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Postoperative Analgesia in Video-Assisted Thoracoscopic Surgery: A Retrospective Analysis

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All the authors have no conflict of interest.

Abstract: Background. Lobectomy by video-assisted thoracic surgery (VATS) has become a well-established and widespread therapeutic method for treating early lung cancer. However, VATS, especially VATS lobectomy, is still associated with moderate acute postoperative pain. The optimal strategy for postoperative analgesia after VATS lobectomy remains undetermined. Anesthesiologists and surgeons thus require an evidence-based VATS pain management approach. **Methods.** We retrospectively analyzed 352 patients who underwent VATS (either lobectomy or wedge resection). The patients were divided into four groups for comparative analysis of analgesic effects and safety: Group A, patient-controlled analgesia (PCA); Group B, PCA + flurbiprofen axetil (FA); Group C, PCA + FA + tramadol hydrochloride; and Group D, PCA + FA + a buprenorphine transdermal system (BTDS). **Results.** All 352 patients were included in the primary analysis. The analgesic effect in Group D was significantly better than that in the other three groups on postoperative days 2 and 3 (P = 0.035 and P = 0.001, respectively). Patients in Group D had better outcomes with respect to the postoperative day of chest tube removal (P = 0.000), volume of chest tube drainage (P = 0.024), and postoperative day of discharge (P = 0.000). However, the medical expense of hospitalization was not significantly different among the four groups (P = 0.809). **Conclusions.** Multimodal analgesia involving PCA + FA + BTDS provides effective analgesia; fewer analgesia-related complications; and a reduced patient economic burden, healthcare workload, and opioid requirement.

Keywords: Buprenorphine Transdermal System, Multimodal Analgesia, Ain, stoperative, Video-Assisted Thoracic Surgery

INTRODUCTION

Lobectomy by video-assisted thoracic surgery (VATS) has become a well-established and widespread therapeutic method for treating early lung cancer[1, 2]. One of the advantages of VATS is less severe postoperative pain compared with thoracotomy[3, 4]. However, VATS, especially VATS lobectomy, is still associated with moderate acute postoperative pain[4, 5]. The optimal strategy for postoperative analgesia after VATS lobectomy remains undetermined[6]. Anesthesiologists and surgeons therefore require an evidence-based VATS pain management approach[7].

Thoracic epidural analgesia (TEA) and the paravertebral block (PVB) are considered the analgesic gold standards for thoracotomy[8]. The difference in surgical trauma between thoracotomy and VATS raises questions about whether TEA and PVB should be considered the gold standards for VATS[7, 9]. Furthermore, Kamiyoshihara et al.[10] reported that thoracic epidural analgesia is not always necessary after VATS and that simpler postoperative pain management is needed.Some authors have described different analgesic techniques in VATS, often comparing local analgesia with placebo or oral/intravenous regimens[7, 9], However, surgeons and anesthesiologists have yet to agree on the best analgesic techniques for VATS.We retrospectively analyzed 352 patients who underwent VATS (either lobectomy or wedge resection) from April 2017 to July 2017 in our hospital for a comparative analysis of the analgesic effects and safety of several multimodal techniques.

METHODS

We retrospectively analyzed 352 consecutive patients who underwent VATS for thoracic diseases from April to July 2017. Eligible patients were ≥18 years of age and underwent thoracoscopic surgery with general anesthesia. Each patient was informed that their clinical

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data may be used for study purposes, and consent was obtained on this basis. The patients' characteristics are shown in Table 1.

Table 1. Characteristics of 352 patients who underwent video-assisted thoracoscopic surgery

Variable	No. of Patients
Age (years) [range]	58.78±10.24[17-79]
Sex	
Male	171 (48.58%)
Female	181 (51.42%)
Body mass index(kg/㎡)	24.48

The patient was placed in the lateral position. A 4- to 7-cm incision was made in the fourth or fifth intercostal space to allow for insertion of the operating port; the specific length of the incision was determined by the size of the specimen to be removed and the operative technique used. An approximately 12-mm incision was made along the axillary midline in the seventh intercostal space to allow for thoracoscopy. The working port was protected with a polyurethane retractor. Spreading of the ribs was avoided. At the end of the operation, a thoracic drainage tube was placed in the seventh intercostal space; the texture and model of the tube varied according to the specific conditions of the patients. The other end of the drainage tube was positioned under pressure of 7 cm H_2O. The indication for tube pullout was a drainage volume of <200 ml, no active bleeding, and no gas overflow. During surgery, propofol was used for induction (0.5 mg/kg over 10 s) and maintenance (4–10 mg/kg per hour) of general anesthesia. The decision regarding patient discharge was based on the principle that the patient should be comfortable at rest and on mobilization, should have no lung inflammation, and should have a white blood cell count within the normal range.

The patients were divided into four groups according to the postoperative analgesic regimen (Table 2).

Table 2. Patient grouping

group	medication regimen	N
A	PCIA	53
B	PCIA+ FA	143
C	PCIA+ FA + TH	67
D	PCIA+ FA +BTDS	89

PCIA, patient-controlled intravenous analgesia with uniform preparation by the anesthesiologist (base amount of 2 ml/h, automatic control of 2 ml/time, locking time of 30 min); FA, flurbiprofen axetil (a nonsteroidal targeted analgesic); TH, tramadol hydrochloride SR tablets (100 mg twice daily, orally); BTDS, buprenorphine transdermal system (5-mg opioid patch; the previous day was used for the patient's scapula).

We used a visual analog scale to evaluate pain. The first pain assessment was performed 6 h after surgery. On postoperative day (POD) 1, 2, and 3, pain scores were obtained by each patient's nurse at 8:00 AM; adverse effects and other analgesic drugs used were also recorded. We analyzed the POD of chest tube removal, volume of chest tube drainage fluid, POD of discharge, medical expenses of hospitalization, supplemental analgesics, and analgesic-related complications.

Statistical Analysis

The data were analyzed using SPSS 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ariables o deviation, and categorical data are shown as number and percentage. The homogeneity of variance test was performed on the continuous variables, and one-way analysis of variance or Tamhane's was selected according to the test results. The chi-square test was used to compare groups with categorical variables. A P value of <0.05 was considered significant.

RESULTS

Patients Characteristics

The patients' characteristics and preoperative and perioperative variables in Groups A, B, C, and D are shown in Table 3. The groups showed a significant difference in sex; no significant differences were found in age, body mass index, or method of lobectomy.

Table 3. Characteristics of patients in each study group

Variable	A(n=53)	B(n=143)	C(n=67)	D(n=89)	P-value
Age(years)	59.66±10.99	58.15±9.97	59.01±10.22	59.09±10.33	0.789
Sex					
Male	34（64.15）	61（42.66）	38（56.72）	38（42.70）	
Female	19（35.85）	82（57.34）	29（43.28）	51（57.30）	0.017*
Body mass index (kg/㎡)	23.42	24.65	24.09	25.27	NS
Type of pulmonary of resection					
Single lobe	36（67.92）	92（64.34）	43（64.18）	61（68.54）	
Single lobe + wedge resection	5（9.43） 9（16.98）	9（6.29） 31（21.68）	3（4.48） 16（23.88）	4（4.49） 20（22.47）	
Wedge resection	3（5.66）	11（7.69）	5（7.46）	4（4.49）	NS
Bilobectomy	141.41±50.60	134.43±48.21	130.32±46.76	123.88±44.94	0.188
Duration of surgery (min)					

Data are presented as n (%) or mean ± standard deviation.
*Statistically significant.

Postoperative Pain Scores

The patients' postoperative pain scores are shown in Table 4. The mean pain score was ≤3.0. The maximum score in Group A was 4.0, and that in the other three groups was 5.0. Although the injectable nonsteroidal anti-inflammatory agent flurbiprofen axetil (FA) was uniformly used uniformly postoperative analgesia in Groups B, C, and D, no common adverse effects such as renal insufficiency, gastritis, or bleeding complications occurred.

Table 4 shows that although the mean pain scores decreased in all groups at both 6 h postoperatively and on POD 1, there was no significant difference among the groups at these two time points (P = 0.095 and P = 0.119, respectively). On PODs 2 and 3, the postoperative pain scores were significantly different among the four groups at these two time points (P = 0.035 and P = 0.001, respectively) (Fig. 1).

Table 4. Visual analog scale pain scores of patients with complete data

Variable	A(n=53)	B(n=143)	C(n=67)	D(n=89)	P-value
Pain scores at the first 6h postoperatively	2.62±1.07	2.25±0.92	2.27±0.67	1.97±1.07	0.095*
Pain scores on POD 1	2.51±0.78	2.51±0.80	2.30±0.85	2.30±0.79	0.119
Pain scores on POD 2	2.21±0.79	2.11±0.75	1.90±0.87	1.90±0.82	0.035
Pain scores on POD 3	1.83±0.80	1.71±0.84	1.72±0.74	1.35±0.74	0.001

POD, postoperative day

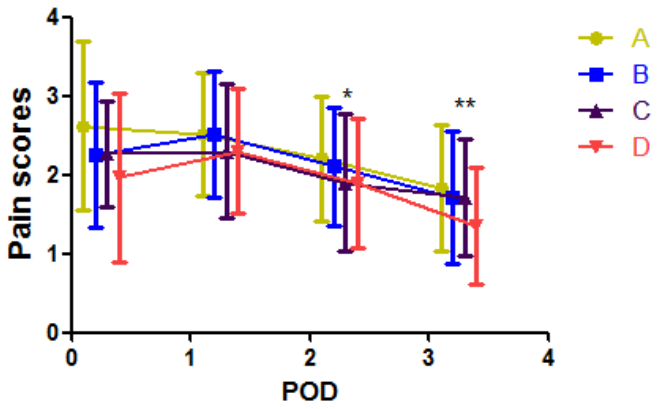

Figure 1. Postoperative pain scores.
POD, postoperative day.

*The postoperative pain scores were significantly higher in Group A than in Groups C and D (P = 0.32 and P = 0.24, respectively). The pain scores were also significantly different between Groups B and D on POD 2 (P = 0.046).
**The postoperative pain scores were significantly higher in Groups A, B, and C than in Group D on POD 3 (P = 0.001, P = 0.001, and P = 0.004).

Postoperative Characteristics and Analgesia-Related Complications

Due to the routine use of glycerin enemas to prevent constipation on POD 2 or 3, the most common analgesia-related complications in our department are nausea and vomiting, dizzy, drowsiness, and hypotension.

As shown in Table 5, the average POD of chest tube removal was significantly higher in Groups A and B than in Groups C and D (P = 0.00) (Fig. 2). The volume of chest tube drainage was significantly different between Groups A and D and between Groups B and D (P = 0.006 and P = 0.037, respectively) (Fig. 3), but no significant differences were found between the other groups (P = 0.766, P = 0.094, P = 0.069, and P = 1.000). The POD of discharge was significantly different between Groups A and D and between Groups B and D (P = 0.002 and P = 0.007, respectively) (Fig. 4). We statistically analyzed the patients' medical expenses during hospitalization and found no significant difference among the four groups (P = 0.809).

The percentage of patients who required supplemental analgesics because of inadequate pain control was significantly higher in Groups A, B, and C than in Group D (Table 6). The incidence of analgesia-related complications in Groups A, B, C, and D was 43.40%, 48.25%, 55.22%, and 49.44%, respectively. The incidence of nausea, vomiting, and dizziness was significantly higher than all other analgesia-related complications.

Table 5. Postoperative characteristics

Variable	A(n=53)	B(n=143)	C(n=67)	D(n=89)	P-value
Postoperative day of chest tube remove (day)	4.08±1.67	3.63±1.83	2.42±1.56	2.70±0.98	*0.000
Liquid volume of chest tub（ml）	699.72±325.24	861.01±1455.12	515.37±499.42	511.43±311.01	*0.024
Postoperative day of discharge (day)	6.57±2.62	5.87±2.33	5.49±2.07	5.07±1.39	*0.000
Hospitalizations medical expense(CNY)	60633.67±10582.53	60312.76±13940.50	61869.38±15586.04	61766.41±12747.46	*0.809

Data are presented as n (%) or mean m standard deviation. *The homogeneity of variance test was <0.05, and Tamhane's test was selected according to the test results. Other data were analyzed using one-way analysis of variance.

Table 6. Supplemental analgesia-related complications

Variable	A(n=53)	B(n=143)	C(n=67)	D(n=89)
Supplemental analgesics	38（71.70）	99（69.23）	36（53.73）	11（12.56）
Adverse reactions	23（43.40）	69（48.25）	37（55.22）	44（49.44）
Nausea and vomiting	8 （34.78）	23（33.33）	14（37.84）	22（50.00）
Dizzy	9 （39.13）	34（49.28）	10（27.03）	14（31.82）
Drowsiness	4 （17.39）	5 （7.25）	5 （13.51）	3 （6.82）
Hypotension	2 （8.70）	7 （10.14）	8 （21.62）	5 （11.36）

Data are presented as n (%).

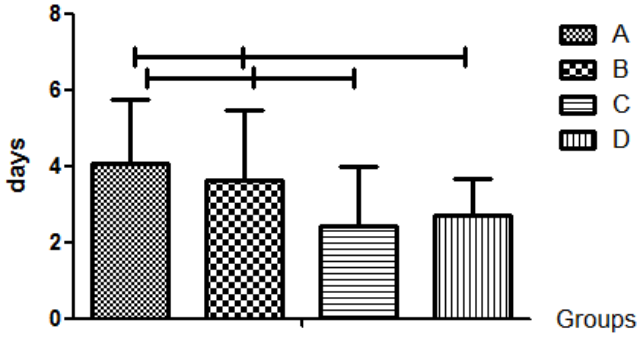

Figure 2. Postoperative day of chest tube removal. Significant differences were present between Groups A and C and between Groups B and C (P = 0.000 for both). No significant differences were present between Groups C and D (P = 0.741).

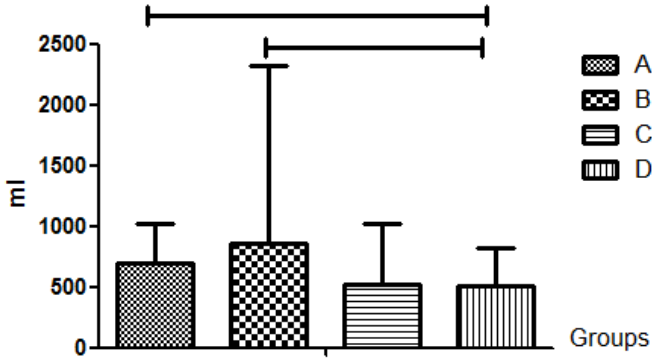

Figure 3. Volume of chest tube drainage fluid. Significant differences were present between Groups A and D and between Groups B and D (P = 0.006 and P = 0.037, respectively).

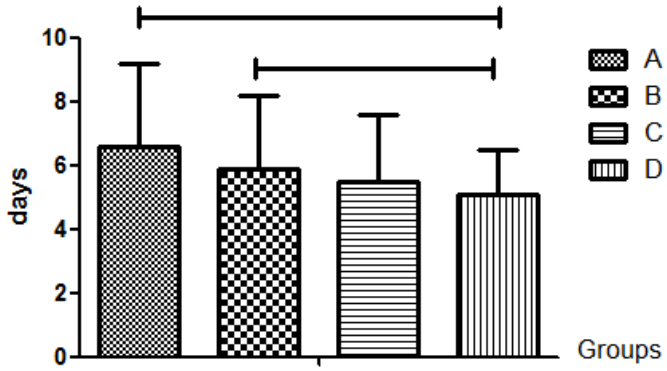

Figure 4. Postoperative day of discharge. Significant differences were present between Groups A and D and between Groups B and D (P = 0.002 and P = 0.007, respectively). No significant differences were present between the other groups.

DISCUSSION

TEA and PVB are now considered the analgesic gold standards for thoracotomy[8]. Postoperative analgesia is very important to reduce complications such as respiratory insufficiency and pneumonia[11]. However, the difference in surgical trauma between thoracotomy and VATS raises questions about whether TEA and PVB should be considered the gold standards for VATS[7, 9]. VATS is a minimally invasive procedure that causes less pain, reduces the duration of hospitalization, and offers esthetically better results than general thoracic surgery[12, 13]. Kamiyoshihara et al.[10] questioned whether epidural analgesia is necessary after VATS lobectomy. The best strategy for postoperative analgesia after VATS remains uncertain[6].

In the present study, we retrospectively analyzed 352 patients who underwent thoracoscopic surgery in our department. Although there was a significant difference in the ratio of male to female patients (P = 0.017), we did not separate the pain data for men and women in the later data analysis. Bjerregaard, et al.[14] analyzed the pain data for male and females separately and found no significant difference in postoperative acute pain between the two sexes.

Multimodal analgesia is a combination of analgesic drugs with different mechanisms of action and synergistic or additive effects that reduce the dose and adverse reactions of single medications, improve the patient's tolerance to the drugs, and accelerate the onset time and prolong the duration of analgesia. We found that multimodal analgesia is more effective than single-agent analgesia. However, which types of analgesic drugs that should be chosen after surgery to achieve synergy is not always clear. Scawn et al.[15] proposed that an ideal analgesia regimen should include three types of drugs: opioids, nonsteroidal anti-inflammatory drugs, and local anesthetics. This postoperative analgesic plan may not meet the needs of Chinese patients. A previous study confirmed that perioperative intravenous injection of FA together with patient-controlled analgesia (PCIA) reduced the postoperative pain intensity and cytokine release of interleukins 6 and 8, tumor necrosis factor α, and other pro-inflammatory cytokines. Thus, in the present study, intravenous injection of FA together with PCIA was routinely used in Groups B, C, and D. The analgesic effect of buprenorphine is mainly regulated by μegulated b. This drug can activate ic effect of buprenorphine is mailow doses to produce effective analgesia; the analgesic intensity of buprenorphine is 25 to 50 times that of an equal dose of morphine, but its analgesic intensity for nociceptive pain is 75 to 100 times that of morphine. The high affinity between buprenorphine and opioid orphine and inte to the very slow dissociation and long-lasting analgesic effect of

this drug[16]. Table 4 shows that the mean pain scores after surgery were lower in Group B than A, but the difference was not statistically significant. This result may be related to the large difference in the sample sizes between the groups. Comparison of Group C or D with Group A or B showed the advantages of multimodal analgesia: reduced postoperative pain, maintenance of effective breathing and circulation, and facilitation of coughing and expectoration to reduce the probability of pulmonary infection, obstructive atelectasis, and other postoperative complications. The facilitation of coughing and expectoration led to earlier PODs for chest tube removal and hospital discharge and a lower volume of chest tube drainage. On the contrary, it is a virtuous cycle because the postoperative day of chest tube remove was obviously decrease, postoperative pain relief, beneficial to cough and expectoration of patients to reduce the probability of pulmonary infection.

The results in the multimodal analgesia groups (Groups C and D, especially Group D) showed that postoperative long-term analgesia is not only effective but also has fewer analgesic-related complications. The only difference between Group C (PCIA + FA + tramadol hydrochloride) and Group D (PCIA + FA + a buprenorphine transdermal system) was the type of opioid used. However, although the proportion of analgesia-related complications in Group D was not significantly higher than that in Groups A and B, it was significantly higher in Group C. The opioid action of buprenorphine mainly occurs at the level of the spinal cord, not the brain, and differs from the actions of morphine and fentanyl[17]. This may be why the number of analgesia-related complications was not higher in Group D.

Emerging data show that many cancers have high expression levels of μ opioid receptors[18, 19] that when activated by opiate narcotics could potentially mediate tumor growth and spread[20, 21]. As more is learned about the interaction between these receptors and perioperative narcotics, oncologic surgeons will seek alternative methods to reduce perioperative opioid delivery. Transdermal buprenorphine is absorbed through the skin; 5 mg can be used for 7 days, providing effective analgesia and reducing the use of opioids during the perioperative period.

Limitations

Retrospective analyses have inherent limitations. For example, in the present study, the diameter of the chest tube could not be unified because of the different conditions of the patients. Postoperative pain scores were determined by the patients' nurses. These nurses were not uniform and were affected by personal factors, thereby introducing the risk of type II error. Because the severity of the patients' conditions were not the same, the type of pulmonary resection and number of lymph nodes removed differed among the patients; this may have affected the POD of chest tube removal, volume of chest tube drainage fluid, POD of discharge, and medical expenses incurred during hospitalization. In addition, this was a single-center study; additional data from multicenter studies will be needed to verify our findings. Finally, this study did not consider other potential risk factors such as preoperative psychosocial factors and genetic susceptibility factors because they cannot be assessed or measured in retrospective studies.

Conclusion

Surgeons and patients desire analgesic plans that are effective, have few analgesia-related complications, have a low economic burden on the patient, and have a low opioid requirement. The present retrospective analysis, which focused mainly on patients who underwent VATS, has shown that PCIA + FA + a buprenorphine transdermal system provides superior postoperative pain control.

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