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帕瑞昔布钠复合舒芬太尼对甲状腺手术患者术后镇痛镇静效果、血流动力学及炎症反应的影响*

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摘要 目的:探讨帕瑞昔布钠复合舒芬太尼对甲状腺手术患者术后镇痛镇静效果、血流动力学及炎症反应的影响。**方法:**选择 2018 年 6 月~2019 年 6 月期间 100 例在我院择期行甲状腺手术患者,根据随机数字表法分为对照组($n=50$,术后镇痛予以舒芬太尼)和研究组($n=50$,术后镇痛予以帕瑞昔布钠复合舒芬太尼),比较两组患者术后镇痛镇静效果、血流动力学、炎症反应及不良反应。**结果:**两组患者术后 8 h、16 h、24 h 视觉疼痛模拟评分(VAS)呈先升高后降低趋势,且研究组低于对照组($P<0.05$);两组患者术后 8 h、16 h、24 h 的 Ramsay 镇静评分呈先降低后升高趋势,且研究组高于对照组($P<0.05$)。对照组患者术后 8 h、16 h、24 h 心率(HR)、平均动脉压(MAP)呈先降低后升高趋势($P<0.05$);研究组术后 8 h、16 h、24 h 的 MAP、HR 与术后即刻比较差异无统计学意义($P>0.05$);研究组术后 8 h、16 h 的 MAP、HR 均高于对照组($P<0.05$)。两组患者术后 6 h、术后 24 h 白介素-6(IL-6)、C 反应蛋白(CRP)、肿瘤坏死因子- α (TNF- α)呈先升高后降低趋势,但研究组低于对照组($P<0.05$)。两组不良反应发生率比较无统计学差异($P>0.05$)。**结论:**行甲状腺手术的患者术后镇痛予以帕瑞昔布钠复合舒芬太尼,可获得较好的镇痛镇静效果,能够维持血流动力学平稳,减轻机体炎症反应,且不增加不良反应发生率。

关键词:帕瑞昔布钠;舒芬太尼;甲状腺手术;镇痛;镇静;血流动力学;炎症反应

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Effects of Parecoxib Sodium Sombined with Sufentanil on Postoperative Analgesia, Sedation Effect, Hemodynamics and Inflammatory Response in Patients Undergoing Thyroid Surgery*

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ABSTRACT Objective: To investigate the effects of parecoxib sodium combined with sufentanil on postoperative analgesia, sedation effect, hemodynamics and inflammatory response in patients undergoing thyroid surgery. **Methods:** From June 2018 to June 2019, 100 patients who underwent elective thyroid surgery in our hospital were selected. The patients were divided into two groups: control group ($n=50$, sufentanil was given for postoperative analgesia) and the study group ($n=50$, parecoxibna combined with sufentanil was given for postoperative analgesia). The effects of postoperative analgesia, sedation, hemodynamics, inflammatory responses and adverse reactions were compared between the two groups. **Results:** The visual pain analogue scale (VAS) in the two groups at 8 h, 16 h and 24 h after operation increased and then decreased, and that in the study group was lower than that in the control group ($P<0.05$). The Ramsay sedation scores of the two groups at 8 h, 16 h and 24 h after operation decreased and then increased, and that in the study group was higher than that in the control group ($P<0.05$). The heart rate (HR) and mean arterial pressure (MAP) of the patients in the control group at 8 h, 16 h and 24 h after operation decreased and then increased ($P<0.05$). There was no significant difference in MAP, HR between 8 h, 16 h and 24 h after operation and immediately after operation in the study group ($P>0.05$). The MAP and HR in the study group were higher than those in the control group($P<0.05$). The levels of interleukin-6(IL-6), C-reactive protein (CRP) and tumor necrosis factor- α (TNF- α) in the two groups at 6 h and 24 h after operation increased and then decreased, however, those in the study group were lower than those in the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** In postoperative analgesia of patients undergoing thyroid surgery, parecoxib sodium combined with sufentanil can obtain

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better analgesic effect, able to maintain hemodynamic stability, reduce inflammatory reaction of the body, and it do not increase the incidence of adverse reactions.

Key words: Parecoxib sodium; Sufentanil; Thyroid surgery; Analgesia; Sedation; Hemodynamics; Inflammatory response

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前言

近年来,随着人们生活结构的改变,甲状腺相关疾病的发病率逐渐增多,甲状腺手术也随之增加^[1]。甲状腺手术作为一种有创操作,因术中麻醉刺激、牵拉、机械通气等原因,可导致炎性细胞激活、疼痛刺激加强,使术后并发症增加,影响患者休息和正常功能恢复^[2,3]。因此,甲状腺手术患者给予合理的术后镇痛可有效提高患者手术治疗效果。现临床有关术后镇痛的方案较多,舒芬太尼是临床常见的麻醉药物,可发挥较好的镇痛、镇静效果,然而舒芬太尼易存在个体差异性,且伴随着剂量的增加,还易发生呼吸抑制,存在一定的局限性^[4,5]。帕瑞昔布钠新型非甾体抗炎镇痛药,静脉注射后迅速转化成伐地昔布,发挥有效的镇痛作用,近年来该药已应用于临床多种手术的术后镇痛^[6,7]。本研究通过对我院收治的部分行甲状腺手术患者的术后镇痛方案予以帕瑞昔布钠复合舒芬太尼,取得了较好的疗效。

1 资料与方法

1.1 基线资料

选择2018年6月~2019年6月100例在我院择期行甲状腺手术患者,纳入标准:(1)所有患者均具备甲状腺手术指征;(2)美国麻醉医师协会分级I~II级;(3)既往无甲状腺手术史者;(4)手术均由同一组医师执行。排除标准:(1)合并心血管疾病史者;(2)长期服用镇静镇痛药者;(3)合并心肝肾等重要脏器功能不全者;(4)对本次麻醉用药存在禁忌症者;(5)妊娠或哺乳期妇女;(6)合并自身免疫性疾病者;(7)精神因素无法配合或者不愿意手术者。根据随机数字表法将患者分为研究组($n=50$)和对照组($n=50$),其中对照组男21例,女29例,年龄23~65岁,平均 (36.59 ± 5.61) 岁;美国麻醉医师协会分级I级28例,II级22例;体质量指数 $21.8 \sim 26.3 \text{ kg/m}^2$,平均 $(23.96 \pm 1.15) \text{ kg/m}^2$ 。研究组男23例,女27例,年龄24~68岁,平均 (35.86 ± 4.32) 岁;美国麻醉医师协会分级I级30例,II级20例;体质量指数 $22.3 \sim 26.5 \text{ kg/m}^2$,平均 $(24.13 \pm 0.98) \text{ kg/m}^2$ 。两组一般资料比较无差异($P>0.05$)。

1.2 方法

1.2.1 麻醉方法 所有患者术前常规禁饮禁食,入室后开放静脉通道,30分钟内输注晶体液 $5 \sim 10 \text{ mL/KG}$ 。常规监测患者心率(Heart rate, HR)、平均动脉压(Mean arterial pressure, MAP)。采用气管插管全麻,麻醉诱导依次静脉注射咪达唑仑(江苏九旭药业有限公司,国药准字:H20153019,规格:2 mL:10 mg)0.05 mg;舒芬太尼(宜昌人福药业有限责任公司,国药准字:H20054256,规格:1 mL:50 μg)0.05 μg ;依托咪酯(江苏恒瑞医药股份有限公司,国药准字:H32022379,规格:10 mL:20 mg)0.3 mg;罗库溴铵(福安药业集团庆余堂制药有限公司,国药准字:H20183106,规格:5 mL:50 mg)0.6 mg,气管插管成功后控

制呼吸及呼吸参数。麻醉维持选用异丙酚-瑞芬太尼(江苏恩华药业股份有限公司,国药准字:H20143315,规格:2mg)持续输注,并间歇吸入七氟烷(上海恒瑞医药有限公司,国药准字:H20070172,规格:120 mL),手术结束即刻停药。

1.2.2 术后镇痛方法 研究组于手术缝皮前和术后给予帕瑞昔布钠(浙江普洛康裕制药有限公司,国药准字:H20193065,规格:40 mg)40 mg,采用生理盐水稀释至5 mL,静脉推注;对照组则于上述同时间点分别静脉推注生理盐水5 mL。手术结束后两组均给予患者自控静脉镇痛泵行术后镇痛,镇痛药配方为舒芬太尼100 μg ,采用生理盐水稀释至200 mL,首次量设置为4 mL,背景流量2 mL/h,追加量1 mL,锁定时间5 min。

1.3 观察指标

1.3.1 镇痛、镇静效果 于术后即刻、术后8 h、术后16 h、术后24 h采用视觉疼痛模拟评分(Visual pain score, VAS)^[8]、Ramsay^[9]评价患者疼痛、镇静情况。其中VAS总分10分,分数越高疼痛感越强;Ramsay评分1~6分,其中烦躁不安为1分、安静合作为2分、嗜睡为3分、浅睡眠为4分、入睡为5分、深睡为6分。

1.3.2 血流动力学指标 记录两组患者术后即刻、术后8 h、术后16 h、术后24 h的MAP、HR。

1.3.3 炎症因子指标 于术前、术后6 h、术后24 h抽取患者肘静脉血4 mL,经离心半径6 cm,3400 r/min离心12 min,分离上清液,置于-40摄氏度冰箱中待测。按照试剂盒(武汉博士德生物科技有限公司)说明书操作,采用酶联免疫吸附试验检测白介素-6 (Interleukin-6, IL-6)、C反应蛋白(C-reactive protein, CRP)、肿瘤坏死因子- α (Tumor necrosis factor - α , TNF- α)水平。

1.3.4 不良反应 记录两组围术期低血压、恶心呕吐、心动过缓的发生情况。

1.4 统计学方法

所有研究数据分析均采用SPSS 25.0统计学软件。计数资料以频数或百分数表示,组间比较采用 χ^2 检验,计量资料以均值 $\pm$ 标准差($\bar{x} \pm s$)表示采用t检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组患者围术期指标比较

两组患者手术时间、麻醉药物的用量、术后清醒时间和气管导管拔管时间组间比较无统计学差异($P>0.05$);见表1。

2.2 两组镇痛、镇静效果比较

两组患者术后即刻VAS评分、Ramsay镇静评分比较无差异($P>0.05$);两组患者术后8 h、16 h、24 h的VAS评分呈先升高后降低趋势,且研究组低于对照组($P<0.05$);两组患者术后8 h、16 h、24 h的Ramsay镇静评分呈先降低后升高趋势,且研究组高于对照组($P<0.05$);详见表2。

表 1 两组患者围术期指标比较($\bar{x} \pm s$)Table 1 Comparison of perioperative indexes between the two groups ($\bar{x} \pm s$)

Groups	Operation time(min)	Dosage of narcotic drugs (mg)	Postoperative wake time (min)	Tracheal tube extubation time(min)
Control group(n=50)	42.56 $\pm$ 3.29	1.91 $\pm$ 0.21	13.89 $\pm$ 2.54	19.31 $\pm$ 1.69
Study group(n=50)	41.92 $\pm$ 4.22	1.87 $\pm$ 0.34	13.02 $\pm$ 2.87	18.97 $\pm$ 1.28
t	0.846	0.708	1.605	1.134
P	0.400	0.401	0.112	0.264

表 2 两组镇痛、镇静效果比较($\bar{x} \pm s$, 分)Table 2 Comparison of analgesic and sedative effects between the two groups ($\bar{x} \pm s$, scores)

Groups	VAS score				Ramsay sedation score			
	Immediately after operation	8 h after operation	16 h after operation	24 h after operation	Immediately after operation	8 h after operation	16 h after operation	24 h after operation
Control group (n=50)	1.51 $\pm$ 0.37	6.03 $\pm$ 0.74 ^a	4.20 $\pm$ 0.83 ^{ab}	2.63 $\pm$ 0.72 ^{abc}	2.80 $\pm$ 0.35	1.29 $\pm$ 0.24 ^a	1.72 $\pm$ 0.32 ^{ab}	2.05 $\pm$ 0.26 ^{abc}
Study group (n=50)	1.44 $\pm$ 0.28	5.22 $\pm$ 0.82 ^a	3.18 $\pm$ 0.91 ^{ab}	1.98 $\pm$ 0.51 ^{abc}	2.87 $\pm$ 0.41	1.76 $\pm$ 0.48 ^a	2.13 $\pm$ 0.36 ^{ab}	2.42 $\pm$ 0.35 ^{abc}
t	1.067	5.185	5.856	5.209	0.918	6.193	6.019	6.001
P	0.289	0.000	0.000	0.000	0.361	0.000	0.000	0.000

Note: compared with immediately after operation, ^a $P<0.05$; compared with 8 h after operation, ^b $P<0.05$; compared with 16 h after operation, ^c $P<0.05$.

2.3 两组患者血流动力学指标比较

两组术后即刻、术后 24 h 的 MAP、HR 比较无差异($P>0.05$); 对照组患者术后 8 h、16 h、24 h 的 MAP、HR 呈先降低后

升高趋势($P<0.05$); 研究组术后 8 h、16 h、24 h 的 MAP、HR 与术后即刻比较差异无统计学意义($P>0.05$); 研究组术后 8 h、16 h 的 MAP、HR 均高于对照组($P<0.05$); 详见表 3。

表 3 两组患者血流动力学指标比较($\bar{x} \pm s$)Table 3 Comparison of hemodynamic indexes between the two groups ($\bar{x} \pm s$)

Groups	MAP(mmHg)				HR(beats/min)			
	Immediately after operation	8 h after operation	16 h after operation	24 h after operation	Immediately after operation	8 h after operation	16 h after operation	24 h after operation
Control group (n=50)	90.71 $\pm$ 3.30	81.88 $\pm$ 4.22 ^a	85.87 $\pm$ 3.64 ^{ab}	89.71 $\pm$ 3.47 ^{bc}	83.69 $\pm$ 4.10	74.10 $\pm$ 4.13 ^a	77.82 $\pm$ 5.65 ^{ab}	82.28 $\pm$ 4.51 ^{bc}
Study group (n=50)	90.73 $\pm$ 3.35	88.32 $\pm$ 4.15	88.84 $\pm$ 4.69	89.12 $\pm$ 4.31	83.82 $\pm$ 4.08	81.33 $\pm$ 5.15	82.86 $\pm$ 5.69	82.97 $\pm$ 5.45
t	0.030	7.694	3.537	0.754	0.159	7.744	4.444	0.690
P	0.976	0.000	0.001	0.453	0.874	0.000	0.000	0.492

Note: compared with immediately after operation, ^a $P<0.05$; compared with 8 h after operation, ^b $P<0.05$; compared with 16 h after operation, ^c $P<0.05$.

2.4 两组患者炎症因子指标比较

两组术前 IL-6、CRP、TNF- α 比较无差异($P>0.05$); 两组术后 6 h、术后 24 h 的 IL-6、CRP、TNF- α 呈先升高后降低趋势, 但研究组低于对照组($P<0.05$); 详见表 4。

2.5 不良反应发生率比较

对照组出现 3 例恶心呕吐、2 例低血压、1 例心动过缓, 不良反应发生率为 12.00%(6/50); 研究组出现 3 例恶心呕吐、4 例低血压、1 例心动过缓, 不良反应发生率为 16.00%(8/50); 两组不良反应发生率比较无统计学差异($\chi^2=0.492$, $P=0.361$)。

3 讨论

传统的甲状腺手术麻醉常选用局麻或者颈丛神经阻滞, 此类麻醉方法术中患者舒适度差, 术中配合不良及不利于手术医生操作^[10]。随着外科技术的飞速发展, 甲状腺手术麻醉逐渐选用全麻, 此类麻醉方法患者舒适度较好, 利于手术操作^[11,12]。术后因手术创伤以及吞咽、颈部活动等可引起不同程度的伤口疼痛, 影响患者术后舒适度及功能恢复^[13,14]。既往研究显示^[15], 甲状腺手术患者术后 24 h 疼痛最为明显, 为了加快康复进程, 需给予有效的术后镇痛。目前甲状腺手术术后镇痛主要采用静脉自控镇痛, 但有关具体镇痛方案尚未完全统一。舒芬太尼属于芬太尼家族, 其镇痛效果确切、持续时间久, 且无组胺释放^[16]。但舒芬太尼若剂量太少则镇痛不足, 而剂量过多又易引起围术

期不良反应,故单独应用舒芬太尼进行术后镇痛治疗在临床上受到了一定的限制^[17,18]。随着人们对术后疼痛机制的深入研究,多模式联合镇痛概念越来越得到人们的重视。帕瑞昔布钠可通

过阻断花生四烯酸合成前列腺素,发挥镇痛抗炎的作用,常用于预防性镇痛及增强术后镇痛效果^[19,20]。

表 4 两组患者炎症因子指标比较($\bar{x} \pm s$)Table 4 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	IL-6 (pg/mL)			CRP (mg/L)			TNF- α (pg/mL)		
	Before operation	6 h after operation	24 h after operation	Before operation	6 h after operation	24 h after operation	Before operation	6 h after operation	24 h after operation
Control group (n=50)	42.48 $\pm$ 5.30	81.73 $\pm$ 6.20 ^a	67.24 $\pm$ 5.13 ^{ab}	1.88 $\pm$ 0.39	3.64 $\pm$ 0.47 ^a	2.97 $\pm$ 0.56 ^{ab}	9.15 $\pm$ 1.38	26.59 $\pm$ 1.31 ^a	18.93 $\pm$ 1.43 ^{ab}
Study group (n=50)	42.35 $\pm$ 6.28	70.28 $\pm$ 5.13 ^a	54.20 $\pm$ 6.23 ^{ab}	1.74 $\pm$ 0.42	3.18 $\pm$ 0.49 ^a	2.41 $\pm$ 0.35 ^{ab}	9.23 $\pm$ 1.40	20.18 $\pm$ 2.24 ^a	13.04 $\pm$ 1.55 ^{ab}
t	0.112	10.061	11.425	1.727	4.791	5.996	0.228	17.467	19.749
P	0.911	0.000	0.000	0.087	0.000	0.000	0.774	0.000	0.000

Note: compared with before operation, ^a $P < 0.05$; compared with 6h after operation, ^b $P < 0.05$.

本次研究结果中,研究组术后不同时间点 VAS 评分、Ramsay 镇静评分均优于对照组,提示帕瑞昔布钠复合舒芬太尼用于术后镇痛,可获得更好的治疗效果。舒芬太尼作为阿片类镇痛药物,可直接与外周神经纤维阿片受体结合发挥镇痛、镇痛作用^[21,22];而帕瑞昔布钠注射后迅速水解为伐地昔布,伐地昔布可高选择性地抑制环氧化酶,进而减少外周前列腺合成,同时还可抑制中枢神经传导,发挥外周、中枢双重镇痛、镇静模式;两种麻醉药物作用于疼痛病理生理机制的不同靶位和不同时间相,发挥良好的协同作用^[23-25]。生理状态下,细胞促炎因子和抗炎因子于平衡状态,但手术作为强烈的应激源,围术期的一系列操作均可引起炎性细胞激活,造成术后不同程度的炎性反应。IL-6 是常见的促炎细胞因子,可提高外周及中枢神经系统的敏感性;TNF- α 作为一种前炎症因子,可促进 IL-6、CRP 的炎症因子分泌;CRP 是一种急性期蛋白,可较好的反映组织损伤程度^[26,27]。本研究两组患者上述炎性因子水平呈先升高后降低趋势,但选用帕瑞昔布钠复合舒芬太尼镇痛的患者其炎性程度较轻。这可能是因为帕瑞昔布钠本身即具备较好的抗炎作用有关。既往动物实验结果显示^[28],帕瑞昔布钠可通过抑制环氧化酶表达而减轻老年大鼠脾切除术后海马炎症反应。徐丽等学者研究亦显示^[29],帕瑞昔布钠联合舒芬太尼多模式镇痛可明显降低宫颈癌根治术患者术后疼痛及炎症反应。HR、MAP 均为反映血流动力学稳定的重要指标,本研究中舒芬太尼可引起患者不同程度的血流波动,而帕瑞昔布钠复合舒芬太尼可较好的维持血流动力学平稳,这可能与复合用药可加强镇痛效果,减少炎性刺激,提高患者术后舒适度,利于患者恢复^[30]。此外两组不良反应发生率比较无差异,表明本次联合镇痛方案用药安全性良好。

综上所述,行甲状腺手术的患者术后镇痛予以帕瑞昔布钠复合舒芬太尼,可获得较好的镇痛镇痛效果,维持血流动力学平稳,减轻机体炎性反应,且不增加不良反应发生率。

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