平稳拔管及不平稳拔管的数据序列

Fig.1 Data sequence of smooth extubation and failed smooth extubation over predetermined concentration of remifentanyl

表 1 2 组患者一般情况、拔管反应及恢复情况的比较($\bar{x} \pm s$)

Tab.1 Comparison of patients' characteristic, response during extubation and recovery profiles between the two groups($\bar{x} \pm s$)

指标	平稳拔管组	不平稳拔管组	统计量值	P 值
患者例数(n)	12	12	/	/
年龄(岁)	69.4 ± 4.9	67.2 ± 3.4	1.308	0.204
睁眼时间(s)	296 ± 109	268 ± 109	0.637	0.531
拔管时间(s)	408 ± 111	388 ± 100	0.475	0.639
拔管反应(1/2/3/4/5)	8/4/0/0/0	0/0/3/9/0	4.333	0.228
PetCO_2 (mmHg)	41 ± 7	39 ± 6	0.964	0.346
PARS	9.2 ± 0.4	8.9 ± 0.5	1.342	0.193
VAS	3.0 ± 1.5	3.5 ± 1.5	-0.804	0.430
SpO_2	97 ± 1	98 ± 1	-1.343	0.193

拔管期间,不同时间点平均动脉压(MAP)($F_1=60.07, P_1<0.001$)和心率(HR)($F_1=57.71, P_1<0.001$)之间有统计学差异。拔管时平稳组及不平稳组 MAP、HR 呈上升趋势,5 min 后逐渐下降。其中平稳组 MAP($F_5=5.41, P_5=0.03$)及 HR($F_5=4.77, P_5=0.04$)明显低于不平稳组。从各时间点看,在拔管时(T1)、拔管后 1 min(T2)及 5 min(T3)平稳组 MAP、HR 明显低于不平稳组($P<0.05$)。总体来看,时间因素与分组因素之间存在交互效应,分别为 MAP($F_{1 \times 5}=11.78, P_{1 \times 5}<0.001$)和 HR($F_{1 \times 5}=4.20, P_{1 \times 5}=0.004$)。见表 2。

3 讨论

Dixon 序贯法是计算 EC_{50} 的常用方法之一^[7],本研究通过该法获得瑞芬太尼用于老年患者在应用丙泊酚-瑞芬太尼 TIVA 后平稳拔管的靶控效应浓度 EC_{50} 0.94 ng/ml,与采用概率单位换算法计算出结果类似。气管拔管时频繁的咳嗽易导致血压、心率、颅内压、眼内压急剧升高,引起心血管的不良

表 2 不同时间点两组血流动力学比较 ($\bar{x} \pm s$)Tab.2 Hemodynamic comparison between the two groups at different time points ($\bar{x} \pm s$)

血流动力学指标		拔管期间不同时刻					F 值	P 值
		Baseline	T0	T1	T2	T3		
MAP (mmHg)	平稳组	96.8 ± 11.1	95.7 ± 10.9	102.5 ± 9.1	106.8 ± 10.3	92.6 ± 8.3	$F_t=60.07$	$P_t=0.000$
	不平稳组	98.9 ± 10.2	96.3 ± 10.2	116.5 ± 9.9	118.3 ± 8.7	106.8 ± 9.7		
	F 值	0.241	0.024	12.912	8.779	14.836	$F_{t \times g}=11.78$	$P_{t \times g}=0.000$
	P 值	0.628	0.878	0.002	0.007	0.001		
HR (bpm)	平稳组	74 ± 11	82 ± 10	90 ± 9	93 ± 11	80 ± 8	$F_t=57.71$	$P_t=0.000$
	不平稳组	78 ± 10	83 ± 12	102 ± 11	106 ± 9	88 ± 9		
	F 值	0.892	0.003	8.448	9.292	5.274	$F_{t \times g}=4.20$	$P_{t \times g}=0.004$
	P 值	0.355	0.956	0.008	0.006	0.032		

注: t 时间因素主效应的统计量和 P 值; g 分组因素主效应的统计量和 P 值; t × g 时间因素与分组因素交互效应的统计量和 P 值

反应^[8]。因而有效地预防并控制拔管时的咳嗽反应, 确保平稳苏醒是麻醉医生必备的技能。

一些研究证实阿片类药物可以抑制咳嗽, 在吸入异氟醚全麻后给予 2 μg/kg 芬太尼或阿芬太尼 15 μg/kg 可以减弱苏醒期咳嗽反应及心血管刺激^[9]。然而 Shaja 等研究认为术后单次输注 0.1 μg/kg 瑞芬太尼可以抑制苏醒期心血管反应, 却不能减少咳嗽的发生^[10]。阿片类药物的镇咳作用以中枢性为主, 由于瑞芬太尼时量半衰期较短, 单次给药难以维持足够的血浆浓度或效应室浓度, 这可能就是其不能减少苏醒期咳嗽发生的原因^[7]。因此本研究认为持续给药更有利于其发挥镇咳特性, 但目前使用剂量尚未统一。据报道, 持续泵注小剂量瑞芬太尼可以有效抑制苏醒期心血管反应, 减少拔管相关的咳嗽反应, 且并不导致全麻苏醒延迟^[8], 维持剂量可以达到 0.1~0.2 μg/(kg·min)^[11]。本研究也发现平稳拔管组的血流动力学改变明显低于不平稳拔管组。但过高剂量的瑞芬太尼可以导致呼吸频率及分钟通气量的减少, Calderon 等研究认为要维持足够的自主呼吸, 瑞芬太尼的剂量不应超过 μg/(kg·min)^[12]。Machata 等则认为泵注最小剂量为 0.025~0.05 μg/(kg·min) 瑞芬太尼, 就可以使开腹术后代管带管的患者在清醒且保留自主呼吸的情况下维持最佳的气管插管耐受性^[13]。

由于老年患者重要脏器功能的下降, 在使用麻醉药物时应重视其特殊性。同传统的输注方法相比, TCI 可以提供更精确、更平稳的血药浓度有利于患者全麻恢复^[14]。有研究认为采用丙泊酚-瑞芬太尼的 TIVA 就具有减少拔管相关的咳嗽反应的优势,

相比基于吸入七氟醚的复合麻醉更有利于苏醒期的稳定^[15]。因此, 本实验采用 TIVA 技术用于老年患者, 旨在明确发挥瑞芬太尼镇咳作用的安全有效靶控效应浓度。Albertin 等研究发现在联合应用其他麻醉药的情况下瑞芬太尼靶控效应浓度 Ce 1~3 ng/ml 可以有效抑制 50% 患者切片刺激引起的交感反应^[16-17]。瑞芬太尼靶浓度达到 Ce 4 ng/ml 时可以满足喉镜检查的需要, Ce 2~5 ng/ml 可以满足手术需要^[18]。Jun 等认为在联合应用七氟醚全麻后抑制苏醒期呛咳反应的理想瑞芬太尼 Ce 为 1.5 ng/ml, 但该浓度也可能造成苏醒延迟^[19]。而 Kim 等则认为输注 Ce 1.0 ng/ml 小剂量的瑞芬太尼便可满足术后 ICU 患者脱机拔管的需要, 且不引起呛咳和血流动力学的明显改变^[20]。为此本实验设定瑞芬太尼靶浓度从较小的剂量开始, 选择 1 ng/ml 作为初始浓度。考虑到大剂量的瑞芬太尼可以导致患者术后痛觉敏感性增加^[21], 在手术结束时给予曲马多作为替代性镇痛, 两组术后均未出现呼吸抑制等不良反应。本次实验也有几点不足, 首先由于丙泊酚麻醉下药效及药代动力学存在性别的差异, 通常女性比男性苏醒更快^[20], 只选择了女性患者作为研究对象以减少干扰; 其次, 该靶浓度是通过 Minto 药代动力学模型计算出来的预测值, 并非实际测血浆浓度, 存在一定的偏差和不准确性, 但并不影响临床应用^[22]。再次, 本研究仅限于颌面部手术, 还有待进一步探索在其他类型手术中的应用。

综上, 通过本实验获得瑞芬太尼用于老年患者 TIVA 后平稳拔管的半数有效剂量 0.94 ng/ml。输注该浓度可以减少 50% 的老年患者拔管相关的咳嗽

反应,抑制苏醒期心血管反应,不导致全麻苏醒延迟,确保了苏醒期的平稳拔管。

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