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羟考酮联合右美托咪定术后镇痛对腹腔镜下结肠癌根治术患者炎症因子、T 细胞亚群和认知功能的影响 *

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摘要 目的:探讨羟考酮联合右美托咪定术后镇痛对腹腔镜下结肠癌根治术患者炎症因子、T 细胞亚群和认知功能的影响。方法:选取我院于 2013 年 1 月~2019 年 12 月期间收治的 80 例行腹腔镜下结肠癌根治术的患者,采用随机数字表法将患者分为 A 组和 B 组,各 40 例,A 组给予舒芬太尼联合右美托咪定术后镇痛,B 组给予羟考酮联合右美托咪定术后镇痛,对比两组围术期指标、炎症因子、T 细胞亚群和认知功能。结果:B 组自主呼吸恢复时间、定向力恢复时间、拔管时间短于 A 组,自控镇痛泵(PCA)总按压次数少于 A 组,PCA 有效按压次数多于 A 组($P<0.05$)。两组术前、术后 1 d、术后 3 d 的白介素-6(IL-6)、C 反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)水平呈先升高后降低趋势($P<0.05$),B 组术后 1 d、术后 3 d 的 IL-6、CRP、TNF- α 水平低于 A 组($P<0.05$)。两组术前、术后 1 d、术后 3 d 的 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 呈先降低后升高趋势,CD8⁺ 呈先升高后降低趋势($P<0.05$),B 组术后 1 d、术后 3 d CD3⁺、CD4⁺、CD4⁺/CD8⁺ 高于 A 组,CD8⁺ 则低于 A 组($P<0.05$)。两组术后 1 d、2 d、3 d 简易精神状态检查表(MMSE)评分呈升高趋势($P<0.05$),B 组术后 1 d、2 d、3 d 的 MMSE 评分高于 A 组($P<0.05$)。结论:腹腔镜下结肠癌根治术患者采用羟考酮联合右美托咪定术后镇痛,可减轻患者炎症反应及免疫抑制,同时还可减轻其认知功能损伤,促进其术后恢复。

关键词:羟考酮;右美托咪定;腹腔镜下结肠癌根治术;炎症因子;T 细胞亚群;认知功能

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Effects of Oxycodone Combined with Dexmedetomidine on Inflammatory Factors, T Cell Subsets and Cognitive Function in Patients Undergoing Laparoscopic Radical Resection of Colon Cancer*

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ABSTRACT Objective: To investigate the effect of oxycodone combined with dexmedetomidine on inflammatory factors, T cell subsets and cognitive function in patients undergoing laparoscopic radical resection of colon cancer. **Methods:** 80 patients undergoing laparoscopic radical resection of colon cancer in our hospital from January 2013 to December 2019 were selected, and randomly divided into group A and group B, with 40 cases in each group. Group A was given sufentanil combine dexmedetomidine for postoperative analgesia, and group B was given oxycodone combine dexmedetomidine for postoperative analgesia. The perioperative indexes, inflammatory factors, T cell subsets and cognitive function were compared between two groups. **Results:** The spontaneous breathing recovery time, the directional force recovery time and extubation time in group B were shorter than those in group A, the total pressing times of PCA was less than that in group A, and the effective pressing times of PCA was more than that in group A ($P<0.05$). The levels of interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor - α (TNF- α) were increased and then decreased in the two groups at before operation, 1 d and 3 d after operation ($P<0.05$). The levels of IL-6, CRP and TNF- α in group B were lower than those in group A at 1d and 3 d after operation ($P<0.05$). The levels of CD3⁺, CD4⁺, CD4⁺/CD8⁺ were decreased and then increased in the two groups at before operation, 1 d and 3 d after operation, and CD8⁺ increased first and then decreased ($P<0.05$). CD3⁺, CD4⁺, CD4⁺/CD8⁺ in group B were higher than those in group A at 1d and 3d after operation, while CD8⁺ was lower than that in group A ($P<0.05$). The Mini Mental State Examination (MMSE) scores in two groups increased at 1 d, 2 d and 3 d after operation ($P<0.05$), and the MMSE scores in group B were higher than those in group A at 1 d, 2 d and 3 d after operation ($P<0.05$). **Conclusion:** Patients undergoing laparoscopic radical resection of colon cancer are treated with oxycodone combined with dexmedetomidine for postoperative analgesia, which can reduce inflammatory reaction and immunosuppression, at the same time, it can also reduce cognitive impairment and promote postoperative recovery of patients.

Key words: Oxycodone; Dexmedetomidine; Laparoscopic radical resection of colon cancer; Inflammatory factors; T cell subsets;

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前言

腹腔镜下结肠癌根治术是临床常见的外科手术,随着人们生活习惯的改变,结肠癌的发病率逐年上升,致使腹腔镜下结肠癌根治术的应用率也相应提高^[1,2]。腹腔镜手术虽作为微创手术,具有创口小、术后创伤轻等诸多优点,但术后疼痛仍是患者不可避免的直观感受^[3,4]。术前患者的复杂心理、术中的操作牵拉、术后的组织损伤引起的继发性炎症反应均可引起术后急性疼痛,造成免疫力下降,年龄偏大者还易出现认知功能障碍,降低手术效果^[5,6]。因此,给予良好的术后镇痛方案对于促进患者恢复具有积极的临床意义。右美托咪定为高选择性 α_2 -肾上腺素能受体激动剂,镇静、镇痛效果显著^[7]。羟考酮作为 μ 、 κ 双受体激动剂,可有效抑制机体疼痛,且不良反应较少^[8]。本次研究通过探讨羟考酮联合右美托咪定术后镇痛对腹腔镜下结肠癌根治术患者炎症因子、T 细胞亚群和认知功能的影响,以期为

临床该术式术后镇痛方案的选择提供参考。

1 资料与方法

1.1 一般资料

选取 2013 年 1 月~2019 年 12 月期间我院收治的 80 例腹腔镜下结肠癌根治术患者,纳入标准:(1)符合腹腔镜下结肠癌根治术手术指征,均择期完成手术;(2)知情本研究并签署同意书;(3)美国麻醉医师协会(ASA)分级 I~II 级者;(4)对本次研究所用药物无禁忌症者;(5)自愿选择术后自控镇痛。排除标准:(1)合并其他恶性肿瘤者;(2)既往有腹部手术史者;(3)伴有心、肝、肾等脏器功能严重障碍者;(4)合并全身感染者;(5)伴有血液或消化系统疾病者;(6)合并自身免疫性疾病者;(7)伴有精神病、癫痫病史者。将患者以随机数字表法分为 A 组和 B 组各 40 例,两组一般资料比较差异无统计学意义($P>0.05$),详见表 1。本研究已经过我院医学伦理委员会批准同意开展实施。

表 1 两组一般资料对比

Table 1 Comparison of general data between two groups

Groups	Male/female	Age(years)	Body mass index (kg/m ²)	ASA classification		Clinical stages	
				Grade I	Grade II	Stage I	Stage II
Group A(n=40)	18/22	48.96± 6.54	23.13± 0.93	17	23	22	18
Group B(n=40)	16/24	49.12± 5.62	23.21± 0.85	19	21	24	16
χ^2/t	0.205	-0.117	-0.402	0.202		0.205	
<i>P</i>	0.651	0.907	0.689	0.653		0.651	

1.2 麻醉方法

术前常规禁饮、禁食,入室后建立静脉通路,常规监测指尖血氧饱和度、心电图,麻醉诱导:依次静脉注射咪达唑仑注射液[国药准字 H20067041,宜昌人福药业有限责任公司,规格:2 mL:10 mg(以咪达唑仑计)]0.04 mg/kg、苯磺顺阿曲库铵注射液[国药准字 H20183042,江苏恒瑞医药股份有限公司,规格:5 mL:10 mg(按 $C_{33}H_{22}N_2O_{12}$ 计)]0.2 mg/kg、枸橼酸舒芬太尼注射液[国药准字 H20054256,宜昌人福药业有限责任公司,规格:5 mL:250 μ g(以舒芬太尼计)]0.4 μ g/kg、丙泊酚乳状注射液(国药准字 H20133360,广东嘉博制药有限公司,规格:50 mL:500 mg)1~2 mg/kg,行气管插管并进行机械通气,呼吸频率为 10~13 次/min,设定潮气量 6~8 mL/kg,吸呼比 1:1.5,二氧化碳分压维持在 35~45 mmHg。术中以吸入用七氟烷(批准文号 H20171047,AbbVie Limited,规格:100%,250 mL)维持麻醉深度,脑电双频指数指标维持在 40~60 之间,术中间断追加枸橼酸舒芬太尼注射液、苯磺顺阿曲库铵注射液。于手术结束前半小时,停用镇痛及肌松药物,在验证患者意识和自主呼吸充分恢复后,拔除气管导管。术后打开自控镇痛泵(PCA),其中 A 组采用枸橼酸舒芬太尼注射液 2.0 μ g/kg 联合盐酸右美托咪定注射液[(国药准字 H20110085,江苏恩华药业股份有限公司,规格:2 mL:0.2 mg(以右美托咪定计)]0.05 μ g/kg·h 自控镇痛;B 组采用盐酸羟考

酮注射液(批准文号 H20170223,NAPP PHARMACEUTICALS LIMITED,规格:2 mL:20 mg)0.8 mg/kg 联合盐酸右美托咪定注射液 0.05 μ g/kg·h 自控镇痛;均以 0.9%的生理盐水配伍至 100 mL,每 15 min 给药,背景输注 2 mL/h,剂量为 0.5 mL。

1.3 观察指标

(1)围术期指标:记录两组 PCA 总按压次数、PCA 有效按压次数、自主呼吸恢复时间、定向力恢复时间、拔管时间。(2)炎症因子、T 淋巴细胞亚群:于术前、术后 1 d、术后 3 d 采集患者静脉血 8 mL,分为两管,1 管采用 Beckman Coulter 公司生产的 XL 型流式细胞仪测定 $CD3^+$ 、 $CD4^+$ 、 $CD8^+$,计算 $CD4^+/CD8^+$ 。另一管经离心半径 16.5 cm,3300 r/min 离心 12 min,取上清液,采用酶联免疫吸附试验(试剂盒购自上海酶联生物科技有限公司)检测血清白介素-6(IL-6)、C 反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)水平。(3)认知功能:于术前、术后 1 d、术后 2 d、术后 3 d 采用简易精神状态检查表(MMSE)^[9]评价两组认知功能。MMSE 包括 30 道题目,答对记 1 分,答错记 0 分,总分 0~30 分,得分越高表明认知功能越好。

1.4 统计学方法

使用 SPSS23.0 进行研究资料分析。观测资料中的计量数据,均通过正态性检验,以 $MEAN \pm SD$ 描述。两组间的比较为成组 t 检验或校正 t 检验(统计量为 t)。重复观测资料则行重复

测量方差分析(球检验校正为 HF 法,统计量为 F)+ 两两组间比较 LSD-t 检验(统计量为 LSD-t)+ 两两组内(时间维度)比较差值 t 检验(统计量为 t)。计数资料以例数及率描述。组间比较为卡方检验或校正卡方检验(统计量为 χ^2)。多组间比较为整体 + 分割卡方检验(统计量为 χ^2)。统计推断的检验水准 $\alpha=0.05$ (双侧检验)。

2 结果

2.1 两组围术期指标对比

B 组自主呼吸恢复时间、拔管时间、定向力恢复时间短于 A 组,PCA 总按压次数少于 A 组,PCA 有效按压次数多于 A 组($P<0.05$),详见表 2。

表 2 两组围术期指标对比($\bar{x} \pm s$)

Table 2 Comparison of perioperative indexes between the two groups($\bar{x} \pm s$)

Groups	Spontaneous breathing recovery time(min)	Extubation time(min)	Directional force recovery time(min)	Total pressing times of PCA (times)	Effective pressing times of PCA(times)
Group A(n=40)	14.77 $\pm$ 1.30	18.82 $\pm$ 2.65	22.10 $\pm$ 2.13	30.88 $\pm$ 1.38	18.97 $\pm$ 1.64
Group B(n=40)	11.36 $\pm$ 1.28	14.86 $\pm$ 2.39	17.33 $\pm$ 1.15	23.32 $\pm$ 1.15	21.84 $\pm$ 1.38
t	11.821	7.018	12.463	26.617	-8.469
P	0.000	0.000	0.000	0.000	0.000

2.2 两组炎症因子指标对比

两组术前血清炎症因子指标组间对比无统计学差异($P>0.05$),两组术前、术后 1 d、术后 3 d 的 IL-6、CRP、TNF- α 呈先升

高后降低趋势($P<0.05$),B 组术后 1 d、术后 3 d 的 IL-6、CRP、TNF- α 低于 A 组($P<0.05$),详见表 3。

表 3 两组炎症因子指标对比($\bar{x} \pm s$)

Table 3 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	Time	IL-6(ng/L)	CRP(mg/L)	TNF- α (pg/L)
Group A(n=40)	Before operation	17.08 $\pm$ 1.87	7.73 $\pm$ 0.97	14.79 $\pm$ 1.68
	1 d after operation	37.58 $\pm$ 2.36 ⁱ	23.28 $\pm$ 2.25 ⁱ	30.92 $\pm$ 1.29 ⁱ
	3 d after operation	31.26 $\pm$ 3.81 ⁱ	15.80 $\pm$ 1.83 ⁱ	24.72 $\pm$ 1.36 ⁱ
Group B(n=40)	Before operation	17.10 $\pm$ 1.63	7.64 $\pm$ 0.84	14.43 $\pm$ 1.59
	1 d after operation	30.28 $\pm$ 3.13 ^{at}	16.31 $\pm$ 2.08 ^{at}	24.17 $\pm$ 1.54 ^{at}
	3 d after operation	24.23 $\pm$ 2.88 ^{at}	10.78 $\pm$ 1.75 ^{at}	19.67 $\pm$ 1.38 ^{at}
The overall analysis	HF coefficient	1.0121	0.8157	0.7699
Comparison between groups	F, P	192.903, 0.000	302.961, 0.000	431.584, 0.000
Comparison in the group	F, P	767.998, 0.000	1,065.341, 0.000	1,579.821, 0.000
Interaction	F, P	45.552, 0.000	90.979, 0.000	102.709, 0.000

Note: compared with before operation, ⁱ $P<0.05$; compared with group A, ^a $P<0.05$.

2.3 两组 T 淋巴细胞亚群指标对比

两组术前 T 淋巴细胞亚群指标组间对比无统计学差异($P>0.05$), 两组术前、术后 1 d、术后 3 d 的 CD3⁺、CD4⁺、CD4⁺/CD8⁺ 先降低后升高,CD8⁺ 先升高后降低 ($P<0.05$),B 组术后 1 d、术后 3 d CD3⁺、CD4⁺、CD4⁺/CD8⁺ 高于 A 组,CD8⁺ 则低于 A 组($P<0.05$),详见表 4。

2.4 两组认知功能评分对比

两组术前 MMSE 评分组间对比无统计学差异($P>0.05$), 两组术后 1 d、术后 2 d、术后 3 d 的 MMSE 评分呈升高趋势($P<0.05$),B 组术后 1 d、术后 2 d、术后 3 d 的 MMSE 评分高于 A 组($P<0.05$),详见表 5。

3 讨论

结肠癌作为消化系统恶性肿瘤疾病,常见的临床症状有疼

痛、消化不良、大便带血等,病情进展迅速,可危及患者生命,应给予重视^[10,11]。手术治疗是结肠癌患者有效的治疗方案,随着我国医疗水平的提升,腹腔镜技术的不断完善,腹腔镜结肠癌根治术已成为结肠癌患者的首选治疗方案^[12-14]。尽管腹腔镜结肠癌根治术对患者的损伤非常小,但依然可使其出现应激反应,导致儿茶酚胺释放增加,交感神经过度兴奋,造成术后疼痛^[15,16]。同时,由于结肠癌患者的主要发病人群为中老年人群,中老年群体身体各项机能明显下降,术后恢复能力较弱,严重者还会引起术后认知功能障碍,影响病情恢复,增加并发症发生率和精神负担,甚至危及生命^[17,18]。因此,最大程度的减轻患者术中应激反应,降低患者术后疼痛,对于促进患者术后恢复具有重要意义。目前临床上最常用的术后镇痛方式为术后自控镇痛,但有关不同种类疾病患者的术后镇痛方案目前尚无统一的规定。

表 4 两组 T 淋巴细胞亚群指标对比($\bar{x} \pm s$)Table 4 Comparison of T lymphocyte subsets between the groups($\bar{x} \pm s$)

Groups	Time	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺
Group A(n=40)	Before operation	49.77± 6.04	41.17± 5.89	25.40± 3.25	1.62± 0.25
	1 d after operation	34.77± 5.88 ⁱ	28.43± 4.46 ⁱ	33.46± 2.84 ⁱ	0.85± 0.14 ⁱ
	3 d after operation	40.94± 5.18 ⁱ	32.34± 5.56 ⁱ	30.99± 3.09 ⁱ	1.04± 0.17 ⁱ
Group B(n=40)	Before operation	50.12± 5.29	41.29± 6.23	25.83± 4.11	1.59± 0.14
	1 d after operation	39.81± 5.90 ^{at}	32.19± 4.51 ^{at}	30.21± 3.19 ^{at}	1.07± 0.16 ^{at}
	3 d after operation	44.82± 5.34 ^{at}	37.22± 5.47 ^{at}	27.86± 3.17 ^{at}	1.33± 0.18 ^{at}
The overall analysis	HF coefficient	0.9856	0.9167	0.9332	0.9607
Comparison between groups	F, P	16.782, 0.000	19.020, 0.000	19.188, 0.000	52.562, 0.000
Comparison in the group	F, P	106.237, 0.000	79.918, 0.000	77.425, 0.000	264.241, 0.000
Interaction	F, P	3.930, 0.049	4.125, 0.044	8.647, 0.004	16.998, 0.000

Note: Same as table 3.

表 5 两组认知功能评分对比($\bar{x} \pm s$, 分)Table 5 Comparison of cognitive function scores between the two groups($\bar{x} \pm s$, scores)

Groups	Time	MMSE scores
Group A(n=40)	Before operation	29.22± 0.34
	1 d after operation	24.37± 0.73 ⁱ
	2 d after operation	25.70± 0.44 ⁱ
	3 d after operation	27.95± 0.44 ⁱ
Group B(n=40)	Before operation	29.15± 0.42
	1 d after operation	26.07± 0.61 ^{at}
	2 d after operation	27.84± 0.51 ^{at}
	3 d after operation	29.13± 0.41 ^{at}
The overall analysis	HF coefficient	0.7015
Comparison between groups	F, P	508.185, 0.000
Comparison in the group	F, P	1,015.929, 0.000
Interaction	F, P	72.031, 0.000

Note: Same as table 3.

右美托咪定是具有高选择性的 α_2 受体激动剂,通过作用于脊髓部位、蓝斑核及外周的肾上腺素受体,进而抑制去甲肾上腺素的释放和神经元的兴奋,发挥抗交感、镇痛、镇静、抑制炎症反应和减轻认知功能障碍的作用,常与阿片类药物联合使用进行镇痛^[19,20]。羟考酮是一种半合成阿片类药物,有研究证明^[21],羟考酮是广泛应用于术后疼痛管理的一种阿片类药物。考虑到右美托咪定、羟考酮的药理特点我们设计并实施了本次研究,研究结果显示,B组的围术期指标改善优于A组,可见羟考酮联合右美托咪定术后镇痛效果确切,可有效促进患者术后恢复。考虑可能与羟考酮在内脏疼痛治疗方面优于其他麻醉类药物,可提供良好的镇痛效果,进而减轻机体应激反应有关。

IL-6、CRP、TNF- α 是临床常见的炎症相关指标,当机体受到伤害性刺激时,其水平可迅速上升^[22]。本研究中两组患者术后均存在不同程度的炎症应激,而羟考酮联合右美托咪定术后镇痛患者的炎症应激程度更轻。笔者推测,这可能是因为右美托咪定可以有效抑制脂多糖所致的活化小神经胶质细胞炎症反应,联合羟考酮后可为患者提供良好的镇痛效果,使患者可以

早期下床,加速胃肠功能康复,进一步减少患者体内炎症因子的释放^[23,24]。T 淋巴细胞亚群主要用于评估机体细胞免疫能力,CD8⁺ 可负向调节免疫应答,CD4⁺ 参与机体免疫应答,两者比值及 CD3⁺ 值是细胞免疫抑制的重要标志。国内外不少研究证实^[25,26],癌症细胞的微转移与患者免疫功能息息相关。可见腹腔镜下结肠癌根治术患者免疫功能受损严重,易增加微转移风险。本研究中显示患者免疫功能呈现降低后逐渐恢复趋势,且羟考酮联合右美托咪定术后镇痛的患者其免疫功能抑制程度更轻。这可能是因为联合镇痛模式的镇痛效果更佳,使患者术后可更早的进食补充营养和能量,进而加快其术后康复速度,改善机体免疫功能^[27-29]。机体的脑血流随年龄增加存在不同程度的减少,代谢功能下降,增高了对脑缺氧的敏感性,减低了机体对全麻药物的耐受性,从而增加了术后认知功能受损的风险^[30-32]。本研究表明 B 组术后 1 d、术后 2 d、术后 3 d 的 MMSE 评分高于 A 组,可见羟考酮联合右美托咪定对认知功能的保护作用更好^[33]。

综上所述,腹腔镜下结肠癌根治术患者采用羟考酮联合右

美托咪定术后镇痛,可更好的保护患者认知功能,还可降低机体炎性应激及免疫抑制程度,促进患者术后康复。

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