Research Article

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Postoperative analgesia effects of sulfentanyl plus dexmedetomidine in patients received VATS

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Abstract: Background To evaluate sulfentanyl combined with dexmedetomidine hydrochloride on postoperative analgesia in patients who received video-assisted thoracic surgery (VATS) and its effects on serum norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (5-HT), and prostaglandin (PGE2).

Material and Methods Ninety-nine non-small cell lung cancer (NSCLC) patients who received VATS were included in the study. All the patients received intravenous inhalation compound anesthesia. Of the 99 cases, 49 subjects (control group) received sulfentanyl for patient controlled intravenous analgesia (PICA) and other 50 cases (experiment group) received sulfentanyl combined with dexmedetomidine hydrochloride for PICA after operation of VATS. The analgesic effects of the two groups were evaluated according to Visual Analogue Scales (VAS) and the Bruggmann Comfort Scale (BCS). The serum pain mediator of NE, DA, 5-HT, and PGE2 were examined and compared between the two groups in the first 24 h post-surgery.

Results The VAS scores for the experiment group were significant lower than that of control group on the time points of 8, 16, and 24 h post-surgery ($p_{\text{all}} < 0.05$), and the BCS scores of the experiment group in the time points of 8, 16, and 24 h were significantly higher than that of controls ($p < 0.05$). However, the VAS and BCS scores were not statistical differently in the time point of 1, 2, and 4 h post-surgery ($p_{\text{all}} > 0.05$). The mean sulfentanyl dosage was $63.01 \pm 5.14 \mu\text{g}$ and $67.12 \pm 6.91 \mu\text{g}$ for the experiment and control groups respectively with significant statistical difference ($p < 0.05$). The mean analgesic pump pressing times were 4.30 ± 1.31 and 5.31 ± 1.46 for experiment and

control groups respectively with significant statistical difference ($p < 0.05$). The serum NE, DA, 5-HT, and PGE2 levels were significantly lower in the experimental group compared to that of control group in the time point of 12 h post-surgery ($p_{\text{all}} < 0.05$). The side effects of nausea, vomiting, delirium, rash, and hypotension atrial fibrillation were not statistically different between the two groups ($p_{\text{all}} > 0.05$).

Conclusion Patient controlled intravenous analgesia of sulfentanyl combined with dexmedetomidine hydrochloride was effective in reducing the VAS score and serum pain mediators in NSCLC patients who received VATS.

Keywords: patient controlled intravenous analgesia; VATS; NSCLC; norepinephrine, dopamine, 5-HT; prostaglandin.

Introduction

Lung cancer is one of the most diagnosed malignant tumors and the leading cause of cancer related death globally [1, 2]. VATS is generally used in the early stages of non-small cell lung cancer (NSCLC) [3, 4]. Compared with traditional thoracotomy, VATS is minimally invasive and causes less postoperative pain [5]. However, moderate to severe chest pain is common in VATS patients. The post-surgery chest pain increases the risk of postoperative complications such as lung infection, arrhythmia, and atelectasis [6, 7]. Therefore, effective postoperative analgesia are important for the patients' recovery.

Patient controlled intravenous analgesia (PCIA) refers to an electronically controlled infusion pump that delivers an amount of intravenous analgesic when the patient presses a button [8]. PCIA is generally used for acute and chronic pain patients. It is also commonly used for postoperative pain management and for end-stage cancer patients [9, 10]. The number of button presses and dosage of analgesic drugs can be self-regulated by patients themselves. Therefore, analgesics can be "supplied on demand". The best effect analgesic can be achieved at the

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lowest dose, and the side effects are minimal. PCIA can also avoid a situation of large fluctuation of in analgesic blood concentration and side effects.

Norepinephrine (NE), dopamine (DA), 5-hydroxytryptamine (5-HT), and prostaglandin (PGE2) are known pain mediators which play an important role in the development of post-operation pain. Sulfentanyl combined with dexmedetomidine for postoperative anesthesia is widely used in patients with cesarean section and upper abdominal surgery. However, sulfentanyl is seldom reported in patients receiving VATS and its effects on serum NE, DA, 5-HT and PGE2 levels are unknown?.

In our present work, a prospective clinical study was performed to evaluate sulfentanyl combined with dexmedetomidine hydrochloride on postoperative analgesia in patients receiving VATS and sulfentanyl effects on serum NE, DA, 5-HT and PGE2 levels.

Material and methods

Patients

Ninety-nine NSCLC patients who received VATS from January 2015 to October 2018 at the Lishui People's Hospital, Zhejiang Province were included in the study. The general characteristics of the included patients are shown in **Table 1**.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Medical Ethics Committee of Lishui People's Hospital, Zhejiang Province.

Informed consent: Informed consent has been obtained from all individuals included in this study

Patient controlled intravenous analgesia

All patients received patient controlled intravenous analgesia after operation. For patients in the control group, 100 µg of sulfentanyl was diluted to 100 mL with a sustained dose of 0.02 µg/kg per hour, a single dose of 0.02 µg/kg by pressing, and the locking time was 10 minutes. For patients in the experiment group, 100 µg sulfentanyl + 200 µg dexmedetomidine (Sichuan Guorui Pharmaceutical Co., Ltd) was diluted to 100 mL, set to a sustained dose of 0.02 µg/kg·per hour sulfentanyl and

Table 1: The main features of the two groups.

Characteristics	Experiment (n=50)	Control (n=49)
Age (y)	56.32 ± 14.21	54.12 ± 15.32
Gender		
Male	32 (64.0%)	30 (61.2)
Female	18 (36.0%)	19 (38.8%)
Weight (kg)	67.21 ± 13.69	66.65 ± 12.71
Surgery		
Lobectomy of the right lung	25 (50.0%)	24 (49.0%)
Lobectomy of the left lung	22 (44.0%)	23 (46.9%)
Wedge resection	3 (6.0%)	2 (4.1%)
Operation time (min)	132.54 ± 36.47	140.12 ± 33.74
ASA physical status (I/II)	26/24	24/25
Clinical sage		
I	10 (20.0%)	11 (22.5%)
II	32 (64.0%)	33 (67.3%)
IIIa	8 (16.0%)	5 (10.2%)
Liver function		
AST(U/L)	22.3 ± 12.4	24.6 ± 11.3
ALT(U/L)	19.2 ± 11.3	22.3 ± 12.1
ALP(U/L)	82.1 ± 45.1	78.6 ± 42.8
Renal function		
Urea (mmol/L)	4.8 ± 2.2	4.6 ± 2.0
Creatinine (µmol/L)	79.2 ± 26.4	77.4 ± 27.3

ASA: American Society of Anesthesiologists

AST: aspartate aminotransferase

ALT: alanine aminotransferase

ALP: alkaline phosphatase

0.05 µg/kg per hour dexmedetomidine, a single press dose of 0.02 µg/kg sulfentanyl + 0.05 µg/kg dexmedetomidine, and the locking time was 10 min. The times of additional pressing analgesic pumps and the dosage of analgesic drugs were observed for 24 h after operation.

Analgesic effects evaluation

The Visual Analogue Scales (VAS) and Bruggmann Comfort Scale (BCS) scores [11] were used to evaluated the pain degree of the two groups.

Figure 1: Visual Analogue Scales (VAS) and Bruggmann Comfort Scale (BCS) score comparison between two groups of different time points (A: VAS score; B: BCS score). * $p < 0.05$.

Serum NE, DA, 5-HT, and PGE2 measurement

5 mL peripheral venous blood was collected in the morning on the day of surgery and 12 h post-operation. The blood was centrifuged for 15 min at 3500 r/min to obtain the serum. The serum was separated and stored in a refrigerator at -80°C for later use. Serum NE, DA, 5-HT, and PGE2 levels were examined by ELISA purchased from Shanghai Enzyme Linked Biotechnology Co., Ltd. All the experiments were carried out according to the kit instructions.

Statistical analysis

Data were analyzed by SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed by mean $\pm$ standard deviation and analyzed by Student's t-test between the experiment and control groups. Enumeration data was expressed by number (%) and tested by chi-square or Fisher's exact test. A two tails p level of < 0.05 was accepted for statistical significance.

Results

Analgesic effects

The VAS scores were significant lower for the experiment group than the control group for the time points of 8, 16 and 24 h post-surgery ($p_{\text{all}} < 0.05$); The BCS scores of the experiment group for the time points of 8, 16 and 24 h were significant higher than that of controls with statistical

Table 2: VAS and BCS score of the two groups ($\bar{x} \pm s$).

Time point	VAS		BCS	
	Experiment	Control	Experiment	Control
1 h	2.56 ± 1.11	2.32 ± 1.20	2.60 ± 0.85	2.51 ± 0.74
2 h	2.96 ± 1.21	2.88 ± 0.98	2.44 ± 0.73	2.32 ± 0.56
4 h	3.68 ± 1.33	4.02 ± 1.32	2.28 ± 0.68	2.21 ± 0.42
8 h	3.21 ± 1.05	$3.96 \pm 0.99^*$	2.93 ± 0.56	$2.46 \pm 0.53^*$
16 h	2.87 ± 1.10	$3.45 \pm 1.01^*$	3.01 ± 0.66	$2.63 \pm 0.61^*$
24 h	2.05 ± 1.14	$2.98 \pm 0.89^*$	3.18 ± 0.70	$2.72 \pm 0.54^*$

VAS: Visual Analogue Scales

BCS: Bruggmann Comfort Scale

* $p < 0.05$

difference ($p_{\text{all}} < 0.05$), **Figure 1**. However, the VAS and BCS scores were not statistically different in the time points of 1, 2 and 4 h post-surgery ($p_{\text{all}} > 0.05$), **Table 2**.

Sulfentanyl dosage

The mean sulfentanyl dosages were $63.01 \pm 5.14 \mu\text{g}$ and $67.12 \pm 6.91 \mu\text{g}$ for the experiment and control groups respectively with significant statistical difference ($p < 0.05$). The mean analgesic pump pressing times were 4.30 ± 1.31 and 5.31 ± 1.46 of experiment and control group respectively with significant statistical difference ($p < 0.05$). The mean sulfentanyl dosages and analgesic pump pressing times in experiment group were significant lower than those of control group, **Figure 2**.

Figure 2: Scatter plot of sufentanil dosage and analgesic pump pressing times distribution (A: sufentanil dosage; B: analgesic pump pressing times).

Table 3: Serum NE, DA, 5-HT, and PGE2 comparison of the two groups ($\bar{x} \pm s$).

Pain mediator	Before surgery		12 h post-surgery	
	Experiment	Control	Experiment	Control
NE (ng/mL)	221.23 ± 35.20	236.87 ± 36.71	396.51 ± 75.21*	465.27 ± 88.65
DA (ng/mL)	9.64 ± 2.12	10.21 ± 2.08	12.45 ± 2.54*	16.21 ± 3.02
5-HT (µmol/L)	0.16 ± 0.04	0.15 ± 0.05	0.49 ± 0.12*	0.68 ± 0.21
PGE2 (µg/L)	13.54 ± 3.32	14.02 ± 3.74	19.36 ± 4.11*	24.36 ± 5.03

NE: norepinephrine
DA: dopamine
5-HT: 5-hydroxytryptamine
PGE2: prostaglandin
* $p<0.05$

Serum NE, DA, 5-HT, and PGE2

The serum NE, DA, 5-HT, and PGE2 levels were not statistically different before surgery between the experimental and control groups ($p_{all}>0.05$). However, the serum NE, DA, 5-HT, and PGE2 levels were significantly lower in the experiment group compared to that of the control group at the time point of 12 post-surgery ($p_{all}<0.05$), **Table 3**.

Side effects

The incidence of nausea, vomiting, delirium, rash, and hypotension atrial fibrillation were 4.0% (1/50), 2.0% (1/50), 2.0%(1/50), 0.0%(0/50), 0.0%(0/50), and 2.0%(1/50) in experiment group and 2.0% (1/49), 4.1%

(2/49), 0.0%(0/49), 2.0%(1/49), 0.0%(0/49), and 2.0%(1/49) respectively without statistical difference ($p_{all}>0.05$).

Discussion

Postoperative chest pain is common in patients who received VATS. Severe chest pain can inhibit coughing and breathing, therefore increase the risk of developing pulmonary infection and hypoxemia. Several studies have reported that the severe postoperative pain always increases the risk of postoperative complications such as lung infection, arrhythmia, and atelectasis [5, 7]. PICA is one of the most clinically used postoperative analgesia methods with the advantages of [12, 13] easy management, almost no contraindication, and the ability to still

Table 4: The risk of side effects in the two groups of patients [N, (%)].

Side effects	Experiment (n=50)	Control (n=49)
Nausea	2 (4.0%)	1 (2.0%)
Vomiting	1 (2.0%)	2 (4.1%)
Delirium	1 (2.0%)	0 (0.0%)
Rash	0 (0.0%)	1 (2.0%)
Hypotension	0 (0.0%)	0 (0.0%)
Atrial fibrillation	1 (2.0%)	1 (2.0%)

be used with epidural or local nerve block technique fails. Publications have confirmed that postoperative PCIA is effective in elevating chest pain and decreasing perioperative complications [14].

Dexmedetomidine is a highly selective α_2 -adrenergic agonist. Unlike opioids and other sedatives such as propofol, dexmedetomidine is able to be effective without causing respiratory depression [15]. Dexmedetomidine hydrochloride is widely used for postoperative sedation [16, 17]. Dexmedetomidine induces sedation by decreasing activity of noradrenergic neurons in the locus ceruleus in the brain stem, thereby increasing the activity of inhibitory gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus [18]. Recently published studies have shown that intravenous opioid analgesia combined with dexmedetomidine can reduce the dosage of opioids thereby decreasing drug related side effects [19, 20].

Sulfentanyl is an opioid used alone as a pain medication and together with other medications for anesthesia. Sulfentanyl combined with dexmedetomidine for postoperative anesthesia is widely used in patients with cesarean section and upper abdominal surgery [21–23]. However, it is seldom reported in patients who received VATS and its effects on serum NE, DA, 5-HT, and PGE2 levels are unknown. In this study, we included 99 patients who received PCIA and found sulfentanyl combined with dexmedetomidine hydrochloride can significantly decrease the chest pain compared only sulfentanyl, and that the total dosage of sulfentanyl was also decreased. The results indicated that a two drugs regimen is more effective in pain control without increasing drug related side effects. However, the pain score was not different in the first 4 h after surgery between the two groups.

NE is one of the most important bioactive substances that plays a role in hypothalamic paraventricular nucleus (PVN) regulating pain process [24]. DA plays a central role for dopaminergic neurotransmission in modulating

pain perception and natural analgesia within supraspinal regions including the basal ganglia, insula, anterior cingulate cortex, thalamus, and periaqueductal gray [25]. NE, DA, 5-HT, and PGE2 are all pain mediators which can directly or indirectly induce pain-causing effects. These effects may be induced by reducing the serum levels of NE, DA, 5-HT, and PGE2. In our work, we found that the serum levels of NE, DA, 5-HT, and PGE2 in the experiment group were significantly lower compared to the control group at 12 h post-surgery. This indicated that the pain score may closely correlated to the serum levels of the pain mediators NE, DA, 5-HT, and PGE2.

In Conclusion

Patient controlled intravenous analgesia of sulfentanyl combined with dexmedetomidine hydrochloride was effective in reducing the VAS score and serum pain mediators in NSCLC patients who received VAST. Additionally, the total sulfentanyl dosage also decreased in the experiment group without increasing the drug related side effects. However, this conclusion needs to be further proven by high quality multicenter prospective randomized controlled clinical studies relevant to sulfentanyl combined with dexmedetomidine hydrochloride on postoperative analgesia in patients who received video-assisted thoracic surgery.

Conflict of interest: Authors state no conflict of interest

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