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Original Article

Postoperative continuous wound infusion of ropivacaine has comparable analgesic effects and fewer complications as compared to traditional patient-controlled analgesia with sufentanil in patients undergoing non-cardiac thoracotomy

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Abstract: Objective: To compare the postoperative analgesic effects of continuous wound infusion of ropivacaine with traditional patient-controlled analgesia (PCA) with sufentanil after non-cardiac thoracotomy. Methods: One hundred and twenty adult patients undergoing open thoracotomy were recruited into this assessor-blinded, randomized study. Patients were randomly assigned to receive analgesia through a wound catheter placed below the fascia and connected to a 2 ml/h ropivacaine 0.5% (RWI group) or sufentanil PCA (SPCA group). Analgesia continued for 48 h. Visual analogue scores (VAS) at rest and movement, Ramsay scores and adverse effects were recorded at 2, 8, 12, 24, 36 and 48 h after surgery. Three months after discharge, patient's satisfaction, residual pain and surgical wound complications were assessed. Results: General characteristics of patients were comparable between two groups. There were no statistical differences in the VAS scores and postoperative pethidine consumption between two groups ($P > 0.05$). However, when compared with SPCA group, the incidences of drowsiness, dizziness and respiratory depression, ICU stay and hospital expenditure reduced significantly in RWI group ($P < 0.05$). Patients' satisfaction with pain management was also improved markedly in RWI group ($P < 0.05$). Conclusion: Continuous wound infusion with ropivacaine is effective for postoperative analgesia and has comparable effects to traditional PCA with sufentanil. Furthermore, this therapy may also reduce the incidences of drowsiness, dizziness, respiratory depression and decrease the ICU stay and hospital expenditure.

Keywords: Ropivacaine, sufentanil, patient-controlled analgesia, continuous wound infusion, non-cardiac thoracotomy

Introduction

Patients undergoing thoracotomy often suffer from severe postoperative pain after surgery especially within first two days [1]. Inadequate pain control may result in some complications such as atelectasis, mucous plugging, hypoxia, and pulmonary infections [2] and can also lead to emotional and psychological distress, which have negative impacts on the quality of life of these patients.

Current analgesic regimens for post-thoracotomy pain include thoracic epidural analgesia, thoracic paravertebral block, and intravenous patient-controlled analgesia (PCA) [3]. Although the post-operative epidural analgesia is effective, epidural puncture may lead to serious complications such as paraplegia due to epidural abscess or epidural hematoma. PCA with opioids may cause respiratory depression, sedation, pruritus, nausea, vomiting, gastrointestinal dysfunction and urinary retention [4]. Thoracic paravertebral block is time-consuming and needs expertise to achieve satisfactory success rate [5]. Nowadays, continuous infusion with local anesthetics is increasingly popular. Postoperative continuous infusion with local anesthetics in the incision is a simple, effective and novel technique, in which an elastomeric pump and a catheter were applied. Some studies have shown that intraoperative infiltration

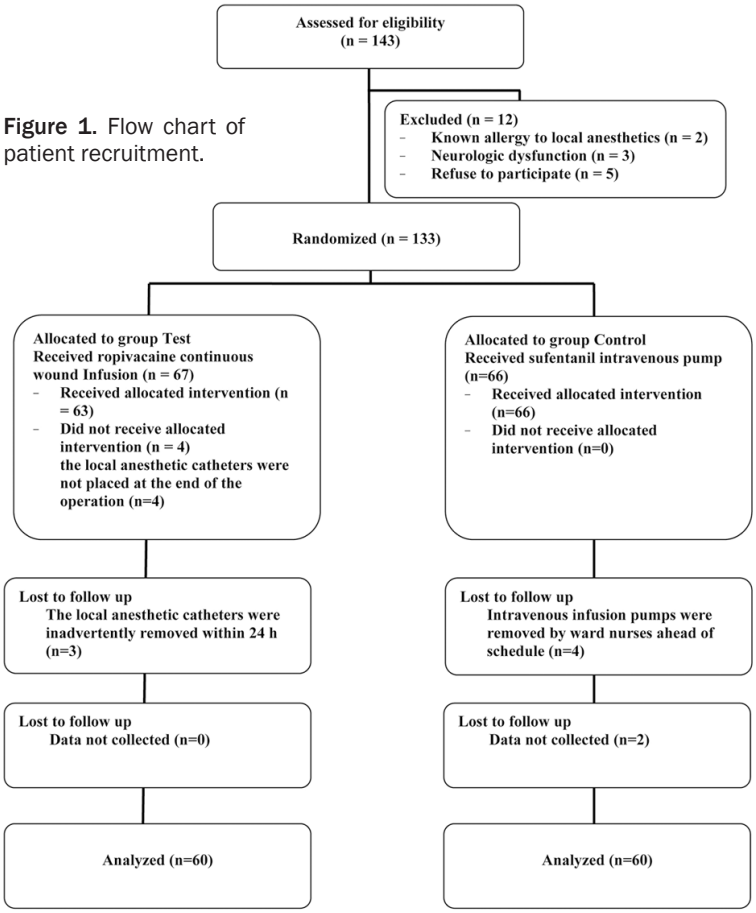

Figure 1. Flow chart of patient recruitment.

with local anesthetics in the incision achieves good postoperative analgesia, decreases pain scores, reduces opioid requirements and improves respiratory function [6].

This study was to evaluate whether a continuous infusion with a local anaesthetic could improve pain control and reduce opioid consumption as compared to standard opioid based analgesia. In addition, we also investigated if the opioid-sparing effects of a local anesthetic would decrease the side effects, facilitate the recovery and improve the patients' outcomes with respect to the satisfaction with pain management.

Materials and methods

Patient data

The study was approved by the Ethics Committee of Nanjing Jinling Hospital, and written informed consents were obtained from each patient. A total of 120 patients undergoing open thoracotomy were recruited into this prospective, observational study from September 2013 to August 2014. In these patients, 38 received lung resection, 12 underwent cardiac cancer surgery and 70 received esophageal resection. However, thirteen patients were excluded because of failure to initiate the therapy or protocol violations. In seven patients, the local anesthetic catheters were either not placed by the surgeon at the end of the operation (n = 4) or inadvertently removed within 24 h (n = 3). Four patients in control group withdrew from this study because their intravenous infusion pumps were removed by ward nurses ahead of time. Two patients with incomplete records were excluded from this study (**Figure 1**). The exclusion criteria included paralysis, known allergy to local anesthetics, active bacterial infection, clinically severe liver or kidney diseases, neurologic dysfunction, chronic use of systemic lidocaine, nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids, insulin-dependent diabetes mellitus and para-aminobenzoic acid.

Grouping

Patients were randomly assigned to continuous wound infusion group (RWI group) or intravenous pump group (SPCA group). In both groups, analgesia pumps were applied for 24 h after surgery until removal. The moment patients entered the operating room, standard monitoring was performed by five-lead Electrocardiography, pulse oximetry, and non-invasive arterial pressure measurement. General anesthesia was induced with midazolam at 0.05 mg/kg, propofol at 1.5-2.5 mg/kg and fentanyl at 3 μg/kg. When loss of consciousness was confirmed, a bolus of 0.8 mg/kg rocuronium was intravenously injected for tracheal intubation. Anesthesia was maintained with continuous infusion of propofol and a bolus of fentanyl at 1-2 μg/kg/h in order to keep the bispectral index monitor (BIS, Aspect 1000, Aspect Medical System Inc., Natick, MA, USA) between

40 and 60. Neuromuscular blockade was conducted by continuous infusion of cis-atracurium at 0.06-0.07 mg/kg/h. Patients in both groups were accessible to rescue analgesia via pethidine, if needed, during the post-operative period.

Continuous wound infusion (RWI)

In the non-cardiac thoracotomy, catheters were placed at either end of the incision site during the wound closure. The catheter was positioned in the subcutaneous tissues above the fascia along the inferior edge of the rib along the incision. The catheter consisted of a multi-orifice tube that was connected to an elastomeric infusion pump (Beijing tech-bio-med medical equipment Corporation, China) for postoperative continuous subcutaneous infusion with an anesthetic at the end of surgery. After skin closure, the infusion pump containing 0.5% ropivacaine (Naropin®-produced by AstraZeneca) was connected, and the wound was infused at 2 mL/h.

Continuous intravenous infusion (SPCA)

For patients who received a continuous intravenous infusion, sufentanil was injected intravenously via an analgesia pump after surgery, followed by intravenous PCA with sufentanil at 2 ml/h.

Follow-up assessments

Postoperative evaluations were performed by an observer blind to this study at 2, 8, 12, 24, 48, and 72 h after tracheal extubation. The level of sedation, severity of pain at rest and movement, the amount of opioid analgesics administered, and patients' satisfaction with their postoperative pain management were assessed. The level of sedation was assessed according to the Ramsay scale [7]. The severity of pain at rest and movement was evaluated with an 11-point verbal rating scale (0 = no pain, 10 = worst pain imaginable). The amount of opioid analgesics administered was determined according to the Pethidine Dosage. Patients' satisfaction with their postoperative pain management was assessed with a 100-point verbal rating scale (1 = highly dissatisfied, 100 = highly satisfied). Analgesia related complications (such as respiratory depression, drowsiness, dizzy, nausea, vomiting and postoperative seroma) were also recorded for further analysis at the mentioned intervals after the surgery The hospital stay, ICU stay and cost for hospitalization were also assessed according to the standardized protocol in all the patients undergoing non-cardiac thoracotomy. Three months after discharge, patients' satisfaction, residual pain, and surgical wound complications (inflammation, edema and others) were assessed. All the patients were followed up via telephone, and their current VAS pain score (chest incision), level of activity, frequency of pain (days per month), chronic pain at the chest wound, and overall satisfaction with the procedure were determined.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software for Windows. Descriptive results of continuous variables are presented as mean ± standard deviation (SD). Categorical data are expressed as counts and percentages. Intergroup comparisons were done with independent-sample t test. The comparisons of qualitative variables were done with chi-square test or Fisher exact test. Repeated-measures analysis of variance with Bonferroni test was used to examine the within-subjects (time) effect, between-subjects (group) effect, and time interaction effect in the data of VAS and Ramsay scores. A value of $P < 0.05$ was considered statistically significant.

Results

General data

In SPCA group, 30 underwent radical surgery for esophageal carcinoma, 21 received lung resection and 9 underwent cardia resection. In RWI group, 33 underwent radical surgery for esophageal carcinoma, 19 received lung resection and 8 underwent cardia resection. There were no significant differences between two groups in general characteristics including age, weight, height, American Society of Anesthesiologists physical status, types of surgery, anesthesia and surgery time and hospital stay (**Table 1**). However, patients in RWI group had significant shorter ICU stay and lower hospital expenditure.

Acute pain

Figures 2 and **3** show the VAS scores at rest and during movement in PACU after surgery.

Table 1. Demographic characteristics

	SII group	RWI group	*P* Value
Patients (n)	60	60	
Age (yrs)	61 ± 10	58 ± 10	0.832
Sex (M/F), n	33/27	36/24	0.580
Weight (kg)	67 ± 9	65 ± 10	0.573
Height (cm)	168.7 ± 7.0	166.2 ± 6.8	0.952
ASA score (I/II), n	23/37	18/42	0.336
Surgery time (min)	156.8 ± 49.9	161.7 ± 54.6	0.118
Hospital stay (d)	12.4 ± 4.0	12.5 ± 4.4	0.589
ICU stay (h)	30.7 ± 14.8	26.2 ± 8.8*	0.005
Hospital cost (RMB)	65831.6 ± 9161.1	46455.0 ± 6194.6*	0.025
Overall satisfaction	78.7 ± 14.7	86.9 ± 9.7*	0.000

Footnotes: ASA = American Society of Anesthesiologists; ICU = intensive care unit. *Control group versus Test group, P < 0.05.

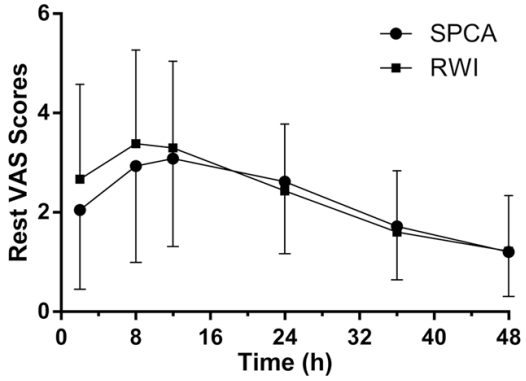

Figure 2. Visual analog scale (VAS) scores at rest. The mean VAS pain scores are plotted for each postoperative day for RWI and SPCA. Data are expressed as mean and standard error.

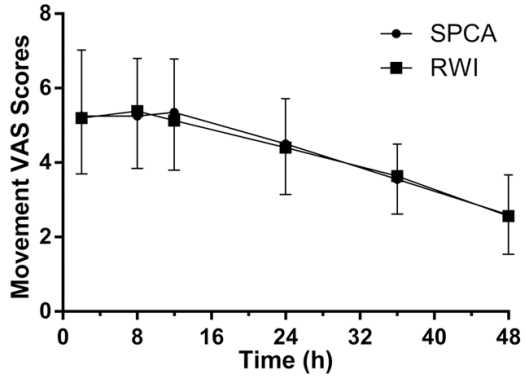

Figure 3. Visual analog scale (VAS) scores during movement. The mean VAS pain scores are plotted for each postoperative day for RWI and SPCA. Data are expressed as mean and standard error.

There were no significant differences between two groups in the pain scores at rest and during movement at postoperative follow-up visits.

Drowsiness and dizziness

Patients in RWI group reported less drowsiness and dizziness than those in SPCA group. As shown in **Figure 3**, about 5% of patients (3/60) in RWI group developed postoperative drowsiness and dizziness while 61.7% (37/60) in SPCA group (**Table 2**) showing marked differences. The Ramsay scores were also significantly different between RWI group and SPCA group (**Figure 4**).

Respiratory depression

There was significant difference between two groups in the incidence of respiratory depression at postoperative follow-up visits. Of 14 patients with postoperative respiratory depression, 23.3% (14/60) had an intravenous infusion pump placement, whereas respiratory depression was not observed in RWI group (**Table 3**).

Nausea and vomiting

There were no significant differences between two groups in nausea and vomiting at postoperative follow-up visits. The overall incidences of postoperative nausea and vomiting within 72 h were 6.7% (4/60) in SPCA group, and 5% (3/60) and RWI group (**Table 2**).

Rescue analgesia

Although more patients in RWI group received pethidine for postoperative rescue analgesia, there was no significantly statistical difference between two groups (17/60 in control group vs. 24/60 in RWI group, P = 0.178). There was no significant difference in the amount of pethidine between the groups at 12, 24 and 48 h if needed (**Table 3**).

Complications

No signs of local infection were observed in the area where the catheter was inserted. There were no statistically significant differences in the incidence of postoperative complications between two groups. Three patients (2.5%) developed wound healing delay because of

Table 2. Frequency of side Effects formation stratified by the two groups

Group	n	Drowsiness and dizziness	Respiratory depression	Nausea and vomiting	Chronic site pain
SII	60	37	14	4	4
RWI	60	3*	0*	3	6

Footnotes: *SII group versus RWI group, P < 0.05.

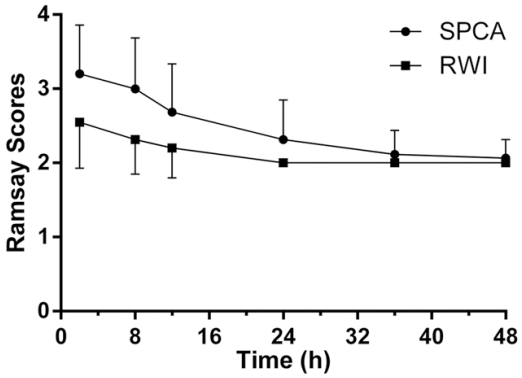

Figure 4. Ramsay scores. The Ramsay scores are plotted for each postoperative day for RWI and SPCA. Data are expressed as mean and standard error. *P < 0.05 versus control group.

incision infection: 2 in RWI group and 1 in SPCA group. Incision edema after operation occurred in five patients (4.2%): 2 (3.3%) in RWI group and 3 (5%) in SPCA group (**Table 4**).

Hospital stay and ICU stay

The overall hospital stay for 120 patients was 12.4 ± 4.2 days (**Table 1**). The average hospital stay was 12.4 ± 4.0 days for SPCA group (n = 60) and 12.5 ± 4.4 days for RWI group (n = 60) (P = 0.589). No statistical difference was observed in the hospital stay between two groups. However, the ICU stay differed significantly between 2 groups (P = 0.005). Patients in RWI group had a shorter ICU stay than those in SPCA group (**Table 1**). The overall ICU stay for 120 patients was 28.4 ± 12.3 h. The average time of ICU stay was 30.7 h and 26.2 h in SPCA and RWI groups, respectively.

Hospital expenditure

The hospital cost differed significantly between 2 groups (P = 0.025). Patients in RWI group had lower hospital cost than those in SPCA group (46455.0 ± 6194.6 RMB vs. 65831.6 ± 9161.1 RMB) (**Table 1**).

Complications at three months after surgery

The questionnaire survey about pain was performed in these patients at 3 months after surgery. Chronic incision pain was recorded as yes or no. An answer of "Yes" indicated that the patient experienced pain every day within past 3 months; an answer of "No" indicated that the patient did not experience pain in a majority of days within past 3 months. Six patients in RWI group (6 of 60) versus 4 patients (4 of 60) in SPCA group reported chronic site pain, but there were no difference (P = 0.743) (**Table 2**).

Overall satisfaction with surgical procedure

In SPCA group, the overall satisfaction was significantly lower as compared to RWI group (78.7 ± 14.7 versus 86.9 ± 9.7, P = 0.000) (**Table 1**).

Discussion

Conventional postoperative analgesia requires multimodal therapies with NSAIDs and opioids [8-10]. Although both medications provide effective analgesia, they are associated with many side effects. For example, opioids may cause drowsiness, dizziness, nausea, vomiting, urinary retention, constipation, sedation, altered mental status, and respiratory depression [11-14]. Patients receiving opioids usually require more ICU nursing [15]. NSAIDs modulate pain by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby decreasing prostaglandin production and, subsequently, pain and inflammation [16]. Adverse effects of NSAIDs include gastrointestinal irritation, bleeding, renal failure, and anemia [12, 17]. Nowadays, the postoperative continuous wound injection with local anesthetics has been applied in the multimodal analgesia and gained popularity as a means for postsurgical analgesia [18].

Local anesthesia is an additional strategy for the treatment of perioperative and postoperative pain [19]. The wound injection with local anesthetics has been well documented for a variety of indications. The continuous wound infusion with local anesthetics has been used post-operatively in some surgeries, including cesarean section, spine surgery, cardiothoracic

Table 3. Postoperative pethidine consumption

Group	Patients receiving pethidine	12 h dosage (mg)	24 h dosage (mg)	Cumulative 48 h dosage (mg)
SII (n = 60)	17	32.3 ± 24.6	82.4 ± 24.6	105.9 ± 39.1
RWI (n = 60)	24	33.3 ± 24.1	64.6 ± 23.2	72.9 ± 36.1
P value	0.178	0.803	0.438	0.926

Footnotes: *SII group versus RWI group, P < 0.05.

Table 4. Frequency of infection and edema formation stratified by the two groups

Group	n	Infection	Edema
SII	60	1	3
RWI	60	2	2

Footnotes: *SII group versus RWI group, P < 0.05.

surgery, laparoscopy, breast carcinoma surgery and surgery at the iliac crest bone graft harvest site [20-26]. The former studies have already confirmed that this type of analgesia is safe and able to reduce postoperative pain. To our knowledge, there are no studies about the use of a local anaesthetic for postoperative analgesia as compared to standard opioid-based intravenous PCA in non-cardiac thoracotomy patients.

In our study, acute pain control as well as patients' outcome (such as narcotic usage, Ramsay scores, side effects, length of hospitalization, ICU stay, chronic site pain formation and overall satisfaction with procedure) was evaluated. Patients in RWI group had the same VAS pain scores as those in SPCA group, suggesting that both methods for postoperative analgesia are safe and effective for analgesia (low pain scores). Although more patients in RWI group receiving pethidine treatment (n = 24) than those in SPCA group (n = 17), RWI decreased the mean pethidine intake within first 24 h (64.6 mg in RWI group versus 82.4 mg in SPCA group) and 48 h after surgery (72.9 mg in RWI group versus 105.9 mg in SPCA group). However, no significant difference was observed between two groups. There was a reduction in the incidence of adverse effects of opioids (sufentanil and pethidine) in RWI group. In addition, patients in RWI group had lower incidences of sedation and respiratory depression as compared to SPCA group. Most patients in RWI group had lower Ramsay scores on the day of surgery. In spite of these findings, patients in RWI group had shorter ICU stay. Therefore, a continuous infusion with a local anaesthetic represents a good strategy for analgesia in patients undergoing thoracotomy.

Another very important issue in thoracotomy is the post-operative chronic pain. Many factors are related to the chronic pain after surgery: genetic susceptibility, psycho-social background, age and gender [9, 27]. It has been proposed that a severe acute postoperative pain is a risk factor for the development of postoperative chronic pain. However, there is growing evidence showing that the use of pre-emptive analgesia have long-term benefits [28]. Pain continues after surgery because of reduced thresholds of nociceptors in the traumatized tissues [29]. Mercanoğlu et al [30] found that patients undergoing thoracotomy and postoperative analgesia had significant decreased incision pain, increased satisfaction and improved quality of life postoperatively as compared to control patients. Three months after thoracotomy, the incidence of chronic pain was comparable between two groups (RWI: 10% versus. SPCA: 7%; P = 0.743). Furthermore, in our study, the incidence of complications after a surgery was also similar between two groups, which was consistent with previously reported.

However, there were still limitations in our study. First, pain is a very subjective experience, and there is a wide variation in the pain reported by patients although they undergo the same surgery, which may bias the results. Second, the analgesic effect was evaluated by using the VAS score. Therefore, for some sleepiness patients, the VAS score might be not accurate. Third, although there were no significant differences in the demographics (such as gender, age, weight and surgical methods) between two groups, some elderly cancer patients were enrolled into our study. The physiological data and the dose-effect might be different from those in younger patients. Due to questionnaire survey was completed via telephone after surgery, some follow-up evaluations were inevitably missed or incompletely Future studies are required to confirm our findings in the present study.

In conclusion, this prospective, randomized study show that the continuous wound injection

with ropivacaine via an elastomeric pump is safe, easy and effective for postoperative analgesia. Continuous wound infusion with a local anesthetic may achieve less postoperative sedation and respiratory depression and has a shorter ICU stay. The elastomeric pump is acceptable for both patients and nursing stuff.

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Disclosure of conflict of interest

None.

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