doi: 10.13241/j.cnki.pmb.2021.15.040

盐酸右美托咪定联合盐酸罗哌卡因胸椎旁神经阻滞对肺癌根治术患者血清炎性因子和免疫学指标的影响*

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摘要 目的：探讨盐酸右美托咪定联合盐酸罗哌卡因胸椎旁神经阻滞（TPVB）对肺癌根治术患者血清炎性因子和免疫学指标的影响。**方法：**选取 2018 年 4 月 ~2020 年 4 月期间于我院行肺癌根治术的患者 400 例，根据信封抽签法分为对照组和观察组，各 200 例，对照组给予盐酸罗哌卡因 TPVB，观察组在对照组基础上联合盐酸右美托咪定，对比两组疼痛、炎性因子、免疫学指标、血流动力学及不良反应。**结果：**观察组术后 6 h（T5）~ 术后 48h（T8）时间点视觉模拟评分法（VAS）评分均低于对照组（P<0.05）。对照组插管后 5 min（T1）~ 术毕（T3）时间点心率（HR）及平均动脉压（MAP）较麻醉诱导前（T0）时间点升高（P<0.013），观察组 T1~T3 时间点 HR、MAP 低于对照组（P<0.05）。两组 T8 时间点白介素 -6（IL-6）、C 反应蛋白（CRP）、肿瘤坏死因子 -α（TNF-α）均较 T0 下降，且观察组低于对照组（P<0.05）。两组 T8 时间点 $CD4^+$、$CD4^+/CD8^+$ 均较 T0 时间点下降，但观察组高于对照组（P<0.05），$CD8^+$ 均较 T0 时间点升高，但观察组低于对照组（P<0.05）。观察组不良反应总发生率低于对照组（P<0.05）。**结论：**盐酸右美托咪定联合盐酸罗哌卡因 TPVB 用于肺癌根治术患者，可稳定血流动力学，且可获得较好的镇痛效果，降低不良反应发生率，减轻术后炎性损伤及免疫抑制。

关键词：盐酸右美托咪定；盐酸罗哌卡因；胸椎旁神经阻滞；肺癌根治术；炎性因子；免疫学指标

中图分类号：R734.2；R614 **文献标识码：**A **文章编号：**1673-6273（2021）15-2991-05

Effects of Dexmedetomidine Hydrochloride Combined with Ropivacaine Hydrochloride Paraspinal Nerve block on Serum Inflammatory Factors and Immunological Indexes in Patients with Lung Cancer Undergoing Radical Resection*

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ABSTRACT Objective: To investigate the effects of thoracic paravertebral nerve block (TPVB) with dexmedetomidine hydrochloride and ropivacaine hydrochloride on serum inflammatory factors and immunological indexes in patients with lung cancer undergoing radical resection. **Methods:** 400 patients with radical resection of lung cancer who were admitted in our hospital from April 2018 to April 2020 were selected, they were randomly divided into control group and observation group, 200 cases in each group, the control group was given ropivacaine hydrochloride TPVB, while the observation group was treated with dexmedetomidine hydrochloride on the basis of the control group, pain, inflammatory factors, immunological indexes, hemodynamics and adverse reactions of the two groups were compared. **Results:** The visual analogue scoring（VAS）score of the observation group was lower than that of the control group at the time point of 6h after operation(T5) ~ 48 h after operation (T8) (P<0.05). Heart rate (HR) and mean arterial pressure (MAP) at the time point of 5 min after intubation (T1) ~ end of operation (T3) in the control group were higher than the time point of before anesthesia induction (T0) (P<0.013), while HR, MAP at the time point of T1-T3 in the observation group were lower than those of the control group (P<0.05). The interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor - α (TNF-α) at the time point of T8 were lower than T0, and the observation group was lower than the control group (P<0.05). The $CD4^+$, $CD4^+/CD8^+$ at the time point of T8 were lower than T0, but the observation group was higher than the control group (P<0.05), $CD8^+$ was higher than T0, but the observation group was lower than the control group (P<0.05). The total incidence of adverse reactions in the observation group was lower than that of the control group (P<0.05). **Conclusion:** Dexmedetomidine hydrochloride combined with ropivacaine hydrochloride TPVB for patients with radical resection of lung cancer, has exact analgesic effect, can maintain the stability of hemodynamics, reduce the incidence of

* 基金项目：湖南省自然科学基金面上项目（2017JJ2285）

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（收稿日期：2021-01-27 接受日期：2021-02-22）

postoperative inflammatory injury and incidence of adverse reactions, and reduce the immunosuppression.

Key words: Dexmedetomidine hydrochloride; Ropivacaine hydrochloride; Thoracic paraspinal nerve block; Radical resection of lung cancer; Inflammatory factors; Immunological indicators

Chinese Library Classification(CLC): R734.2; R614 Document code: A

Article ID: 1673-6273(2021)15-2991-05

前言

肺癌是临床发病率、死亡率均最高的恶性肿瘤，我国每年新发的肺癌患者约有 78.1 万例，死亡人数则高达 62.6 万例，且其发病率呈现逐年递增趋势[1,2]。肺癌根治术是治疗早期肺癌的首选方法，但手术作为一种创伤性操作，其导致的疼痛和创伤等伤害性刺激往往会影响患者循环功能和免疫功能，增加肿瘤转移和术后感染风险[3-5]。有效的麻醉方案有利于维持肺癌患者围术期的免疫平衡，促进肺癌患者康复。胸椎旁神经阻滞（TPVB）可抑制伤害性刺激传导，减轻术中应激，具有确切的镇痛效果[6,7]。盐酸罗哌卡因是 TPVB 麻醉中常用的药物，但单次注射局麻药通常难以满足术后镇痛需求[8,9]。盐酸右美托咪定是高选择性α2 肾上腺素受体激动药，具有镇静、镇痛效果，且不会造成患者呼吸抑制[10,11]。本研究通过探讨盐酸右美托咪定联合盐酸罗哌卡因 TPVB 对肺癌根治术患者血清炎性因子和免疫学指标的影响，旨在为临床肺癌根治术麻醉方案的选择提供参考，整理如下。

1 资料和方法

1.1 一般资料

选取 2018 年 4 月 ~2020 年 4 月期间于我院行肺癌根治术的患者 400 例。纳入标准：(1)均符合《中国原发性肺癌诊疗规范(2015 年版)》的相关诊断标准[12]；(2)均经病理学、实验室检查等确诊；(3)均具备手术指征，择期完成手术；(4)知情本研究，且已签署了同意书；(5)美国麻醉医师协会（ASA）分级：I 级 ~II 级。排除标准：(1)合并严重心脑血管疾病；(2)有胸部手术史者；(3)合并心肝肾等脏器功能障碍者；(4)术前有放疗或化疗史；(5)有肺部感染疾病史者；(6)有局麻类药物过敏史。研究方案已通过我院伦理学委员会批准进行。纳入研究的患者根据信封抽签法分为对照组和观察组，各 200 例，两组一般资料均衡可比（P>0.05），见表 1。

表 1 两组患者一般资料对比

Table 1 Comparison of general data between the two groups

Groups	Male/Female	Age(year)	Body mass index (kg/m²)	ASA class		Pulmonary lesion area	
				I	II	Left	Right
Control group (n=200)	123/77	46.82± 4.39	23.97± 0.86	102	98	99	101
Observation group(n=200)	125/75	47.27± 5.12	23.81± 0.77	103	97	100	100
t/x^2	0.208	0.422	0.877	0.051		0.050	
P	0.648	0.674	0.383	0.822		0.823	

1.2 方法

均择期行开胸肺癌根治术。入室前常规禁食禁饮并完善心电图、血尿常规、电解质等检查，入室后吸氧并监测血压、心电图、心率（HR）及平均动脉压（MAP），开通上肢静脉通道。患者侧卧位，采用 Sonosite 公司生产的 SNERVE 便携式超声仪和德国贝朗公司生产的 Stimulplex 外周神经丛刺激器行患侧 TPVB 置管。超声探头置入无菌手套，扫描患侧棘突连线旁开 3 cm 处，使棘突连线与超声纵轴处于平行位置。探头放置在横突平面，探头与脊柱垂直，获取椎旁间隙图像。回抽无血无气后固定针尾，对照组患者于椎旁间隙内注射 0.5%盐酸罗哌卡因 [国药准字 H20173193，广东嘉博制药有限公司，规格：20 mL:150 mg(按盐酸罗哌卡因计)]30 mL，观察组患者则于椎旁间隙内注射 0.5%盐酸罗哌卡因联合盐酸右美托咪定 [国药准字 H20090248，江苏恒瑞医药股份有限公司，规格：2 mL:200 μg (按右美托咪定计)]的混合液 30ml。观察两组患者，10 min 后若麻醉平面出现支配区域感觉功能减退则提示阻滞成功。随后给予丙泊酚（国药准字 H20123318，西安力邦制药有限公司，规格：50 mL:1.0 g）1~2 mg/kg、苯磺顺阿曲库铵注射液（批准文号 H20181158，Aspen Pharma Trading Limited，规格：5 mL:10 mg）0.15 mg/kg、舒芬太尼（国药准字 H20054171，宜昌人福药业有限责任公司，规格：按 $C_{22}H_{30}N_2O_2S$ 计 1 mL:50 μg）0.2~0.5 μg/kg 常规麻醉诱导，插入双腔支气管导管并行机械通气。采用静脉输注舒芬太尼 4~8 μg/kg·h、丙泊酚 4~8 mg/kg·h 维持麻醉，间断静脉注射苯磺顺阿曲库铵 2~5 mg 维持肌松。

1.3 观察指标

（1）记录两组麻醉诱导前（T0）、插管后 5 min（T1）、术中 30 min（T2）、术毕（T3）、术后 1 h（T4）的 HR、MAP。（2）记录两组患者 T4、术后 6 h（T5）、术后 12 h（T6）、术后 24 h（T7）、术后 48 h（T8）的视觉模拟评分法（VAS）[13]评分，赋值 0~10 分，分数越高，疼痛感越强。（3）抽取两组患者 T0、T8 的肘静脉血 6 mL 分装为两管，其中一管经常规离心处理（离心半径 12.5 cm，3800 r/min 离心 12 min），分离上清液待测，白介素 -6（IL-6）、C

反应蛋白(CRP)、肿瘤坏死因子 -α(TNF-α)采用酶联免疫吸附法检测,严格遵守试剂盒(上海桑戈生物工程有限公司)说明书进行。另一管通过 XL 型流式细胞仪[赛默飞世尔科技(中国)有限公司]测定 $CD4^+$、$CD8^+$,计算 $CD4^+/CD8^+$。(4)记录两组不良反应发生情况。

1.4 统计学处理

以 SPSS23.0 处理数据。性别、ASA 分级、肺损伤区域等计数资料以例数及率描述,比较为校正卡方检验或卡方检验。VAS 评分、HR、MAP 等计量数据符合正态分布,以 MEAN± SD 描述,比较为校正 t 检验或成组 t 检验,重复观测资料行两两组间比较 LSD-t 检验或两两组内(时间维度)比较差值 t 检验 + 重复测量方差分析。统计推断的检验水准α=0.05(双侧检验)。重复测量分析之时间维度的多次比较按 Bonferroni 校正法调整检验水准。

2 结果

2.1 两组炎症因子对比

T0 时间点两组 TNF-α、CRP、IL-6 比较无统计学差异(P>0.05);T8 时间点两组 TNF-α、CRP、IL-6 均较 T0 下降,且观察组低于对照组(P<0.05),详见表 2。

表 2 两组炎症因子对比($\bar{x}\pm s$)

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

Groups	Time	IL-6(pg/mL)	CRP(mg/L)	TNF-α(ng/mL)
Control group(n=200)	T0	61.98± 7.31	43.74± 5.82	56.12± 5.61
	T8	48.52± 5.57	32.76± 5.73	41.38± 5.28
	Difference	-13.46± 12.65	-10.98± 8.89	-14.74± 11.42
	Pair test t,P	6.730,0.000	7.811,0.000	8.163,0.000
Observation group(n=200)	T0	61.39± 5.64	43.46± 4.15	56.35± 4.36
	T8	31.92± 5.15	25.40± 3.17	29.07± 3.28
	Difference	-29.47± 6.27	-18.06± 3.24	-27.28± 7.14
	Pair test t,P	29.726,0.000	35.254,0.000	24.164,0.000
Comparison between groups	T0	0.404,0.687	0.248,0.805	0.205,0.838
(Unit test t,P)	T8	13.840,0.000	7.108,0.000	12.525,0.000

2.2 两组不同时间点 HR、MAP 比较

两组 T0 时间点 HR、MAP 比较无统计学差异(P>0.05);对照组 T1~T3 时间点 HR、MAP 较 T0 时间点升高(P<0.013),观察组 T1~T4 时间点 HR 均较 T0 时间点升高(P<0.013);观察组 T1~T3 时间点 HR、MAP 低于对照组(P<0.05),详见表 3。

表 3 两组不同时间点 HR、MAP 比较($\bar{x}\pm s$)

Table 3 Comparison of HR and MAP between the two groups at different time points ($\bar{x}\pm s$)

Groups	Time	HR(beats/min)	MAP(mmHg)
Control group(n=200)	T0	79.03± 5.08	92.11± 6.91
	T1	87.10± 5.67^{t}	103.02± 8.05^{t}
	T2	84.70± 6.56^{t}	103.19± 6.54^{t}
	T3	84.51± 5.49^{t}	100.85± 7.22^{t}
	T4	79.22± 5.59	94.19± 7.26
Observation group(n=200)	T0	77.42± 5.90	94.29± 6.07
	T1	80.66± 5.38^{at}	95.28± 4.91^{a}
	T2	81.39± 5.57^{at}	93.45± 5.82^{a}
	T3	81.11± 6.18^{at}	94.66± 5.15^{a}
	T4	80.19± 5.17^{t}	93.91± 6.48
Overall analysis	HF coefficient	1.0006	0.9974
Comparison between groups	F,P	27.069,0.000	44.904,0.000
Intra group comparison	F,P	14.275,0.000	13.589,0.000
Interaction	F,P	4.424,0.002	12.166,0.000

Note: the significance marker t was the comparison with the first time point in the group P<α', α' was the Bonferroni corrected test level =0.05/4=0.013; compared with control group, ^{a}P<0.05.

2.3 两组不同时间点 VAS 评分比较

两组 T4 时间点 VAS 评分对比差异无统计学意义(P>0.05)；两组 T5~T8 时间点 VAS 评分呈升高后下降趋势(P<0.013)；观察组 T5~T8 时间点 VAS 评分低于对照组(P<0.05)，详见表 4。

表 4 两组不同时间点 VAS 评分比较($\bar{x}\pm s$，分)

Table 4 Comparison of VAS scores between the two groups at different time points ($\bar{x}\pm s$, score)

Groups	Time	VAS score
Control group(n=200)	T4	1.57± 0.31
	T5	2.27± 0.88[t]
	T6	2.82± 0.53[t]
	T7	3.96± 0.45[t]
	T8	3.24± 0.64[t]
Observation group(n=200)	T4	1.55± 0.31
	T5	1.83± 0.42[at]
	T6	2.35± 0.53[at]
	T7	3.08± 0.34[at]
	T8	2.77± 0.44[at]
Overall analysis	HF coefficient	0.9814
Comparison between groups	F,P	68.038,0.000
Intra group comparison	F,P	189.134,0.000
Interaction	F,P	7.398,0.000

Note: Same as table 3.

2.4 两组免疫功能指标对比

T0 时间点两组 $CD4^+/CD8^+$、$CD8^+$、$CD4^+$ 比较无统计学差异(P>0.05)，两组 T8 时间点 $CD4^+$、$CD4^+/CD8^+$ 均较 T0 下降，但观察组高于对照组(P<0.05)，$CD8^+$ 较 T0 升高，但观察组低于对照组(P<0.05)，详见表 5。

表 5 两组免疫功能指标对比($\bar{x}\pm s$)

Table 5 Comparison of immune function indexes between the two groups ($\bar{x}\pm s$)

Groups	Time	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$
Control group(n=200)	T0	40.13± 4.81	24.58± 4.72	1.63± 0.26
	T8	31.94± 4.45	28.45± 3.48	1.12± 0.23
	Difference	-8.19± 7.38	3.87± 4.17	-0.51± 0.53
	Pair test t,P	7.019,0.000	5.870,0.000	6.086,0.000
Observation group(n=200)	T0	40.06± 5.14	24.34± 3.27	1.65± 0.24
	T8	36.28± 5.59	26.13± 2.84	1.39± 0.18
	Difference	-3.78± 12.05	1.79± 5.49	-0.26± 0.21
	Pair test t,P	1.984,0.054	2.062,0.046	7.830,0.000
Comparison between groups (Unit test t,P)	T0	0.063,0.950	0.264,0.792	0.357,0.722
	T8	3.842,0.000	3.267,0.002	5.847,0.000

2.5 两组不良反应发生情况

观察组不良反应总发生率为 5.00%(10/200)，包括 7 例恶心、3 例嗜睡；对照组不良反应总发生率为 20.00%(40/200)，包括 3 例呕吐、9 例呼吸抑制、13 例嗜睡、15 例恶心；观察组不良反应总发生率低于对照组(x^2=4.114，P=0.043)。

3 讨论

手术和麻醉可导致患者发生许多的生理变化，包括炎症、代谢及免疫功能异常等，进而导致机体脏器功能也发生一系列变化，这一系列变化统称为应激反应，人体的应激反应系统被激活后，可产生大量的炎性介质，抑制机体免疫功能[14,15]。以往的多项研究证实[16,17]，肺癌发生发展与机体免疫功能变化具有一定相关性，肺癌患者通常处于免疫功能低下或抑制状态。传统的开胸肺癌根治术可直接或间接的造成肋间神经的损伤，疼痛刺激大，可激活多种神经内分泌通路，引起大量的儿茶酚胺、下丘脑 - 垂体 - 肾上腺轴激素的分泌释放，而上述物质能影响

微循环,产生血流波动,加重肺癌患者自身免疫功能抑制,增加微肿瘤病灶转移风险,不利于患者预后[18,19]。因此,如何抑制麻醉和手术等因素带来的机体应激反应,对于改善患者预后具有重要的临床意义。胸椎旁神经的前支沿途支配胸壁各肌层,其皮支则分布于相应区域的皮肤,TPVB 正是依此解剖学基础产生的一种区域阻滞方法[20,21]。罗哌卡因是 TPVB 中常用的局麻药物,具有一定镇痛效果,但由于 TPVB 所需的局麻药容量较大,麻醉效果仍有待提升[22]。

盐酸右美托咪定具有镇痛、镇静、抗焦虑等作用[23]。同时,盐酸右美托咪定还可发挥抗炎、减少器官缺血再灌注损伤、神经保护、抑制应激反应、改善术后认知功能等作用,故其被广泛应用于胸外科患者围手术期的麻醉管理中[24]。本次研究结果显示,相对于单用盐酸罗哌卡因相比,盐酸右美托咪定联合盐酸罗哌卡因 TPVB 用于肺癌根治术中,可维持机体血流稳定,获得更好的镇痛效果。盐酸罗哌卡因主要是通过阻断钠离子穿过神经纤维细胞膜进而阻滞神经冲动的传导[25]。盐酸右美托咪定可以通过刺激脑干蓝斑核α2 受体充分发挥其镇痛作用,使患者镇定感提升,血流波动减轻,利于手术的顺利进行[26]。盐酸右美托咪定联合盐酸罗哌卡因能达到药理性 " 交感切除 " 效应,如延长盐酸罗哌卡因镇痛时间、增加盐酸罗哌卡因镇痛效能等。IL-6、CRP、TNF-α 是机体在急性创伤或感染时全身炎症反应的启动和触发因子,$CD4^+/CD8^+$ 的水平降低则预示着免疫功能的下降[27,28]。本研究中,盐酸右美托咪定联合盐酸罗哌卡因 TPVB 在降低术后炎性损伤、减轻免疫抑制方面效果更为显著。以往的研究结果证实[29],右美托咪定可有效抑制促炎因子的释放,降低血清炎性因子的水平。而盐酸右美托咪定对免疫功能的作用可能跟以下几点有关:(1) 其可与 T 淋巴细胞上的 α2 受体结合直接作用于免疫细胞;(2)可降低内源性儿茶酚胺水平,改善患者血管麻痹、提高体内缩血管受体敏感性等;(3) 机体炎性损伤减轻,各组织损伤也相对减轻,免疫抑制程度较轻[30]。对比两组安全性可知,观察组不良反应总发生率低于对照组。可能与盐酸右美托咪定可减少阿片类药物用量有关。

综上所述,盐酸右美托咪定联合盐酸罗哌卡因 TPVB 用于肺癌根治术患者,可稳定机体血流动力学,镇痛效果较好,降低不良反应发生率,减轻免疫抑制及术后炎性损伤。

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