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依托咪酯持续输注对乳腺癌根治术患者血流动力学及炎症介质的影响 *

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摘要 目的:研究依托咪酯持续输注用于乳腺癌根治术患者的镇痛效果及对血流动力学与炎症介质的影响。**方法:**选取 2015 年 8 月至 2016 年 7 月我院收治的 84 例乳腺癌根治术患者,根据患者入院顺序分为观察组和对照组,42 例每组。观察组持续输注依托咪酯,对照组持续输注丙泊酚。比较两组患者手术后不同时点视觉模拟评分(VAS),拔管时舒张压(DBP)、收缩压(SBP)、心率(HR)及血清白介素-2(IL-2)、IL-10、IL-12 水平的变化。**结果:**拔管时,观察组的 DBP、SBP、HR 水平显著低于对照组($P<0.05$)。观察组在术后 1、5、10、24、48 h 的 VAS 评分均显著低于对照组($P<0.05$)。观察组术后 3 天时血清 IL-2 水平显著高于对照组($P<0.05$),IL-10、IL-12 水平显著低于对照组($P<0.05$)。**结论:**依托咪酯持续输注用于乳腺癌根治术患者中的镇痛效果良好,且对患者血流动力学与炎症反应的影响较小。

关键词:依托咪酯;乳腺癌;镇痛效果;血流动力学;炎症介质

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Analgesic Effect of Etomidate Infusion for Radical Mastectomy in Breast Cancer and Its Effect on Hemodynamics and Inflammatory Mediators*

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ABSTRACT Objective: To study the analgesic effect of etomidate infusion for radical mastectomy in breast cancer and its effect on hemodynamics and inflammatory mediators. **Methods:** From August 2015 to July 2016, 84 patients with radical mastectomy were divided into the observation group and the control group according to the order of admission. The observation group was given continued infusion of etomidate, the control group was given continued infusion of propofol. The visual analogue (VAS) at different time points after operation, diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) at the time of extubation and serum IL-2, IL-10, IL-12 levels at 72 hours after operation were compared between two groups. **Results:** At the time of extubation, the DBP, SBP and HR were significantly lower in the observation group than in the control group ($P<0.05$). The VAS scores of observation group were significantly lower than those of the control group at 1, 5, 10, 24 and 48 hours after operation ($P<0.05$). The serum levels of IL-2 in the observation group was significantly higher than that of the control group ($P<0.05$), IL-10 and IL-12 levels were lower than control group ($P<0.05$). **Conclusion:** Sustained infusion of etomidate had good analgesic effect in the treatment of breast cancer patients underwent radical mastectomy with little effect on the hemodynamics and inflammatory mediators.

Key words: Etomidate; Breast cancer; Analgesic effect; Hemodynamics; Inflammatory mediators

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前言

乳腺癌患者的机体免疫状态本身已处于低下的状态,在加上手术给机体带来的伤害性刺激,短期内会抑制机体细胞免疫功能^[1]。在围术期使用阿片类药物及术后镇痛能缓解应激反应,有利于减轻患者术后疼痛感,进而降低患者术后免疫抑制^[2]。但相关研究显示芬太尼、吗啡等阿片类药物本身具备免疫抑制功能,不利于乳腺癌根治术患者的炎症介质及血流动力学维持在平稳状态^[3]。依托咪酯作为咪唑类衍生物的麻醉镇静药,具有作用时间短、起效快、可迅速平稳恢复的特点,尤为适用于心血管疾病或老年体弱患者,已广泛应用于全身麻醉^[4,5]。为给临床在

乳腺癌根治术麻醉中提供更多可借鉴之处,本研究主要探讨了依托咪酯持续输注用于乳腺癌根治术患者的镇痛效果及对血流动力学与炎症介质的影响。

1 资料与方法

1.1 临床资料

选取 2015 年 8 月至 2016 年 7 月我院收治的 84 例行乳腺癌根治术治疗的患者视为本次研究对象。纳入标准:① 美国麻醉医师协会分级 I~II 级^[6];② 无精神、神经等系统性疾病者;③ 依从性较好者,能配合医务人员完成本次试验;④ 无恶病质、过度肥胖患者。排除标准:① 肝、肾、脑、肺、心、肾、内分泌疾病者;

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① 肾上腺皮质功能异常者;② 乙醇依赖史者;③ 长时间使用抗癫痫、镇静催眠药。本次研究已取得我院伦理委员会批准,及得到患者及家属同意。根据患者入院顺序分为观察组和对照组,42 例每组。观察组年龄为 34~58 岁,平均(44.21± 4.02)岁;体质量为 52~66 kg,平均(58.21± 1.45)kg。对照组年龄为 35~60 岁,平均(44.27± 4.13)岁;体质量为 51~65 kg,平均(58.17± 1.51)kg。两组患者年龄、体质量比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

术前患者需禁饮、禁食,静脉点滴 9 mL·kg⁻¹·h⁻¹ 的乳酸林格液,和静脉麻醉泵相连接,对脑电双频指数(BIS)、呼气末二氧化碳分压(PETCO₂)、脉搏氧饱和度(SpO₂)、呼吸(RR)、无创血压(NBP)、心率(HR)、心电图(ECG)等生命体征进行常规监测。术前 20 min 注射 0.5 mg 阿托品,静脉注射 8 mg 地塞米松。麻醉诱导,常规给氧去氮 5 min,观察组静脉注射 0.6 mg·kg⁻¹ 罗库溴铵,0.3 mg·kg⁻¹ 依托咪酯(生产厂家:江苏恩华药业股份有限公司,生产批号:20150203,规格:20 mg/10 mL),2~3 μg·kg⁻¹ 芬太尼进行快速诱导,肌肉松弛后插入喉罩,随之控制呼吸。对照组予以 1~1.5 mg·kg⁻¹ 的丙泊酚(生产厂家:英国阿斯利康公司,生产批号:20150105,规格:50 mg/50 mL)进行诱导,其余诱导和观察组一致。将潮气量设定为 8~10 mL·kg⁻¹,PETCO₂ 保持在 35~45 mmHg,呼吸比为 1:2,呼吸频率为 12 次/min。麻醉维持:持续静脉输注 0.3 μg·kg⁻¹·min⁻¹ 芬太尼,观察组用依托咪酯 10~15 μg·kg⁻¹·min⁻¹ 的依托咪酯维持麻醉;对照组用 6~8 mg·kg⁻¹·min⁻¹ 的丙泊酚维持麻醉。所有患者均需开展全凭静脉麻醉,在外科手术过程中,清扫腋尖淋巴结时,可予以 10 mg 阿曲

库铵。为避免术后疼痛的发生,在手术结束前 20 min 需给予 5 mg 地佐辛。术后患者呼之睁眼、自主呼吸恢复后拔管。

1.3 观察指标

比较两组患者麻醉前、拔管时舒张压(DBP)、收缩压(SBP)、心率(HR)血流动力学指标变化。比较两组患者术后 1 h、5 h、10 h、24 h、48 h 的视觉模拟评分(VAS),在 10 cm 的刻度尺上进行标注,其中 10 表示剧痛,0 表示无痛,中间则为不同程度上的疼痛,让患者自我感觉对当前疼痛感做出相应的标注,分数越高则表明疼痛程度越为严重。比较两组患者麻醉前和术后 3 d 白细胞介素 -2(IL-2)、白细胞介素 -10(IL-10)、白细胞介素 -12(IL-12)水平变化,分别在麻醉前和术后 3 d 抽取两组患者 3 mL 的空腹静脉血,转速 3000 r/min,离心 15 min,分离血清后,提取上清液,放置在 -50℃ 低温箱中待测,使用酶联免疫吸附法检测 IL-2、IL-10 浓度。分析两组患者术后不良反应情况,包括呼吸抑制、体动、恶心呕吐等。

1.4 统计学处理

选取 spss11.5 软件包对本次实验数据予以处理,计量资料以($\bar{x} \pm s$)表示,采用 t 检验,计数资料以[n(%)]表示,采用 χ^2 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者麻醉前后血流动力学指标的比较

麻醉前,两组患者 DBP、SBP、HR 水平比较差异无统计学意义($P>0.05$)。拔管时,两组患者 DBP、SBP、HR 水平较麻醉前显著升高($P<0.05$),和观察组相比,对照组 DBP、SBP、HR 水平升高的幅度更为显著($P<0.05$),见表 1。

表 1 两组患者麻醉前后血流动力学指标变化($\bar{x} \pm s$)

Table 1 Comparison of the changes of hemodynamics between two groups before and after anesthesia ($\bar{x} \pm s$)

Items	Control (n=42)		Observation (n=42)	
	Before anesthesia	Extubation	Before anesthesia	Extubation
DBP(mmHg)	74.21± 5.25	83.98± 7.12*	74.18± 5.24	80.13± 6.26**
SBP(mmHg)	124.21± 11.02	142.02± 14.12*	124.18± 11.05	135.98± 13.21**
HR(time·min ⁻¹)	75.32± 7.15	91.25± 9.11*	75.38± 7.13	83.67± 8.02**

Note: Compared with before anesthesia,* $P<0.05$; Compared with control group extubation, ** $P<0.05$.

2.2 两组患者术后不同时间点 VAS 评分的比较

两组患者术后 1 h、5 h、10 h、24 h、48 h 的 VAS 评分呈不

同程度上的下降趋势,和对照相比,观察组在术后 1 h、5 h、10 h、24 h、48 h 的 VAS 评分明显较低($P<0.05$),见表 2。

表 2 两组患者术后不同时间点 VAS 评分的比较($\bar{x} \pm s$)

Table 2 Comparison of the VAS score at different time points after surgery between two groups($\bar{x} \pm s$)

Groups	At 1h after surgery	At 5h after surgery	At 1h after surgery	At 24h after surgery	At 48h after surgery
Observation (n=42)	2.41± 0.26*	2.05± 0.21*	1.85± 0.16*	1.64± 0.13*	1.23± 0.09*
Control (n=42)	3.21± 0.32	2.76± 0.32	2.35± 0.21	2.02± 0.18	1.87± 0.13

Note: Compared with control group,* $P<0.05$.

2.3 两组患者麻醉前后血清 IL-2、IL-10、IL-12 水平的比较

麻醉前,两组患者血清 IL-2、IL-10、IL-12 水平比较差异无统计学意义($P>0.05$),术后 3 d,两组患者血清 IL-2 水平较术前显著降低($P<0.05$),血清 IL-10、IL-12 水平较术前显著升高($P<0.05$),与观察组相比,对照组上述指标的变化更为显著($P<0.05$),见表 3。

2.4 两组患者不良反应发生情况的比较

观察组中有 1 例患者发生呼吸抑制,2 例患者发生恶心呕吐;对照组中有 2 例患者发生呼吸抑制,3 例患者发生恶心呕吐。观察组和对照组的不良反应的发生率比较差异无统计学意义($P>0.05$)。

表 3 两组患者麻醉前后血清 IL-2、IL-10、IL-12 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum IL-2, IL-10 and IL-12 levels between two groups before and after anesthesia($\bar{x} \pm s$)

Items	Control (n=42)		Observation (n=42)	
	Before anesthesia	After surgery 3d	Before anesthesia	After surgery 3d
IL-2(pg/mL)	74.48 $\pm$ 7.15	62.39 $\pm$ 6.02*	74.51 $\pm$ 7.09	68.94 $\pm$ 6.34**
IL-10(pg/mL)	18.32 $\pm$ 1.09	28.98 $\pm$ 2.45*	18.39 $\pm$ 1.12	23.48 $\pm$ 2.01**
IL-12(pg/mL)	54.12 $\pm$ 5.02	78.43 $\pm$ 7.53*	54.18 $\pm$ 5.06	67.97 $\pm$ 6.21**

Note: Compared with before anesthesia, *P<0.05; Compared with control group after surgery 3d, **P<0.05.

3 讨论

手术创伤会对神经末梢造成直接刺激性影响,进而出现疼痛反应,疼痛感应器敏感性也会随之加强,扩大中枢神经系统对伤害的敏感性,导致中枢神经敏感化^[7-9]。乳腺癌根治术后会遗留较大的手术范围,术后伴存在相应的疼痛感,伴有多种细胞和化学因子生成和引发组织释放,对伤害性感受器起着激活的作用,给患者造成痛苦^[10-12]。尽管阿片类镇痛药物能在缓解围术期疼痛以及应激反应情况下,进而缓解术后免疫抑制反应^[13,14]。然而相关研究表明吗啡有着较为显著的免疫抑制效应,芬太尼能阻碍细胞因子的产生及 T 淋巴细胞功能,并且呈现出剂量依赖性。相关研究者提出 u- 阿片受体选择性激动剂 DANGO 能对丝裂原所诱导的 T 淋巴细胞增殖发挥阻碍作用,但是 k-阿片受体激动剂并没有此类变化^[15-17]。可见,在临床中选取合理的术后镇痛方案或缓解免疫抑制的镇痛药物显得颇为关键。

丙泊酚在中性粒细胞所参与的炎性反应众多环节中能发挥有效抑制作用,能阻碍机体过度炎性反应,在人外周血淋巴细胞功能中并不会产生显著的抑制作用,是会对细胞免疫功能造成损害的静脉麻醉药^[18-20]。但依托咪酯给循环系统所造成的影响较小,相关研究者提出和丙泊酚相比,用依托咪酯维持麻醉给乳腺癌根治术患者围术期血浆细胞因子所带来的影响相似,主要是在剂量合理的范围内,依托咪酯给循环功能所造成的干扰较小,并且具有一定程度的皮质抑制作用^[21-23]。本次研究结果显示给予乳腺癌根治术患者持续输注依托咪酯后,其在术后 1、5、10、24、48 h 的 VAS 评分显著低于丙泊酚麻醉诱导者,并且给 DBP、SBP、HR 所造成的影响相对小于丙泊酚麻醉者,提示依托咪酯的镇痛效果良好,能使患者血流动力学状态维持在相对稳定的状态。

IL-2 主要由 Th1 细胞分泌,能有效刺激 CTL、CD8⁺ 的分化和增殖,激活 NK 细胞,进而增强细胞毒性^[24,25]。一旦机体细胞免疫功能受到抑制,IL-2 诱生水平会显著降低^[26]。IL-10 由 Th2 细胞等产生,一旦机体发生肿瘤时,IL-10 会在多方面机制作用下对机体细胞免疫发挥抑制作用,抑制抗原提呈细胞的抗原提呈能力,阻碍 CD8⁺CTL 的增殖及细胞毒效应,阻碍 CD4⁺Th1 细胞因子合成和细胞分化,还会影响肿瘤细胞在 NK 细胞中的敏感性及降低 NK 细胞的抗肿瘤活性^[27,28]。IL-12 的产生来自于单核吞噬细胞,能促进 B 细胞合成分泌免疫球蛋白,能促进淋巴因子活化的杀伤能力和杀伤细胞增殖分化及自然杀伤细胞能力^[29,30]。本次研究结果显示给予持续输注依托咪酯的乳腺癌根治术患者术后 3 d 的血清 IL-2 水平显著降低,IL-10、IL-12 水平明显上升,但上述指标波动幅度显著小于丙

泊酚麻醉者,提示依托咪酯能安全抑制乳腺癌根治术患者术后的炎症反应。

总之,依托咪酯持续输注用于乳腺癌根治术患者中的镇痛效果良好,且对患者血流动力学与炎症反应的影响较小。

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