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Original Article

Effect of preemptive analgesia with parecoxib sodium in patients undergoing radical resection of lung cancer

Jing Lu[1,2*], Zhongkai Liu[2*], Kunpeng Xia[2], Changzhong Shao[2], Shengdong Guo[2], Shenggang Wang[2], Kezhong Li[3]

[1]The Second Hospital of Shandong University, Jinan 250033, Shandong Province, P. R China; [2]Department of Anesthesiology, Linyi People's Hospital, Linyi 276003, Shandong Province, P. R China; [3]Department of Anesthesiology, The Second Hospital of Shandong University, Jinan 250033, Shandong Province, China. [*]Equal contributors.

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Abstract: Objective: To discuss the effect of preemptive analgesia with parecoxib sodium in patients undergoing radical resection of lung cancer. Methods: 115 cases of lung cancer patients with American society of anesthesiologists class (ASA) grade I~II who received selective operation were randomly divided into the research group and the control group. The research group patients were given preoperative parecoxib sodium 40 mg plus postoperative normal saline 2 ml, while the control group patients were treated with preoperative normal saline 2 ml plus postoperative parecoxib sodium 40 mg. The pain condition at postoperative 1, 2, 4, 8, 12, 24 and 48 h were evaluated by visual analogue scale (VAS), and emergence agitation was tested by agitation score. Results: Finally there were 56 cases and 57 cases can be used for evaluation in the research group and control group. The VAS scores after 1, 2, 4, 8, 12, 24 and 48 h in the research group and control group were [2.23±0.45, 2.35±0.48, 2.51±0.51, 2.41±0.45, 2.28±0.42, 2.16±0.39, 2.11±0.40] and [3.80±0.62, 4.01±0.64, 4.31±0.67, 4.10±0.64, 3.65±0.70, 3.12±0.66, 2.46±0.53], respectively. The research group were obviously lower than the control group, the difference were statistically significant ($P<0.05$). The rate of agitation was 24.44% (11/56) in the research group, significantly lower than the control group of 59.65% (34/57) ($P<0.05$). Conclusion: Preemptive analgesia with parecoxib sodium can obviously relieve acute pain using in patients undergoing radical resection of lung cancer, and is helpful to reduce the incidence of emergence agitation.

Keywords: Parecoxib sodium, preemptive analgesia, radical resection of lung cancer, visual analogue scale

Introduction

Preemptive analgesia, or pre-emptive analgesia, is mainly referred to therapies that could mitigate noxious stimulation penetrating into nerve center, thereby reducing or preventing peripheral and central sensitization [1]. Parecoxib is a non-steroidal anti-inflammatory drug, whose prodrug valdecoxib is a selective inhibitor of cyclo-oxygenase 2 (COX-2) that alleviates inflammation and pain by reducing the production of prostaglandin [2]. This article aims to evaluate the analgesic efficacy of parecoxib on postoperative pain of patients recovered from lung cancer.

Material and methods

General information

One hundred and fifteen patients with lung cancer underwent radical resection at XX hospital during the period of January 2011 to June 2013 was enrolled in this study. Those patients were all classified as ASA I-II, affected with non-small cell lung cancer at staging IIIb-IV, and without history of chronic pain or chronicle analgesic drug use. Written informed consents and hospital Ethics Committee approval were obtained. This study was designed a randomized control trial, in which 115 individuals were allocated randomly to research group (58 subjects) and control group (57 subjects).

Anaesthesia

Intravenous access was obtained for all patients after entering in operation room. Regular detection was performed, including blood pressure, heart rate, pulse, electrocardiogram (EGG) and oxyhemoglobin saturation, etc. Total intravenous anesthesia was applied:

Table 1. Comparison of general data between the two groups

General data	Research group (n=56)	Control group (n=57)	*P* Value
Age (Year)	66.43±8.14	65.96±8.56	>0.05
Sex (Male/Female)	38/18	40/17	>0.05
ASA Grade (I/II)	32/24	30/27	>0.05
Tumor classification (IIIb/IV)	40/16	38/19	>0.05
Body weight (kg)	62.61±6.92	63.01±7.14	>0.05
Operation time (min)	165.41±32.84	159.04±34.85	>0.05

anesthesia induction drugs consisted of 2 $mg{\cdot}kg^{-1}$ propofol, 4 μg/kg fentanyl and 0.1 mg/kg vecuronium bromide. Maintenance drug comprised 4 $mg{\cdot}(kg{\cdot}h)^{-1}$ propofol, 0.2 μg $(kg\ min)^{-1}$ remifentanil, and intermittent injection of vecuronium bromide. Patients in the research group were treated with 2 ml parecoxib (40 mg parecoxib dissolved in 2 ml saline) I.V. 30 min before operation, and 2 ml saline I.V. after operation; Patients in the control group were treated with 2 ml I.V. 30 min before operation and 2 ml parecoxib immediately after operation.

Measurement

Pain assessment: Pain was assessed at a gradient of time span after operation: 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h, using 10-point visual analogue scoring (VAS), in which 0 represents no pain and 10 denotes worst pain.

Restlessness in recovery period: Four-scale scoring: 1 for quietness and cooperation, 2 for restlessness under stimuli such as sputum suction, 3 for restless under no stimuli but controllable without intervention of medical stuff, and 4 for strong restlessness uncontrollable without forced fixation. Rating of 3 to 4 points was defined as restlessness.

Statistical analysis: Analyses were all intent-to-treat (ITT). Data were processed with SPSS v12.0, in which continuous data presented as $\bar{x}\pm s$ were subject to Student's t test and enumeration data presented as percentage (%) were performed with hi-square test. Statistical significance when $P<0.05$.

Results

Comparison of general data

Two patients in the research group were excluded due to hospital transfer, and all patients in the control group completed the experiment. There were 56 and 57 patients in the research group and the control group, respectively. Statistics showed no significant difference between the general information of the research group and the control group (P>0.05, **Table 1**).

Comparison of VAS scores

There were significant differences between the two groups in VAS scores rated at 1, 2, 4, 8, 12, 24 and 48 hours after operation (P>0.05). The VAS in both groups increased at 2 and 4 hours after operation, and decrease at 8 hours after operation (**Table 2**). To rule out confounding fators that might affect postoperation pain, we conduct multivariate logistic regression of VAS scores with variables including age, sex, ASA classes, tumor classification, body weight and operation time (**Table 4**). Age, sex and body weight did not show as high odd ratios and without statistical significance. Next, we removed these three variables, consequently the odd ratios of the other variables were not obviously changed (**Table 5**), which indicates age, sex and body weight or any combination of them have little, if any, effect on ASS classes, tumor classification or operation time. For the rest three variables, we separately removed operation time and ASA classes to detect the interactions between any two of them. As shown in **Tables 6** and **7**, the odd ratios of the rest two variables almost stayed at the same level. Since no interaction was detected in our sample by multivariate logistic regression, the comparibility of research group and control group is justified.

Comparison of restlessness scores

Occurrence of restlessness were 24.44% and 59.65% in the research group and the control group, respectively, with statically significant difference (P<0.05, **Table 3**).

Discussion

In recent years, multiple studies [3-5] showed that tissue injury could lead to sensitization of central and peripheral nerves followed with lower pain threshold. It results in both spontaneous pain that arises without any apparent peripheral stimulus and hypersensitivity to

Table 2. Comparison of VAS scores between the two groups ($\bar{x} \pm s$)

Group	number	VAS scores taken after a gradient period of time						
		1 h	2 h	4 h	8 h	12 h	24 h	48 h
Research group	56	2.23±0.45	2.35±0.48	2.51±0.51	2.41±0.45	2.28±0.42	2.16±0.39	2.11±0.40
Control group	57	3.80±0.62	4.01±0.64	4.31±0.67	4.10±0.64	3.65±0.70	3.12±0.66	2.46±0.53
p-value	NA	P<0.05	P<0.05	P<0.05	P<0.05	P<0.05	P<0.05	P<0.05

Table 3. Comparison of restlessness scores between the two groups

Group	Restlessness Scores				Restlessness occurrence rate
	n	1~2	3	4	
Research group	56	45	11	0	11 (24.44)
Control group	57	23	26	8	34 (59.65)
p-value	NA	P<0.05	P<0.05	P<0.05	P<0.05

Table 4. Multivariate logistic regression of VAS scores with clinical features

Outcome variable: VAS scores		
Independent Variable	β (95% CI)	*p*-value
Age	0.12 (-0.46, 0.70)	0.672
Sex	0.15 (-0.39, 0.70)	0.115
ASA Class	2.32 (-0.57, 5.21)	0.023
Tumor Classification	3.25 (0.54, 5.96)	0.044
Body Weight	0.28 (0.01, 0.55)	0.532
Operation Time	4.83 (2.62, 7.04)	<0.001

peripheral stimuli, which exacerbates the intensity of pain and prolongs the duration. A typical cause of tissue injury is operation. Precautionary intervention before or at early stage of penetration of stimuli could prevent neuropathic reactions due to noxious stimuli and would possibly blockade conversion into a chronic pain through maintaining adequate analgesic duration. Therefore, timing of preemptive analgesia treatment is of vital importance. For non-steroidal drugs, several indicators should be taken into consideration: i) Pharmacokinetics and pharmacodynamics of drugs should be carefully considered; ii) Drug concentration needs to reach its maximum level before skin incision. Pharmacokinetics of parecoxib suggested that the time to peak concentration of valdecoxib, the metabolic product of parecoxib, is 30 min after intravenous injection of parecoxib. Therefore, in this study, I.V. of parecoxib was given 30 min before operation; iii) Adequate dosage should be guaranteed to inhibit the sensitization of central and peripheral nerves. Clinical studies suggest a proper effect could be produced with 40 mg parecoxib; iv) The changes in analgesic efficacy of drugs during metabolism should be observed during the evaluation. Valdecoxib is an active metabolite whose half-life is 8 h, while our observation lasted for 48 h, totally covering the whole process; v) research group and control group should be treated with same dosage of drugs at different timing, for paralleled comparison. In this study, research group and control group were both treated with 2 ml parecoxib and 2 ml saline, but in different time order (30 min prior to operation and after operation).

A couple of studies [6-8] reported a significant increase of mRNA and associated proteins of COX-2 in spinal marrow when peripheral inflammation or nerve injury occurred. This subsequently increases products of prostaglandins (PGs), which substantially enhance the excitation of spinal nerves, leading to central sensitization. The role of COX-2 in neuropathic pain development highlights the importance of application of selective inhibitors of COX-2 at early stage of pain development. Parecoxib could be converted to valdecoxib in vivo, which is a selective inhibitor of COX-2, reducing the production of PGs. Our result showed an extremely significant difference between the VAS of research group and control group observed 1 h after operation, suggesting that preemptive analgesia of parecoxib can be used for immediate pain relief. In contrast, a satisfactory analgesic efficacy was not observed for treatment after operation, indicating a mitigated role of COX-2 in neuropathic pain at this stage. This was because central neuronal system had been sensitized by PGs, and became refractory to the reduction of PGs resulting from inhibition of COX-2 by parecoxib. Overall, we observed that the VAS of research group first increased and then decreased. This was because that treatment of parecoxib 30 min

Table 5. Multivariate logistic regression of VAS scores with tumor classification, ASA class and operation time

Outcome variable: VAS scores		
Independent Variable	β (95% CI)	*p*-value
ASA Class	2.41 (-0.46, 5.28)	0.018
Tumor Classification	3.32 (0.63, 6.01)	0.025
Operation Time	4.88 (2.70, 7.06)	<0.001

Table 6. Multivariate logistic regression of VAS scores with tumor classification and ASA Class

Outcome variable: VAS scores		
Independent Variable	β (95% CI)	*p*-value
ASA Class	2.35 (-0.51, 5.22)	0.011
Tumor Classification	3.21 (0.54, 5.88)	0.023

Table 7. Multivariate logistic regression of VAS scores with tumor classification operation time

Outcome variable: VAS scores		
Independent Variable	β (95% CI)	*p*-value
Tumor Classification	3.18 (0.54, 5.82)	0.019
Operation Time	4.92 (2.79, 7.05)	<0.001

before incision culminated in maximum drug concentration when incision was carried, whilst the surgical injury was the most acute, and after that concentration dropped, whereas physical injury also lessened, and thus pain was further alleviated. Treated with parecoxib after operation, which is 3 h after cases were treated, control group present a significant lower analgesic efficacy. Analgesic efficacies of parecoxib treatment within 8 h after operation were not satisfactory, which during the observation period, display same trends as control. In addition, the degree of restlessness in the research group was lower than that in the control group, which may indicate better pain relief in research group, considering restlessness is positively correlated with pain.

In summary, we concluded that treatment of 40 mg parecoxib 30 min before incision could substantially alleviate acute pain at early stage of post-surgery, and reduce the occurrence of restlessness in anesthesia recovery period.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kezhong Li, Department of Anesthesiology, The Second Hospital of Shandong University, 247 Beiyuan Road, Jinan 250033. E-mail: kezhongznli@163.com

References

[1] Yang L, Zhang J and Zhang Z. Preemptive analgesia effects of Ketamine in patients undergoing surgery. A meta-analysis. Acta Cir Bras 2014; 29: 819-825.

[2] Xu LL, Shen JJ and Zhou HY. Effects of parecoxib sodium preemptive analgesia on perioperative cytokine responses and stress responses in patients undergoing ophthalmology surgery. Zhonghua Yi Xue Za Zhi 2010; 90: 1893-1896.

[3] Li XY, Ko HG and Chen T. Alleviating neuropathic pain hypersensitivity by inhibiting PKMzeta in the anterior cingulate cortex. Science 2010; 330: 1400-1404.

[4] Tender GC, Li YY and Cui JG. Brain-derived neurotrophic factor redistribution in the dorsal root ganglia correlates with neuropathic pain inhibition after resiniferatoxin treatment. Spine J 2010; 10: 715-720.

[5] Zhang W, Gardell S and Zhang D. Neuropathic pain is maintained by brainstem neurons coexpressing opioid and cholecystokinin receptors. Brain 2009; 132: 778-787.

[6] Zhang F, Lv Y and Dong J. Expression of two cyclooxygenases in spinal cords of formalin rats. China Medicine 2011; 6: 431-433.

[7] Seybold VS, Jia YP and Abrahams LG. Cyclooxygenase-2 contributes to central sensitization in rats with peripheral inflammation. Pain 2003; 105: 47-55.

[8] Lui PW and Lee CH. Preemptive effects of intrathecal cyclooxygenase inhibitor or nitric oxide synthase inhibitor on thermal hypersensitivity following peripheral nerve injury. Life Sci 2004; 75: 2527-2538.