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右美托咪啶联合布托啡诺对老年腹腔镜胃肠肿瘤根治术后 认知功能障碍的影响*

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摘要 目的: 探究右美托咪啶联合布托啡诺对老年腹腔镜胃肠肿瘤根治术后认知功能障碍的影响。**方法:** 选取 2015 年 8 月~2018 年 9 月在我院行腹腔镜胃肠肿瘤根治术的老年患者 80 例进行回顾性分析,根据术前用药情况不同分为两组,观察组术前给予右美托咪啶联合布托啡诺,对照组术前给予等量生理盐水。比较两组患者的 Ramsay 镇静评分、术前和术后不同时间点认知功能评分、血清 S-100 β 蛋白 (S-100 β protein, S-100 β)、神经元特异性烯醇酶 (Neuron-specific enolase, NSE) 和白介素 -6 (Interleukin-6, IL-6) 水平的变化及不良反应的发生情况。**结果:** 观察组患者拔管时、拔管后 4 h、拔管后 8 h 和拔管后 12 h 的 Ramsay 镇静评分显著优于对照组 ($P<0.05$)。两组患者手术前 1d(T0) 时简易智能精神状态检查量表 (mini-mental state examination, MMSE) 各项评分及总分相比均无统计学差异 ($P>0.05$), 观察组手术后 1d(T1) 和手术后 2d(T2) 时 MMSE 各项评分及总分均显著高于对照组 ($P<0.05$)。观察组患者 T1 时血清 S-100 β 和 IL-6 水平显著低于对照组, T1 和 T2 时血清 NSE 水平均显著低于对照组 ($P<0.05$)。两组患者恶心、呕吐、嗜睡和头晕的发生率相比均无统计学差异 ($P>0.05$)。**结论:** 老年腹腔镜胃肠肿瘤根治术前应用右美托咪啶联合布托啡诺可显著改善患者的术后认知功能, 提高麻醉效果, 且不增加并发症的发生率。

关键词: 右美托咪啶; 布托啡诺; 腹腔镜; 老年胃肠肿瘤根治术; 术后认知功能障碍

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Effect of Dexmedetomidine Combined with Butorphanol on the Cognitive Dysfunction after Gastrointestinal Tumors Laparoscopic Radical in the Elderly Patients*

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ABSTRACT Objective: To investigate the effect of dexmedetomidine combined with butorphanol on cognitive dysfunction after gastrointestinal tumors laparoscopic radical in elderly patients. **Methods:** 80 elderly patients who underwent laparoscopic radical for gastrointestinal tumors in our hospital from August 2015 to September 2018 were selected for retrospective analysis. According to the different preoperative drug use, they were divided into two groups. The observation group was given dexmedetomidine combined with butorphanol preoperatively, and the control group was given the same amount of normal saline preoperatively. Ramsay sedative score, Ramsay sedative score, preoperative and postoperative cognitive function score, S-100 β , NSE and IL-6 levels and adverse reactions were compared between the two groups. **Results:** The Ramsay sedative score of patients in the observation group was significantly better than that in the control group ($P<0.05$) at the time of extubation, at 4h, 8h and 12h after extubation. There was no statistically significant difference in the MMSE score and total score between the two groups at T0 before surgery ($P>0.05$). The MMSE scores and total scores in the observation group at T1 and T2 were significantly higher than those in the control group ($P<0.05$). At T1, the serum levels of S-100 β and IL-6 in the observation group were significantly lower than those in the control group, and serum NSE levels at T1 and T2 were significantly lower than those in the control group ($P<0.05$). There was no statistically significant difference in the incidence of nausea, vomiting, drowsiness and dizziness between the two groups ($P>0.05$). **Conclusion:** The application of dexmedetomidine combined with butorphanol before laparoscopic radical can significantly improve the postoperative cognitive function, anesthesia effect for the elderly patients with gastrointestinal tumors, and it won't increase the incidence of complications.

Key words: Dexmedetomidine; Butorphanol; Laparoscopic; Gastrointestinal tumors radical in elderly patients; Postoperative cognitive impairment

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前言

术后认知功能障碍是手术后出现的一种中枢神经系统并发症,临床表现为注意力、记忆力、语言理解等方面的功能下降,多发于老年患者^[1,2]。有研究显示普通全麻患者术后约有19%出现认知功能障碍,而老年患者高达25.8%左右^[3]。老年患者术后认知功能障碍一般发生在术后1~3 d,部分患者发生的时间更长,甚至可持续至术后数月甚至数年,可延迟患者康复,延长住院时间,甚至出现自理能力下降和老年痴呆,严重影响老年患者的健康与生活^[4,6]。目前,老年胃肠肿瘤的发病率显著上升,有大量的老年甚至高龄患者接受手术治疗,术后认知功能对老年患者的影响成为关注的热点^[7,8]。

术后认知功能障碍的发病机制目前尚不完全清楚,研究表明可能与手术、麻醉药物的使用和年龄等因素有关^[9-11]。目前,临床对于术后认知功能障碍并没有绝对有效的防治措施。布托啡诺是一种混合型阿片受体激动-拮抗剂,具有较高的中枢神经受体选择性,对神经递质的影响较小,从而减轻对认知功能的影响^[12-14]。右美托咪啶为 α_2 肾上腺素能受体激动剂,具有镇静、镇痛、抗炎及显著的神经保护作用^[15-17]。因此,本研究主要探讨了右美托咪啶联合布托啡诺对老年腹腔镜胃肠肿瘤根治术术后认知功能障碍的影响。

1 资料与方法

1.1 一般资料

选取2015年8月~2018年9月在我院行腹腔镜胃肠肿瘤根治术的老年患者80例进行回顾性分析,纳入标准:①年龄65~85岁;②行腹腔镜下胃肠肿瘤根治术。排除标准:①长期服用抗炎、抗抑郁药物及镇静剂者;②有血管意外及神经系统手术史者;③合并严重视听觉障碍者;④合并心、肝、肾等重要器官功能障碍者。根据术前用药情况不同分为两组,对照组40例,男17例,女23例;年龄65~82岁,平均 72.52 ± 3.57 岁;观察组40例,男19例,女21例;年龄66~83岁,平均 73.84 ± 3.86 岁。两组患者一般资料比较无统计学差异($P > 0.05$),具有可比性。

1.2 方法

两组患者术前均禁食8~12 h,禁水8 h,入室后监测患者的心电图、血氧饱和度、无创血压,在局麻下行右侧颈内静脉穿刺置管及桡动脉穿刺置管并监测有创血压。静脉注射咪达唑仑

0.05 mg/kg、舒芬太尼0.5 μ g/kg、依托咪酯0.3 mg/kg,顺式阿曲库铵0.2 mg/kg进行麻醉诱导。麻醉诱导后行气管插管并行机械通气控制呼吸,维持PETCO₂在35~45 mmHg。术中吸入1%~2%的七氟醚联合丙泊酚和瑞芬太尼静脉输注,丙泊酚4~6 mg/(kg·h),瑞芬太尼10 μ g/(kg·h)维持麻醉,间断推注顺式阿曲库铵维持肌松。术中监测BIS,维持BIS值为40~60。观察组患者在麻醉诱导前15 min静脉泵注右美托咪啶0.5 μ g/kg,然后以0.5 μ g/(kg·h)维持至手术结束前30 min,麻醉诱导前5 min静脉注射布托啡诺1 mg。对照组患者给予等量生理盐水。如手术过程中血压低于正常值30%,给予麻黄碱,心率慢于50次/min则给予阿托品。术后患者均采用舒芬太尼进行自控静脉镇痛,舒芬太尼2 μ g/kg加入生理盐水100 mL,负荷量为2 mL,持续输注量为2 mL/h,PCA量为2 mL,锁定时间15 min。

1.3 观察指标

①比较两组患者的Ramsay镇静评分,分别于拔管时、拔管后4 h、拔管后8 h和拔管后12 h对患者进行Ramsay镇静评分。1分:患者清醒、焦虑、不安;2分:患者清醒合作,定向力良好;3分:患者清醒,仅对指令有反应;4分:患者睡眠,对轻叩眉间或强声刺激反应敏捷;5分:患者睡眠,对轻叩眉间或强声刺激反应迟钝;6分:患者睡眠,对轻叩眉间或强声刺激无反应。

②比较两组患者的认知功能,采用简易智能精神状态检查量表(MMSE)分别于T₀、T₁、T₂进行评分,该量表包括汉字旋转测验、简单计算能力、单词再忆测试和图片再认。满分为30分,术后低于术前2分以上且总分 ≤ 24 分为术后认知功能障碍。

③比较两组患者的血清学相关指标,分别于T₀、T₁、T₂抽取两组患者空腹静脉血3 mL,采用ELISA检测患者的S-100 β 、NSE和IL-6水平,试剂盒均由苏州卡尔文生物科技有限公司提供。④比较两组患者的不良反应发生情况。

1.4 统计学方法

使用SPSS16.0对采集的数据实施分析,计数资料以率(%)的形式表示,组间比较采用卡方检验,计量资料以($\bar{x} \pm s$)的形式表示,组间比较采用t检验,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者 Ramsay 镇静评分比较

观察组患者拔管时、拔管后4 h、拔管后8 h和拔管后12 h的Ramsay镇静评分显著高于对照组($P < 0.05$),具体数据如表1所示:

表1 两组患者 Ramsay 镇静评分比较

Table 1 Comparison of the Ramsay sedation score between two groups

Groups	Cases	Tube drawing	4 h after extubation	8 h after extubation	12 h after extubation
Control group	40	1.91 $\pm$ 0.41	1.95 $\pm$ 0.46	2.01 $\pm$ 0.51	2.00 $\pm$ 0.49
Observation group	40	2.54 $\pm$ 1.65	2.47 $\pm$ 1.53	2.36 $\pm$ 0.48	2.26 $\pm$ 0.41
t	-	-2.344	-2.058	-3.161	-2.574
P	-	0.024	0.045	0.002	0.012

2.2 两组患者不同时间点认知功能 MMSE 评分比较

两组患者T₀时MMSE各项评分及总分相比无统计学差

异($P > 0.05$),观察组T₁和T₂时MMSE各项评分及总分均显著高于对照组($P < 0.05$),具体数据如表2所示。

表 2 两组患者不同时间点认知功能 MMSE 评分比较($\bar{x} \pm s$, 分)Table 2 Comparison of the MMSE score at different time points between two groups($\bar{x} \pm s$, score)

Groups	Time	Chinese characters rotation	Words have again	Simple calculation	Image recognition	Total score
Control group (n=40)	T0	4.23 $\pm$ 1.03	8.01 $\pm$ 2.35	2.95 $\pm$ 0.71	12.32 $\pm$ 3.12	26.56 $\pm$ 6.84
	T1	1.81 $\pm$ 0.48	3.01 $\pm$ 0.84	0.81 $\pm$ 0.21	7.58 $\pm$ 2.03	13.52 $\pm$ 3.47
	T2	3.12 $\pm$ 0.85	5.85 $\pm$ 1.16	1.41 $\pm$ 0.34	10.25 $\pm$ 3.01	20.47 $\pm$ 6.32
Observation group (n=40)	T0	4.31 $\pm$ 1.11	7.98 $\pm$ 2.13	2.78 $\pm$ 0.65	11.36 $\pm$ 3.27	25.85 $\pm$ 6.14
	T1	2.45 $\pm$ 0.68*	4.02 $\pm$ 0.98*	1.32 $\pm$ 0.35*	10.58 $\pm$ 3.04*	18.26 $\pm$ 5.14*
	T2	4.23 $\pm$ 0.88*	7.56 $\pm$ 2.04*	2.58 $\pm$ 0.57*	12.41 $\pm$ 3.21*	25.85 $\pm$ 6.11*

注:与对照组相比, * $P < 0.05$ 。Note: Compared with the control group, * $P < 0.05$.

2.3 两组患者不同时间点血清 S-100 β 、IL-6 及 NSE 水平的比较 对照组, T1 和 T2 时血清 NSE 水平均显著低于对照组 ($P < 0.05$), 具体数据如表 3 所示。

表 3 两组患者不同时间点血清 S-100 β 、IL-6 及 NSE 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum S-100 β , IL-6 and NSE levels at different time points between two groups($\bar{x} \pm s$)

Groups	Time	S-100 β (μ g/L)	NSE(μ g/L)	IL-6(pg/mL)
Control group (n=40)	T0	0.19 $\pm$ 0.05	5.78 $\pm$ 1.32	21.33 $\pm$ 6.02
	T1	0.29 $\pm$ 0.08	10.21 $\pm$ 3.02	37.98 $\pm$ 10.12
	T2	0.20 $\pm$ 0.04	11.55 $\pm$ 3.32	25.59 $\pm$ 7.04
Observation group (n=40)	T0	0.20 $\pm$ 0.05	5.79 $\pm$ 1.41	22.08 $\pm$ 6.14
	T1	0.21 $\pm$ 0.06*	6.03 $\pm$ 1.87*	22.87 $\pm$ 6.51*
	T2	0.22 $\pm$ 0.06	5.89 $\pm$ 1.41*	23.95 $\pm$ 6.38

注:与对照组相比, * $P < 0.05$ 。Note: Compared with the control group, * $P < 0.05$.

2.4 两组患者的不良反应发生情况的比较 学差异($P > 0.05$), 具体数据如表 4 所示。

两组患者恶心、呕吐、嗜睡和头晕的发生率相比均无统计

表 4 两组患者的不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	Cases	Nausea	Vomiting	Drowsiness	Dizzy
Control group	40	3(503.00)	0(37.50)	6(12.50)	5(87.50)
Observation group	40	6(62.50)	2(32.50)	10(4.00)	8(95.00)
χ^2	-	1.127	2.051	1.250	0.827
P	-	0.481	0.494	0.264	0.363

3 讨论

认知是机体认识和获取知识的一种智能加工过程, 而认知的基础是大脑皮层的正常生理功能, 任何引起大脑皮层结构和功能变化的因素均能够导致认知功能障碍^[18-20]。术后认知功能障碍多见于接受大手术后的老年患者, 随着微创技术的发展, 腹腔镜手术以创伤小、恢复快等优势广泛应用于老年患者, 但由于腹腔镜手术在术中实施 CO₂ 气腹, 改变体位等, 对麻醉技术的要求更高。目前认为术后认知功能障碍是多种因素相互作用的结果, 在老年患者神经退化的基础上, 由于手术、麻醉等多种因素联合作用而诱发神经功能的减退, 包括中枢神经系统、

内分泌系统和免疫系统^[21-23]。有研究显示^[24]麻醉药物会导致神经系统的病理变化, 可引起神经细胞凋亡、神经变性, 最终引起认知功能损害。手术应激可引起大量炎性介质的释放, 而炎症反应参与了中枢神经的病理生理过程^[25,26]。因此, 如何降低神经细胞损伤及炎性因子对于认知功能的损害成为防治术后认知功能障碍的关键。

NSE 主要存在于神经元中, 是一种神经元损伤的特异性蛋白^[27]。S-100 β 是一种钙结合蛋白, 主要存在于神经胶质细胞, 是神经胶质细胞损伤的标记性蛋白^[28]。当神经元和神经胶质细胞受损时, 血脑屏障遭到破坏, NSE 和 S-100 β 释放入血。因此, 血清 NSE 和 S-100 β 水平可反映神经损伤程度。当机体受到手术

创伤时,免疫系统被激活,产生强烈的炎性反应,使得患者的中枢神经和外周组织中炎症细胞升高,且增加的程度与认知功能下降的程度具有相关性。IL-6 是一种广泛参与中枢神经系统病理和生理过程的炎性因子^[29]。本研究结果显示右美托咪啶联合布托啡诺可显著改善老年腹腔镜胃肠肿瘤根治术患者术后早期的血清 NSE、S-100 β 和 IL-6 水平。MMSE 量表是评价老年患者术后认知功能障碍的工具之一,具有较高的特异性和敏感性。本研究结果显示右美托咪啶联合布托啡诺可改善老年腹腔镜胃肠肿瘤根治术患者术后认知功能障碍。这可能是由于右美托咪啶不仅具有镇静镇痛的作用,可使麻醉过程更加平稳,减轻由于手术、气管插管和拔管等引起的血液流动学改变和炎性反应,还能够使患者保持良好的定向力和唤醒能力,降低谵妄和躁动发生率^[30,31]。布托啡诺通过激动 K 阿片受体产生镇痛作用,可降低或消除损伤导致的中枢神经敏感受体,达到良好的镇静效果。两者联合使用不仅具有较好的麻醉效果,还可降低各种原因所致的大脑神经系统损伤,进而显著改善患者的认知功能。此外,右美托咪啶联合布托啡诺并未增加患者的不良反应发生率,安全性较好。

综上所述,老年胃肠肿瘤腹腔镜根治术患者由于年龄、CO₂ 气腹、麻醉药物的使用和手术刺激等因素极易发生术后认知功能障碍,且麻醉难度较大。术前应用右美托咪啶联合布托啡诺可显著改善患者的认知功能,提高麻醉效果,且不增加并发症的发生率。

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