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帕瑞昔布钠与氟比洛芬酯用于甲状腺术后的镇痛效果及对血流动力学与炎性细胞因子的影响比较 *

宋 云[1,2] 闵 苏[1] 程 波[1] 魏 珂[1] 刘家硕[3] 朱长江[3△]

（1 重庆医科大学附属第一医院 麻醉科 重庆 400013；2 重庆市妇幼保健院 麻醉科 重庆 400013；
3 重庆市九龙坡区人民医院 麻醉科 重庆 400013）

摘要 目的：探讨甲状腺手术患者分别应用帕瑞昔布钠与氟比洛芬酯的术后镇痛效果及对其血流动力学、炎性细胞因子的影响。**方法：**选取我院 2014 年 6 月 ~2016 年 11 月收治并择期行甲状腺手术治疗的 122 例患者，依据随机数字表法均分为两组。观察组于手术结束前 30 min 缓慢静脉注射 40 mg 帕瑞昔布钠，对照组采用相同的方式注射 50 mg 氟比洛芬酯。记录比较两组术后各时点 Ramsay 镇静评分(RSS)、视觉模拟评分(VAS)，血流动力学指标，血清炎性细胞因子水平以及术后不良反应的发生情况。**结果：**两组患者术后均可获得较为理想的镇静镇痛效果，两组术后 2、4、6 h 的 RSS、VAS 组间相比差异均无统计学意义(P>0.05)。与对照组同期对比，观察组术后 12、24 h 的 RSS、VAS，均显著更优(P<0.01)。两组麻醉诱导前(T0)、术毕(T1)、术后 12 h(T2)、术后 24 h (T3)的 HR、MPA 及 SpO_2，组内及组间比较差异均无统计学意义(P>0.05)。与本组 T0 对比，两组 T1、T2、T3 的血清 TNF-α、IL-6、hs-CRP 水平，均显著上升(P<0.01)；与本组 T1 相比，两组 T2、T3 的血清炎性细胞因子水平，均显著降低(P<0.01)；两组各时点血清炎性细胞因子水平组间对比差异均无统计学意义(P>0.05)。观察组不良反应率为 4.9%，较对照组(8.2%)对比差异无统计学意义(P>0.05)。**结论：**与氟比洛芬酯相比，甲状腺手术患者于手术结束前 30 min 应用帕瑞昔布钠在稳定血流动力学、控制术后炎症反应及安全性方面优势相当，但帕瑞昔布钠的镇静镇痛维持时间更长，术后镇痛效果更为理想。

关键词：帕瑞昔布钠；氟比洛芬酯；甲状腺手术；术后镇痛；血流动力学；炎性细胞因子

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Comparison of the Postoperative Analgesic Effect of Parecoxib Sodium and Flurbiprofen Axetil for Thyroid Operation and Their Impact on the Hemodynamics and Inflammatory Cytokines*

SONG Yun[1,2], MIN Su[1], CHENG Bo[1], WEI Ke[1], LIU Jia-shuo[3], ZHU Chang-jiang[3△]

(1 Department of anesthesia, First Affiliated Hospital of Chongqing Medical University, Chongqing, 400013, China;
2 Department of anesthesia, Chongqing Maternal and Child Health-Care Hospital, Chongqing, 400013, China;
3 Department of Anesthesiology, Jiulongpo District of Chongqing City People's Hospital, Chongqing, 400013, China)

ABSTRACT Objectives: To explore the postoperative analgesic effect of parecoxib sodium and flurbiprofen axetil for thyroid operation and their impact on the hemodynamics and inflammatory cytokines. **Methods:** 122 cases of patients who receive thyroid operation in our hospital from June 2014 to November 2016 were selected and randomly divided into two groups. At 30 minutes before operation finishes, 40mg parecoxib sodium was slowly injected intravenously to the patients in the observation group, and the control group was injected with 50mg flurbiprofen axetil in the same way. The Ramsey sedation score (RSS) and visual analogue score (VAS) , hemodynamic and inflammatory cytokines, postoperative adverse reaction at any postoperative time were recorded and compared between two groups. **Results:** Both groups received good sedation analgesic effect. No statistical difference was found in the RSS and VSA at 2nd, 4th, 6th postoperative hour between groups (P>0.05). The RSS and VAS at 12th and 24th postoperative hour in the observation group were significantly better than those of the control group at the same time point (P<0.01). The HR, MPA and SpO_2 before anesthesia induction (T0), when operation finish (T1), at 12th postoperative hours (T2), and 24th postoperative hours (T3) of both groups showed no statistical difference compared with the internal group or between groups (P>0.05). The serum TNF-α, IL-6 hs-CRP levels at T1, T2, T3 were significantly increased compared with those at T0 within the same group (P<0.01). The inflammatory cytokines level at T2, T3 were significantly de- creased compared with those at T1 within the same group (P<0.01). There was no statistical difference in the serum inflammatory cy- tokines levels between groups at any time point(P>0.05). There was no statistical difference in the incidence of adverse reactions between two groups (P>0.05). **Conclusion:** The application of parecoxib sodium and flurbiprofen axetil on patients with thyroid

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作者简介：宋云(1980-)，女，副主任医师，研究方向：麻醉学，电话：13012345227

△ 通讯作者：朱长江(1962-)，男，主任医师，电话：15923250802

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at 30 minutes before operation ends had similar effort on stabilizing the hemodynamics and controlling the postoperative inflammatory response and safety, but parecoxib sodium could provide longer sedation and analgesia time and better postoperative analgesic effect.

Key words: Parecoxib sodium; Flurbiprofen axetil; Thyroid operation; Postoperative analgesic; Hemodynamics; Inflammatory cytokines

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前言

目前,甲状腺手术主要在全身麻醉下进行,患者术后疼痛表现为咳嗽痛、吞咽痛及切口痛等[1]。研究显示[2]手术患者术后疼痛极易引发肺不张及应激性高血压、溃疡及心律失常等术后并发症。临床对于术后镇痛的处理以阿片类药物为基础用药,其镇痛效果已获得临床广泛认可,但同时该类镇痛药的不良反应较多[3]。因此,临床亟需一种更为安全、有效的镇痛手段。非甾体抗炎药 (Nonsteroidal antiinflammatory drugs,NSAIDs) 在消炎、镇痛及解热等方面优势显著[4],近年来已普遍应用于各类手术的术后镇痛[5,6]。本研究通过分析甲状腺手术患者分别应用帕瑞昔布钠与氟比洛芬酯的术后镇痛效果及对其血流动力学、炎性细胞因子的影响,以期为临床合理用药提供参考,现报道如下。

1 资料与方法

1.1 一般资料

选取我院 2014 年 6 月 ~2016 年 11 月收治并择期行甲状腺手术治疗的 122 例患者,入选标准:① 术前均确诊为结节性甲状腺肿,手术方式为甲状腺次全切除术;② 麻醉方式为气管内插管麻醉;③ 患者均无气管压迫症状;④ 美国麻醉医师协会(ASA)分级为Ⅰ~Ⅱ级[7];⑤ 年龄 20~60 岁;⑥ 体重指数(BMI)为 18.5~30 kg/m^2;⑦ 术前 24 h 内未有镇痛药使用史;⑧ 临床资料齐全;⑨ 均自愿参加本研究,已签署知情同意书。排除标准:① 合并严重呼吸系统疾病、心脑血管疾病、凝血或肝肾功能障碍者;② 对本研究所用药物过敏或本身为过敏体质者;③ 有长期服用镇痛镇静药或精神类药物史者;④ 患有恶性肿瘤、感染性疾病、精神疾患或慢性疼痛者;⑤ 哺乳或妊娠期妇女;⑥ 有胃肠道出血或消化道溃疡史者。依据随机数字表法均分为两组。本研究已通过我院医学伦理委员会审核。两组基线资料相比差异均不显著(P>0.05),临床可比。具体见表 1。

表 1 两组基线资料比较

Table 1 Comparison of the baseline data between two groups

Groups	n	Gender		Age(year)	BMI(kg/m^2)	ASA classification		Intraoperative blood loss(ml)	Operation time(min)
		Female	Male			Grade I	Grade Ⅱ		
Observation group	61	42	19	44.7± 5.6	25.7± 2.3	38	23	56.3± 11.2	55.2± 9.8
Control group	61	45	16	45.4± 5.3	25.3± 2.4	40	21	57.1± 11.5	54.4± 10.1
P		0.548	0.480	0.349		0.706		0.698	0.658

1.2 方法

所有患者均行气管内插管麻醉,具体包括:① 术前常规禁食 8 h、禁饮 6 h,且均无用药;② 入手术室后,开放外周静脉,连接监护仪 (美国 Draeger Medical Systems, Inc., 型号 Infinity Delta),常规无创监测心率(HR)、血压、心电图(ECG)、血氧饱和度(SpO_2)等;③ 麻醉诱导:0.02 mg/kg 咪达唑仑(江苏恩华药业股份有限公司,国药准字 H10980025)+0.3 mg/kg 依托咪酯(德国 B.BraunMelsungenAG(贝朗),注册证号 H20090131)+2 μg/kg 芬太尼(宜昌人福药业,国药准字 H20003688)+0.6 mg/kg 罗库溴铵(欧加农公司,荷兰,注册证号 H20140847),将上述药物采取缓慢依次静脉推注;④ 而后行气管插管,完成后再予以机械通气,使呼气末二氧化碳分压($PetCO_2$)维持在 35~45 mmHg(1 mmHg=0.133 kPa);⑤ 麻醉维持:术中持续泵注 0.25 μg/kg^{-1}·min^{-1} 瑞芬太尼 (宜昌人福药业, 国药准字 H20030197)+4~8 mg/kg^{-1}·h^{-1} 丙泊酚(astrazeneca,注册证号 H20130504),以使脑电双频指数(BIS)维持在 40~65;⑥ 于手术结束前 30 min:观察组缓慢静脉注射 40 mg 帕瑞昔布钠(辉瑞制药有限公司进口分装 国药准字 J20130044),对照组采用相同的方式注射 50 mg 氟比洛芬酯 (北京泰德制药股份有限公司, 国药准字 H20041508)。两组患者术后均不予以自控镇痛。

1.3 观察指标

记录比较两组术后各时点 Ramsay 镇静评分(RSS)、视觉模拟评分(VAS),血流动力学指标,血清炎性细胞因子水平,术后不良反应情况。

1.3.1 RSS 标准 烦躁不安为 1 分,清醒但安静合作为 2 分,嗜睡但对指令仍反应敏捷为 3 分,浅睡眠状态但可迅速唤醒为 4 分,入睡且已对呼叫反应迟钝为 5 分,深睡并已呼唤不醒为 6 分;1 分为镇静不足,2~4 分为镇静满意,5~6 分为镇静过度[8]。

1.3.2 VAS 标准 共包括 11 个等级,无痛感为 0 分,最为剧烈的疼痛为 10 分,分数越高说明疼痛越强烈;>7 分视为镇痛无效,5~7 分为镇痛效果差,3~4 分为基本满意,<3 分为镇痛良好;⑥ 每位患者均于术后 2、4、6、12、24 h 时各评定 1 次 RSS、VAS[9]。

1.3.3 血流动力学指标监测 以麻醉诱导前(T0)、术毕(T1)、术后 12 h(T2)、术后 24 h(T3)为监测点,对每位患者各记录 1 次 HR、平均动脉压(MAP)、SpO_2。

1.3.4 炎性细胞因子水平测定 于 T0、T1、T2、T3 时各采集每位患者 3 mL 静脉血,离心分离血清;检测肿瘤坏死因子 -α (TNF-α)、白细胞介素 -6(IL-6)、超敏 C 反应蛋白(hs-CRP);TNF-α、IL-6 运用酶联免疫吸附法(ELISA)检测,hs-CRP 应用免疫透

射比浊法测定；仪器选用全自动酶标仪(美国安图斯，型号 Anthos2010)及配套试剂盒。

1.4 统计学分析

采用统计软件 SPSS19.0 处理数据，计数资料以(%)表示，运用 x^2 检验，计量资料以($\bar{x}\pm s$)表示，采取 t 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组术后不同时点的镇痛效果比较

两组患者术后均可获得较为理想的镇静镇痛效果。两组术后 2、4、6 h 的 RSS、VAS 组间相比差异均无统计学意义(P>0.05)；与对照组同期对比，观察组术后 12、24 h 的 RSS、VAS，均显著更优(P<0.01)。见表 2。

表 2 两组术后不同时点的镇痛效果比较

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

Groups	n	index	2 h	4 h	6 h	12 h	24 h
Observation group	61	RSS	2.87± 0.33	2.75± 0.44	2.63± 0.31	2.51± 0.19*	2.38± 0.17*
		VAS	1.42± 0.23	1.53± 0.25	1.60± 0.21	1.65± 0.27*	1.87± 0.31*
Control group	61	RSS	2.89± 0.32	2.73± 0.45	2.59± 0.35	2.39± 0.20	2.30± 0.14
		VAS	1.39± 0.24	1.51± 0.26	1.63± 0.19	1.80± 0.33	2.06± 0.38

Note: observation group's RSS at any postoperative time are 2~4 scores, only 2 cases of control group RSS reaches 1 score at 24th postoperative hours. None RSS reaches 5~6 scores in two groups. All case's VAS scores ≤ 4 at any postoperative hours, if compared with the control group at same time point, P*<0.01.

2.2 两组不同时点的血流动力学指标比较

两组组内及组间 T0、T1、T2、T3 的 HR、MPA 及 SpO_2 比较差异均无统计学意义(P>0.05)，见表 3。

表 3 两组不同时点的血流动力学指标比较

Table 3 Comparison the hemodynamic parameters at different time points of two groups($\bar{x}\pm s$)

Groups	N	Indexes	T_0	T_1	T_2	T_3
Observation group	61	HR(times/min)	78.2± 11.3	81.5± 10.9	80.8± 11.4	79.7± 11.5
		MPA(mmHg)	83.8± 12.2	86.5± 11.9	85.3± 12.4	84.6± 12.5
		SpO_2(%)	98.4± 0.8	98.1± 1.1	98.3± 0.7	98.5± 0.6
Control group	61	HR(times/min)	79.1± 11.2	82.3± 10.7	81.4± 11.6	80.5± 10.5
		MPA(mmHg)	84.3± 12.0	87.2± 11.7	85.8± 12.3	85.1± 11.9
		SpO_2(%)	98.2± 0.8	98.0± 1.0	98.1± 0.8	98.3± 0.7

2.3 两组不同时点的炎性细胞因子水平比较

与本组 T_0 对比，两组 T_1、T_2、T_3 的血清 TNF-α、IL-6、hs-CRP 水平均显著上升(P<0.01)；与本组 T_1 相比，两组 T_2、T_3 的血清炎性细胞因子水平均显著降低(P<0.01)；两组各时点血清炎性细胞因子水平组间对比差异均无统计学意义(P>0.05)。见表 4。

表 4 两组不同时点的炎性细胞因子水平比较

Table 4 Comparison of serum inflammatory cytokines levels in two groups at different time points($\bar{x}\pm s$)

Groups	N	Indexes	T_0	T_1	T_2	T_3
Observation group	61	TNF-α(mg/ml)	23.8± 4.5	61.7± 6.3*	45.6± 5.4*#	37.2± 4.9*#
		IL-6(pg/ml)	16.3± 2.7	34.5± 4.1*	28.3± 3.7*#	21.4± 3.2*#
		Hs-CRP(mg/L)	4.3± 0.7	52.4± 6.2*	31.8± 5.1*#	19.3± 3.4*#
Control group	61	TNF-α(mg/ml)	24.1± 4.4	62.5± 6.1*	46.3± 5.5*#	39.3± 5.1*#
		IL-6(pg/ml)	16.6± 2.5	34.1± 4.2*	28.8± 3.9*#	22.1± 3.0*#
		Hs-CRP(mg/L)	4.1± 0.8	53.1± 6.0*	32.7± 5.3*#	20.5± 3.6*#

Note: compared with T_0 in this group, *P<0.01; compared with T_1 in this group, #P<0.01.

2.4 两组术后不良反应的发生情况比较

观察组术后有头晕、头痛、恶心呕吐各 1 例；对照组出现 2 例头晕，1 例头痛，2 例恶心呕吐。观察组不良反应率为 4.9%(3/61)，较对照组的 8.2%(5/61) 对比差异无统计学意义(P=0.465)。两组均未见严重不良事件。

3 讨论

研究显示[10]理想的术后镇痛可有效缓解或消除疼痛所致的应激反应，减少并发症，保护机体免疫功能，促进患者康复，改善其生活质量。目前，术后镇痛的方式较多，基础用药以阿片

类药物为主,且多用于伤害性刺激发生后,虽可满足一定镇痛需求,但其不良反应明显,不利于术后快速恢复[3]。故临床迫切寻求一类操作简便、镇痛效果理想、安全的镇痛药。

帕瑞昔布钠属 NSAIDs,其在体内经肝脏酶水解后,可迅速转化为活性物质伐地昔布。研究显示[11]该活性物质对环氧化酶-2(COX-2)具有高选择性抑制作用,使得帕瑞昔布钠成为一种 COX-2 的特异性抑制剂,主要是通过抑制 COX 活性阻断花生四烯酸(AA)转化为前列腺素(PG),从而发挥消炎、镇痛等多种药理作用[12]。动物实验已证实[13]帕瑞昔布钠可通过下调成年大鼠机体 COX-2/PGE2 通路,致使其海马部位 TNF-α、IL-1β 的正常表达受到限制,从而对手术引起的神经炎症具有改善效果。基于此,近年来此药物已广泛用于临床多种手术的术后镇痛与抗炎[14,15]。氟比洛芬酯亦属 NSAIDs,是一种靶向镇痛药,其活性物质为氟比洛芬,对 COX 的抑制作用不具备选择性[16]。现阶段,临床已将其用于各种癌症及手术后的镇痛。有研究已证实[17]该药物经静注后会靶向聚集于炎症部位和手术切口,通过抑制 COX 活性、减少 PG 合成,进而对由手术创伤所致的外周敏感化与中枢敏感化起到靶向抵制效果。同时,其用于术后镇痛的优势还包括不产生中枢抑制,对麻醉病人的苏醒亦无影响。

本研究显示于手术结束前 30 min 给予临床常用剂量帕瑞昔布钠的观察组和予以常用剂量氟比洛芬酯的对照组术后镇静镇痛效果均较为理想,但与对照组同期对比,观察组术后 12、24 h 的 RSS 均显著更高,VAS 均显著更低,提示帕瑞昔布钠镇静镇痛的维持时间更长,有助于延长甲状腺手术患者的无痛时间,术后镇痛效果更佳。从血流动力学角度分析,本研究中两组 T_0、T_1、T_2、T_3 的 HR、MPA 及 SpO_2 组内、组间比较差异均无统计学意义,说明此两种 NSAIDs 对甲状腺手术患者血流动力学的影响均较小,且有利于维持患者围术期血流动力学的稳定,亦间接佐证了上述两种药物术后镇痛效果显著。

有研究表明[18]机体在经历手术创伤后将出现持续数天的炎症反应,其形成机制较为复杂,但细胞因子反应是其过程中的主要环节。当机体炎性细胞因子过度表达时,可引发过度应激,继而发生术后并发症,对患者术后恢复不利。有关研究已证实[19,20]TNF-α 是术后早期炎症反应的关键细胞因子,对炎性反应具有触发与启动的作用。IL-6 属促炎性细胞因子,在机体遭受创伤后,其水平会短时间内迅速升高,其持续时间、升高程度与创伤程度呈正相关,可作为反映患者围术期炎症程度的重要指标;CRP 属急性时相反应蛋白,当机体受到组织损伤等炎症性刺激时,由肝细胞合成并分泌,正常情况下人体含量极微,而在遭受组织损伤时,其浓度会迅速升高。因此,监测患者术后上述三种炎性细胞因子可有效反映组织损伤的严重程度。本研究结果显示与本组 T_0 对比,两组 T_1、T_2、T_3 的血清 TNF-α、IL-6、hs-CRP 水平均显著上升,表明甲状腺手术创伤可激活机体炎性反应机制,促使相关炎性细胞因子大量释放。同时,与本组 T_1 相比,两组 T_2、T_3 的血清炎性细胞因子水平,均显著降低;两组各时点血清炎性细胞因子水平组间对比差异均无统计学意义,可见上述两种 NSAIDs 均能显著降低机体炎性反应,控制炎性因子的释放,缓解术后炎性反应,进而减轻术后疼痛,改善预后,且疗效相当。

此外,从用药安全的角度来看,观察组术后不良反应率为 4.9%,略低于对照组的 8.2%;分析原因可能与帕瑞昔布对 COX-2 抑制的高选择性,而对 COX-1 并不产生实际药理作用,从而有助于避免因抑制 COX-1 而产生的不良反应相关,但两组对比差异无统计学意义,可能与本研究样本量相对较小有关。两组术后症状均为一过性,且未见严重事件,表明两种 NSAIDs 均相对较为安全。

综上所述,与氟比洛芬酯相比,甲状腺手术患者于手术结束前 30min 应用帕瑞昔布钠在稳定血流动力学、控制术后炎症反应及安全性方面优势相当,但帕瑞昔布钠的镇静镇痛维持时间更长,术后镇痛效果更为理想。

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