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·临床研究·

羟考酮在腹腔镜胆囊切除术后镇痛中的应用及对凝血功能的影响*

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摘要 目的:分析羟考酮在腹腔镜胆囊切除术后镇痛中的应用及对凝血功能的影响。**方法:**选择2015年5月~2016年5月于我院行腹腔镜胆囊切除术患者106例,依据抽签法分成对照组与实验组,各有53例,对照组予以芬太尼镇痛,实验组予以羟考酮镇痛,比较两组痛觉指标[5-羟色胺(5-HT)、P物质]、疼痛数字评分(NRS)、凝血功能[凝血酶原时间(PT)、纤维蛋白原(Fg)、活化部分凝血酶原时间(APTT)、血小板计数(PLT)]、血流动力学、炎症因子、应激指标、麻醉效果和安全性。**结果:**干预后,实验组5-HT、P物质水平、NRS评分、PT、Fg、APTT、PLT以及血流动力学、炎症因子、应激指标均低于对照组,差异具有统计学意义(P<0.05)。两组麻醉效果比较差异无统计学意义(P>0.05)。实验组不良反应率显著低于对照组(P<0.05)。**结论:**腹腔镜胆囊切除术应用羟考酮的镇痛作用与芬太尼相当,但能够更有效减轻术后血液的高凝状态。

关键词:腹腔镜胆囊切除术;羟考酮;镇痛;凝血功能

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Application of Oxycodone on the Analgesia and Its Influence on the Blood Coagulation Function after Laparoscopic Cholecystectomy*

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ABSTRACT Objective: To analyze the application of oxycodone on the analgesia after laparoscopic cholecystectomy and its influence on the blood coagulation function. **Methods:** 106 cases of laparoscopic cholecystectomy patients from May 2015 to May 2016 in our hospital were selected and divided into the control group and experimental group according to the lottery method with 53 cases in each group, the control group was given fentanyl analgesia, the experimental group was given oxycodone analgesia, the pain index [serotonin (5-HT) and substance P], numerical rating scale(NRS), blood coagulation function [prothrombin time (PT), fibrinogen (Fg), activated partial prothrombin time (APTT), platelet count (PLT)], hemodynamic, inflammatory factor, stress index, anesthetic effect and safety were compared between the two groups before and after intervention. **Results:** After the operation, the 5-HT, substance P levels, NRS score, Fg, APTT, PT, PLT, hemodynamic, inflammation factors, stress index in the experimental group were significantly lower than those of the control group(P<0.05). No statistical significance was found in the anesthesia effect between two groups(P>0.05). The adverse reaction rate in experimental group was obviously lower than that of the control group (P<0.05). **Conclusion:** The analgesic action was equal of oxycodone in laparoscopic cholecystectomy to Fentanyl, which could reduce the blood high condensation state.

Key words: Laparoscopic cholecystectomy; Oxycodone; Analgesia; Blood coagulation function

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前言

胆囊切除术是良性胆囊疾病外科治疗的常用术式,具有手术创面小、术后恢复快、并发症少等优势[1]。虽然腹腔镜技术已很大程度的降低创伤,但仍属创伤性手术,术后均存在不同程度的疼痛,因此良好的镇痛手段具有重要的临床价值[2]。羟考酮对k、μ受体激动均存在激动作用,从而发挥镇痛效果,多用于术后镇痛[3]。临床研究显示腹腔镜胆囊切除术由于术中气腹、体位等因素可对患者凝血功能产生影响,易形成高凝状态[4]。目前,临床上关于羟考酮对此类患者凝血功能的研究报道甚少,本研究旨在分析腹腔镜胆囊切除术后应用羟考酮镇痛的临床效果。

1 资料与方法

1.1 一般资料

选择2015年5月~2016年5月于我院行腹腔镜胆囊切除

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术患者 106 例,对照组男性有 28 例,女性有 25 例;年龄在 22 至 60 岁, 平均 (41.35± 2.08) 岁; 体重在 47 至 78 kg, 平均 (66.31± 2.42)kg; 身高在 150 至 178 cm, 平均 (169.21± 1.32) cm;ASA Ⅰ级有 29 例,Ⅱ级有 24 例;疾病类型:胆囊息肉有 8 例,慢性结石性胆囊炎有 22 例,急性结石性胆囊炎有 23 例。实验组男性有 24 例, 女性有 29 例; 年龄在 22 至 63 岁, 平均 (42.89± 2.27)岁;体重在 45 至 80 kg,平均(65.21± 2.73)kg;身高在 152 至 180 cm,平均(167.41± 1.16)cm;ASA Ⅰ级有 26 例,Ⅱ级有 27 例;疾病类型:胆囊息肉有 10 例,慢性结石性胆囊炎有 20 例,急性结石性胆囊炎有 23 例。本研究已得到医院伦理委员会许可,且家属及患者均签署知情同意书,依据抽签法分成对照组和实验组,每组 53 例。比较两组基线资料无明显差异(P>0.05),有可比性。

1.2 纳入与排除标准

纳入标准[5]:经肝胆彩超、胆管造影等检查确诊为胆囊良性病变;腹腔镜胆囊切除术指征明确;无腹膜炎体征;凝血系统正常;ASA 分级在Ⅰ~Ⅱ级;近期未使用激素、抗氧化剂、抗血小板等影响本研究临床指标药物;非妊娠或者哺乳期。排除标准:心、肝肾等器官显著病变;恶性肿瘤或内分泌系统明显异常;急性创伤、炎症及全身其他疾病者;胆囊可见明显萎缩。

1.3 治疗方法

患者入室后行血压、心率、脑电双频指数、血氧饱和度等常规监测。依次静脉注射 0.2~0.25 μg 舒芬太尼、1.5~2 mg/kg 丙泊酚、0.02~0.03 mg/kg 咪哒唑仑、0.15~0.20 mg/kg 顺式阿曲库铵,待完全肌松后接通麻醉机实施机械通气。参数设置:潮气量在 8~10 mL/kg、呼吸比在 1:2、呼吸频率在 10~12 次 / 分钟。单次追加静脉注射 0.4 mg/kg 顺式阿曲库铵,并吸入 2%~3%七氟醚进行麻醉维持。手术结束前 5 分钟停用所有麻醉药物,对照组于缝皮前予以 0.001 μg/kg 芬太尼,实验组予以 0.1 mg/kg 羟考酮。待患者出现吞咽反射,自主呼吸规律并在 10 次 / 分钟以上,呼气末二氧化碳分压为 35~25 mmHg,且可被唤醒时将气管插管拔除。

1.4 观察指标

采集患者入室时及术毕 6 h 外周静脉血 3mL,肝素抗凝后常规分离血清。5- 羟色胺(5-HT)及 P 物质予以酶联免疫吸附法测定;凝血酶原时间(PT)、纤维蛋白原(Fg)、活化部分凝血酶原时间(APTT)、血小板计数(PLT)予以放射免疫沉淀法测定;白细胞介素 -6(IL-6)、肿瘤坏死因子 -α(TNF-α)、C 反应蛋白(CRP)予以酶联免疫双抗体夹心法测定;血浆去甲肾素腺素(NE)及皮质醇(Cor)予以放射免疫法测定,血糖(Glu)予以葡萄糖氧化酶法测定。疼痛数字评分(NRS)[6]:分值为 0 至 10 分,0 分表示无痛;3 分以下表示轻微疼痛,能够耐受;4 至 6 分表示疼痛已对睡眠产生影响,但能够耐受;7 至 10 分表示疼痛剧烈,无法耐受。记录患者术毕各指标恢复时间, 入室及术毕 6 h 的平均动脉压(MAP)及心率(HR),并观察术后的不良反应。

1.5 统计学分析

选择 SPSS18.0 行数据统计, 计量资料用均数± 标准差($\bar{x}$± s)表示,用 t 检验比较,计数资料用[(n)%]表示,用 x^2 检验比较,等级资料用秩和检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者手术前后痛觉指标的比较

术前,两组血清 5-GT、P 物质水平比较差异无统计学意义(P>0.05);术后,两组血清 5-HT、P 物质水平均上升,但实验组上升幅度更小,两组比较差异有统计学意义(P<0.05),见表 1。

表 1 两组患者手术前后痛觉指标比较($\bar{x}$± s)

Table 1 Comparison of the pain index between two groups before and after the operation($\bar{x}$± s)

Groups		5-HT(μg/L)	P substance(ng/L)
Control group(n=53)	Before operation	461.35± 10.81	123.47± 7.20
	After operation	726.84± 15.40[a]	225.80± 10.31[a]
Experimental group(n=53)	Before operation	459.29± 10.13	120.51± 7.01
	After operation	642.20± 12.90[ab]	197.60± 8.42[ab]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.2 两组患者手术前后 NRS 评分的比较

术前,两组 NRS 评分比较差异无统计学意义(P>0.05);术后,两组 NRS 评分均较治疗前显著降低,且实验明显低于对照组,两组比较差异有统计学意义(P<0.05),见表 2。

表 2 两组患者手术前后 NRS 评分比较($\bar{x}$± s)

Table 2 Comparison of the NRS score between two groups before and after the operation($\bar{x}$± s)

Groups		NRS (points)
Control group(n=53)	Before operation	1.20± 0.31
	After operation	3.48± 0.36[a]
Experimental group(n=53)	Before operation	1.19± 0.25
	After operation	2.97± 0.41[ab]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.3 两组患者手术前后凝血功能的比较

术前, 两组凝血功能比较差异无统计学意义 (P>0.05);术后,两组 PT、FIB、APTT、PLT 均较治疗前上升,但实验组上升幅度更小,两组比较差异有统计学意义(P<0.05),见表 3。

表 3 两组患者手术前后凝血功能比较($\bar{x}\pm s$)

Table 3 Comparison of the blood coagulation function between two groups before and after the operation($\bar{x}\pm s$)

Groups		PT(s)	Fg(g/L)	APTT(s)	PLT(s)
Control group(n=53)	Before operation	11.14± 1.25	2.71± 0.54	26.17± 5.43	206.53± 23.58
	After operation	14.76± 1.76[a]	2.99± 0.62[a]	31.73± 6.85[a]	249.73± 28.52[a]
Experimental group (n=53)	Before operation	10.23± 1.36	2.67± 0.49	25.69± 5.40	204.41± 22.40
	After operation	12.89± 1.50[ab]	2.86± 0.60[ab]	28.93± 6.45[ab]	226.39± 25.70[ab]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.4 两组患者手术前后血流动力学的比较

术前,两组 MAP、HR 比较差异无统计学意义(P>0.05);术后,两组 MAP、HR 均上升,但实验组上升幅度更小,两组比较差异有统计学意义(P<0.05),见表 4。

表 4 两组患者手术前后血流动力学的比较($\bar{x}\pm s$)

Table 4 Comparison of the hemodynamics between two groups before and after the operation($\bar{x}\pm s$)

Groups		MAP(mmHg)	HR(次 /min)
Control group(n=53)	Before operation	83.76± 11.25	73.86± 7.65
	After operation	91.40± 12.94[a]	86.50± 8.41[a]
Experimental group(n=53)	Before operation	81.40± 10.89	72.45± 7.53
	After operation	84.40± 10.76[b]	74.43± 8.43[b]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.5 两组患者手术前后炎症因子水平的比较

术前,两组炎症因子(IL-6、TNF-α、CRP)水平比较差异无统计学意义(P>0.05);术后,两组血清 IL-6、TNF-α、CRP 水平均上升,但实验组上升幅度更小,两组比较差异有统计学意义(P<0.05),见表 5。

表 5 两组患者手术前后血清 IL-6、TNF-α、CRP 水平的比较($\bar{x}\pm s$)

Table 5 Comparison of the serum IL-6, TNF-α, CRP levels between two groups before and after the operation($\bar{x}\pm s$)

Groups		IL-6(ng/L)	TNF-α(μg/L)	CRP(mg/L)
Control group(n=53)	Before operation	10.87± 2.34	13.41± 1.93	7.81± 1.28
	After operation	30.76± 5.40[a]	35.81± 2.60[a]	15.60± 2.43[a]
Experimental group(n=53)	Before operation	11.23± 2.42	12.31± 1.78	765± 1.17
	After operation	22.69± 2.57[ab]	28.60± 2.23[ab]	11.71± 2.86[ab]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.6 两组患者手术前后应激指标比较

术前, 两组应激指标比较差异无统计学意义 (P>0.05);术后,两组应激指标水平均上升,且实验组上升幅度更小,两组比较差异有统计学意义(P<0.05),见表 6。

表 6 两组患者手术前后应激指标比较($\bar{x}\pm s$)

Table 6 Comparison of the stress index between two groups before and after the operation($\bar{x}\pm s$)

Groups		Cor(nmol/L)	NE(mmo//L)	Glu(ng/L)
Control group(n=53)	Before operation	137.26± 17.40	84.90± 5.32	5.56± 0.63
	After operation	176.39± 21.40[a]	112.43± 9.60[a]	7.89± 0.72[a]
Experimental group(n=53)	Before operation	135.54± 17.91	82.79± 5.93	5.41± 0.68
	After operation	145.20± 19.60[ab]	98.53± 8.61[ab]	6.60± 0.68[ab]

Note: Compared with before treatment [a]P<0.05; Compared with control group [b]P<0.05.

2.7 两组患者麻醉效果的比较

两组自主呼吸恢复时间、苏醒时间、拔管时间比较差异均无统计学意义(P>0.05),见表 7。

表 7 两组患者麻醉效果的比较($\bar{x}\pm s$)

Table 7 Comparison the anesthesia effect between two groups($\bar{x}\pm s$)

Groups	Spontaneous breathing recovery time (min)	Wake-up time (min)	Extubation time (min)
Control group(n=53)	6.45± 1.40	11.32± 2.31	14.24± 2.76
Experimental group(n=53)	5.83± 1.28	10.76± 2.15	13.67± 2.65

2.8 两组患者不良反应发生情况的比较

实验组不良反应率低于对照组，两组比较差异有统计学意义(P<0.05)，见表 8。

表 8 两组不良反应发生情况的比较(例)

Table 8 Comparison of the incidence of adverse reactions between two groups(n)

Groups	Nausea, vomiting	Dizziness	Lethargy	Respiratory depression	Skin itching	Adverse reaction rate
Control group(n=53)	4(7.54)	8(15.09)	7(13.20)	7(13.20)	8(15.09)	34(64.15)
Experimental group(n=53)	3(5.66)	5(9.43)	5(9.43)	1(1.88)	4(7.54)	18(33.96)[b]

Note: Compared with control group [b]P<0.05.

3 讨论

腹腔镜胆囊切除术是普外科胆囊切除的经典术式，但存在化学因素、膈神经牵拉、麻醉因素等刺激，仍伴切口及内脏疼痛等，导致患者不适，甚者可导致患者出现内环境紊乱，降低免疫功能，进而影响患者的恢复[7]。目前，临床上主要使用阿片类药物镇痛，但大部分对 k 受体无激动作用，对内脏痛的抑制效果欠佳[8]。芬太尼存在起效时间短、半衰期短等特点，但其能够诱导痛觉过敏，导致患者躁动，降低麻醉质量[9]。羟考酮是阿片类双受体激动药，代谢产物对其镇痛作用无影响，镇痛效果确切，且无封顶效应[10]。

5-HT 和 P 物质是传递特疼痛的主要介质，二者可互相影响。5-HT 主要于外周血液及组织中分布，正常状态下血液中 5-HT 浓度较低，当机体受到疼痛等刺激时能够增加释放[11]。P 物质可于初级神经纤维组织内广泛分布，可经外周末端及神经中枢释放，进而传递疼痛[12]。本研究显示，羟考酮干预后 5-HT 及 P 物质浓度低于芬太尼干预者，提示羟考酮能够抑制疼痛介质的分布，减轻疼痛，且羟考酮干预后 NRS 评分更低，与刘艳丽等研究报道结果一致[13]。腹腔镜胆囊切除术由于气腹建立、头高足低位等能够使门脉和下肢的血流出现瘀滞，导致内皮细胞受损，进而诱导血液纤溶和凝固系统激活，对凝血因子的稀释和清除产生影响，导致高凝状态，增加血栓的危险性[14,15]。本研究结果显示两组术后 6 h 时凝血功能指标均升高，表明腹腔镜胆囊切除术可导致血液凝固，但羟考酮干预后凝血功能指标上升幅度更小，提示羟考酮能够使血液纤溶及凝固系统受到抑制[16]。

腹腔镜胆囊切除术由于导管刺激、麻醉药物残留、疼痛等因素，能够使患者血流动力学产生变化，主要表现为血压上升、心率增快等[17]。本研究显示羟考酮干预后患者血流动力学比较稳定，MAP、HR 仅有轻微上升，可能与羟考酮更能减轻疼痛有关[18]。手术创伤、疼痛能够诱导外周组织合成并释放系列炎症因子，进而促进血管的扩张，并可导致组织出现水肿[19]。IL-6、TNF-α、CRP 是典型的促炎症因子，能够互相作用造成持续性炎症反应，加重疼痛[20]。本研究显示羟考酮干预后炎症因子上升幅度更小，提示羟考酮干预后能够抑制炎性因子的释放，减轻术后患者的炎症反应。同时，腹腔镜胆囊切除术能够诱导机体的应激反应，诱导 Cor、NE、Glu 等应激指标的表达[21]。本研究显示羟考酮干预后 Cor、NE、Glu 浓度更低，提示羟考酮能够使机体的应激反应减轻，缓解其对机体造成的损伤[22]。此外，两组麻醉效果无差异，但羟考酮干预后的安全性更高。

综上所述，腹腔镜胆囊切除术应用羟考酮的镇痛作用与芬太尼相当，但能够更有效减轻术后血液的高凝状态。

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