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氟比洛芬酯复合小剂量芬太尼对腹腔镜胆囊切除术患者镇痛效果及凝血功能的影响*

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摘要 目的:探讨氟比洛芬酯复合小剂量芬太尼在腹腔镜胆囊切除术后静脉自控镇痛中的应用及对患者凝血功能的影响。**方法:**选择2015年11月~2016年11月于我院行腹腔镜胆囊切除术的患者102例,随机分为对照组和研究组,每组51例。对照组患者术后采用小剂量芬太尼静脉自控镇痛,研究组患者术后采用氟比洛芬酯复合小剂量芬太尼静脉自控镇痛。观察并比较两组患者手术前后血清纤维蛋白原(Fg),活化部分凝血酶原时间(APTT),凝血酶原时间(PT),血小板计数(PLT),P物质,5-羟色胺(5-HT),白细胞介素-6、8(IL-6、IL-8)水平以及术后并发症的发生情况。**结果:**术前,比较两组Fg、APTT、PT、PLT、P物质、5-HT、IL-6、IL-8无差异($P>0.05$);术后,两组Fg、APTT、PT、PLT、P物质、5-HT、IL-6、IL-8均较术前上升,研究组低于对照组,差异均有统计学意义($P<0.05$)。研究组术后并发症率低于对照组($P<0.05$)。**结论:**氟比洛芬酯复合小剂量芬太尼能够提高腹腔镜胆囊切除术患者静脉自控镇痛的效果,改善凝血功能,降低炎症因子水平。

关键词:腹腔镜胆囊切除术;氟比洛芬酯;小剂量芬太尼;静脉自控镇痛;凝血功能

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Effect of Flurbiprofen Compound Small Dose Fentanyl on Intravenous Analgesia and Blood Coagulation Function of Patients with Laparoscopic Cholecystectomy*

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ABSTRACT Objective: To research the application of flurbiprofen compound small dose fentanyl with self-control vein analgesia after laparoscopic cholecystectomy and the influence on blood coagulation function. **Methods:** 102 cases with laparoscopic cholecystectomy who were treated in our hospital from November 2015 to November 2016 were selected and divided into the control group and the research group, with 51 cases in each group. The patients in the control group were treated with postoperative intravenous analgesia with low-dose fentanyl, while the patients in the research group were treated with postoperative intravenous analgesia with flurbiprofen ester compound low-dose fentanyl. Then the fibrinogen (Fg), activated partial prothrombin time (APTT), prothrombin time (PT), platelet count (PLT), substance P, 5-hydrocarbon serotonin (5-HT), interleukin 6, 8 (IL-6, IL-8) and complications between two groups were observed and compared. **Results:** Before treatment, there was no statistically significant difference about the Fg, APTT, PT, PLT, substance P, 5-HT, IL-6 and IL-8 between two groups ($P>0.05$); After treatment, the Fg, APTT, PT, PLT, substance P, 5-HT, IL-6 and IL-8 increased in the two groups, while the research group was lower than that of the control group, and the differences were statistically significant ($P<0.05$). The postoperative complication rate of research group was lower than that of the control group ($P<0.05$). **Conclusion:** Flurbiprofen ester compound small dose fentanyl with self-control vein analgesia can relieve coagulation function, and inhibit the levels of inflammatory factors.

Key words: Laparoscopic cholecystectomy; Flurbiprofen ester; Small dose fentanyl; Venous self-control analgesia; Coagulation function

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前言

胆囊切除术是胆道外科的一种较为常用术式,开腹胆囊切

除术的切口相对较大、出血多、不利于术后恢复等不足,有一定局限性^[1,2]。近年来,腹腔镜胆囊切除术由于创伤小、安全性高等特点已成为胆囊切除的主要术式,能够明显降低创伤,但其仍

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属创伤性手术,术后均存在不同程度的疼痛,良好的镇痛手段具有重要的临床价值^[34]。芬太尼是既往术后自控镇痛的主要药物,但剂量过大容易出现多种并发症,目前多模式镇痛已应用于临床,旨在通过复合多种镇痛药物以起到多重机制的镇痛^[9]。氟比洛芬酯为非甾体类的一种消炎镇痛药,能够使前列腺素的合成受到抑制,从而发挥镇痛效果,存在不良反应少、起效快等特点^[6]。有研究显示,腹腔镜胆囊切除术因术中气腹、体位等因素能够对患者的凝血功能形成影响,形成高凝状态^[7]。本研究主要探讨腹腔镜胆囊切除术采用氟比洛芬酯复合小剂量芬太尼静脉自控镇痛中的应用以及对凝血功能的影响。

1 资料与方法

1.1 一般资料

腹腔镜胆囊切除术患者 102 例按抽签法进行分组,入选标准^[9]:经肝胆彩超、胆管造影等检查确诊为胆囊良性病变;伴明确腹腔镜胆囊切除术指征;凝血系统正常;ASA 分级在 I~II 级;未见腹膜炎体征。排除标准:胆囊可见明显萎缩;近期使用激素、抗氧化剂、抗血小板等药物;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;妊娠或者哺乳阶段。对照组男 27 例,女 24 例;年龄 22~63 岁,平均 (43.56 ± 5.87) 岁;身高 152~180 cm,平均 (168.32 ± 3.68) cm;体重 45~80 kg,平均 (64.87 ± 4.61) kg;疾病类型:急性结石性胆囊炎有 21 例,慢性结石性胆囊炎有 19 例,胆囊息肉有 11 例;ASA I 级有 24 例,II 级有 27 例。研究组男 23 例,女 28 例;年龄 20~61 岁,平均 (44.12 ± 6.12) 岁;身高 151~180 cm,平均 (167.95 ± 3.93) cm;体重 46~81 kg,平均 (65.25 ± 4.95) kg;疾病类型:急性结石性胆囊炎有 22 例,慢性结石性胆囊炎有 17 例,胆囊息肉有 10 例;ASA I 级有 26 例,II 级有 25 例。

1.2 方法

1.2.1 麻醉方法 两组患者入室后均接通心电监护仪,常规监测心率、平均动脉压、血氧饱和度、呼吸频率、心电图等,建立静脉通路。静脉注射 2~3 mg/kg 咪达唑仑(江西神田制药有限公司,1 mL:5 mg,151023)、0.2~0.3 mg/kg 依托咪酯(河北凯威制

药有限责任公司,10 mL:20 mg,151014)、0.4~0.6 μ g/kg 舒芬太尼(安徽恒星制药有限公司,1 mL:50 μ g,151027)、0.15 mg/kg 顺阿曲库铵(重庆润康药业有限公司,10 mg,151025)以麻醉诱导。后实施气管插管,行机械通气,参数设置:潮气量在 8~10 mL/kg、吸入氧浓度为 100%、氧流量在 1 L/min、通气频率在 10~12 次/min。予以 0.1~0.2 μ g/kg·min 瑞芬太尼(山西博华制药有限公司,2 mL:0.1 mg,151015)、2~3 mg/kg·h 丙泊酚(江西长江药业有限公司,20 mL:200 mg,151020)以麻醉维持,确保血压与心率波动幅度在术前 20%以下。

1.2.2 镇痛方法 对照组术后静脉自控镇痛(小剂量芬太尼),将 10 μ g/kg 芬太尼(广东隆赋药业有限公司,2 mL:0.1 mg,151021)、2.5 mg 氟哌利多(沈阳红旗制药有限公司,2 mL:5 mg,151024)与 100 mL 生理盐水配制成 PCIA 泵。研究组术后静脉自控镇痛(氟比洛芬酯复合小剂量芬太尼),将 10 μ g/kg 芬太尼、2 mg/kg 氟比洛芬酯(上海庆安药业有限公司,5 mL:50 mg,151022)、2.5 mg 氟哌利多与 100 mL 生理盐水配制成 PCIA 泵。两组 PCIA 泵剂量均设定在 2 mL/h,自控剂量在 0.5 mL,锁定时间在 5 min。

1.3 观察指标

于入室时及术后 6 h 抽取患者 2 mL 空腹静脉血,纤维蛋白原(Fg)、活化部分凝血酶原时间(APTT)、凝血酶原时间(PT)、血小板计数(PLT)予以放射免疫沉淀法进行。P 物质、5-羟色胺(5-HT)予以酶联免疫吸附法进行。白细胞介素-6、8(IL-6、IL-8)予以电化学发光法进行。

1.4 统计学分析

数据处理选用 SPSS18.0 进行,用 $(\bar{x} \pm s)$ 表示计量资料,组间比较用 t 检验,用 [(例)%] 表示计数资料,比较用 χ^2 检验, $P < 0.05$ 有统计学意义。

2 结果

2.1 两组手术前后凝血功能比较

术前,比较两组凝血功能无差异($P > 0.05$);术后,两组 Fg、APTT、PT、PLT 均较术前上升,研究组上升幅度更小,差异显著($P < 0.05$)。

表 1 比较两组手术前后凝血功能($\bar{x} \pm s$)

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

Groups	Time	Fg(g/L)	APTT(s)	PT(s)	PLT($\times 10^9/L$)
Control group(n=51)	Preoperative	3.25 $\pm$ 0.42	33.56 $\pm$ 4.17	13.24 $\pm$ 1.65	154.06 $\pm$ 19.27
	Postoperative	3.91 $\pm$ 0.49 ^b	42.13 $\pm$ 5.35 ^b	18.81 $\pm$ 2.41 ^b	165.82 $\pm$ 20.61 ^b
Research group(n=51)	Preoperative	3.31 $\pm$ 0.40	33.27 $\pm$ 4.23	13.56 $\pm$ 1.63	154.51 $\pm$ 19.86
	Postoperative	3.67 $\pm$ 0.46 ^{ab}	37.08 $\pm$ 4.65 ^{ab}	16.28 $\pm$ 2.04 ^{ab}	160.31 $\pm$ 20.25 ^{ab}

Note: Compared with control group, ^a $P < 0.05$; Compared with before operation, ^b $P < 0.05$.

2.2 比较两组手术前后痛觉指标

术前,比较两组痛觉指标无差异($P > 0.05$);术后,两组 P 物质、5-HT 及 VAS 均较术前上升,研究组上升程度小于对照组,差异显著($P < 0.05$),见表 2。

2.3 比较两组手术前后炎症因子

术前,比较两组炎症因子无差异($P > 0.05$);术后,两组

IL-6、IL-8 均较术前上升,研究组上升幅度小于对照组,差异明显($P < 0.05$),见表 3。

2.4 比较两组术后并发症

两组均有嗜睡、皮肤瘙痒、呼吸抑制、恶心呕吐发生,研究组并发症率较对照组低,差异明显($P < 0.05$),见表 4。

表 2 比较两组手术前后痛觉指标($\bar{x}\pm s$)Table 2 Comparison of pain indicators between two groups before and after the operation ($\bar{x}\pm s$)

Groups	Time	P substance(ng/L)	5-HT($\mu\text{g/L}$)	VAS(分)
Control group(n=51)	Preoperative	122.65 $\pm$ 15.34	460.21 $\pm$ 57.51	1.16 $\pm$ 0.15
	Postoperative	231.21 $\pm$ 28.87 ^b	725.08 $\pm$ 90.63 ^b	2.85 $\pm$ 0.34 ^b
Research group(n=51)	Preoperative	121.45 $\pm$ 15.78	461.65 $\pm$ 58.13	1.15 $\pm$ 0.16
	Postoperative	196.40 $\pm$ 24.50 ^{ab}	645.87 $\pm$ 80.34 ^{ab}	2.23 $\pm$ 0.27 ^{ab}

Note: Compared with control group, ^aP<0.05; Compared with before operation, ^bP<0.05.

表 3 比较两组手术前后炎症因子($\bar{x}\pm s$)Table 3 Comparison of inflammatory factor between two groups before and after the operation ($\bar{x}\pm s$)

Groups	Time	IL-6(ng/L)	IL-8(ng/L)
Control group(n=51)	Preoperative	48.76 $\pm$ 6.09	10.35 $\pm$ 1.29
	Postoperative	62.61 $\pm$ 7.80 ^b	20.33 $\pm$ 2.51 ^b
Research group(n=51)	Preoperative	48.21 $\pm$ 6.35	10.21 $\pm$ 1.32
	Postoperative	54.87 $\pm$ 6.89 ^{ab}	16.45 $\pm$ 2.07 ^{ab}

Note: Compared with control group, ^aP<0.05; Compared with before operation, ^bP<0.05.

表 4 比较两组术后并发症[(例)%]

Table 4 Comparison of postoperative complications between two groups[(n)]

Groups	Sleepiness	Skin itching	Respiratory depression	Nausea and vomiting	Complication rate
Control group(n=51)	4	3	2	6	15(29.41)
Research group(n=51)	2	1	1	2	6(11.76) ^a

Note: Compared with control group, ^aP<0.05.

3 讨论

腹腔镜胆囊切除术由于存在化学因素、膈神经牵拉、麻醉因素等刺激,能够导致患者出现疼痛等不适,术后疼痛能够诱导记忆免疫功能及自主神经出现系列改变,造成机体出现病理的变化,为机体一种伤害性刺激^[9]。目前临床上主要使用术后静脉自控镇痛,其中阿片类药物应用较为广泛,但大部分对k受体无激动作用,对疼痛的抑制效果欠佳^[10]。芬太尼是一种阿片受体的激动剂,能够起到与吗啡相同的麻醉效果,存在起效时间短、半衰期短等特点,但大剂量芬太尼能够引起呼吸抑制、嗜睡、呕吐等并发症,并能够诱导痛觉过敏,导致患者躁动,降低镇痛效果^[11,12]。氟比洛芬酯是一种靶向镇痛药物,亲脂性较高,药效持久,能够使疼痛阈值提高,起到良好的镇痛效果^[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,从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]。Fg作为纤维蛋白的前体,能够发挥抗血小板、抗凝作用;PT、APTT能够分别客观反映机体外源性与内源性凝血系统的状态;PLT能够提示机体血液状态^[15]。本研究显示,术后两组Fg、PT、APTT、PLT均有上升,但复合氟比洛芬酯组上升幅度更小,说明腹腔镜胆囊切除术能够引起血液出现凝固,但二者联合镇痛能够使血液纤溶及凝固系统受到抑制,缓解机体凝血功能。

同时临床研究发现,腹腔镜胆囊切除术后痛觉指标显著上

升,P物质和5-HT是传递特疼痛的主要介质,两者可互相影响,P物质能够神经纤维组织内大量分布,并经外周末端及神经中枢释放,传递疼痛^[16,17]。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^[18]。本研究显示,术后两组P物质及5-HT均有上升,但复合氟比洛芬酯组上升幅度更小,且VAS评分低于小剂量芬太尼组,说明二者联合镇痛能够有效缓解患者术后疼痛,减轻其痛苦,利于恢复,可能与氟比洛芬酯镇痛存在靶向性、抢先性、缓释性、转运性有关^[19]。疼痛、手术创伤等外界刺激能够诱导机体产生显著的应激反应,其中炎症反应是其主要表达方式,IL-6是机体最强的炎症因子,多来自于单核细胞、巨噬细胞、淋巴细胞等,可刺激炎症因子的释放,导致全身炎症反应,是机体组织损伤及炎症反应程度的特异性指标^[20]。IL-8是多源性的炎症细胞因子,对T淋巴细胞、嗜碱性粒细胞及中性粒细胞的趋化作用比较强,能够造成炎症细胞集聚,并产生大量活性物质^[21]。本研究显示,复合氟比洛芬酯组IL-6、IL-8低于小剂量芬太尼组,说明二者联合镇痛能够抑制机体的炎症反应,进一步缓解炎症疼痛。同时本研究显示,氟比洛芬酯复合小剂量芬太尼术后并发症率较低,说明二者联合镇痛的安全性更高,能够使患者的痛苦减轻。

综上,腹腔镜胆囊切除术患者采用氟比洛芬酯复合小剂量芬太尼静脉自控镇痛能够使凝血功能缓解,并能使疼痛及炎症因子受到抑制。

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