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Original Article

Influence of Regional Anesthesia on the Rate of Chronic Postthoracotomy Pain Syndrome in Lung Cancer Patients

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Purpose: Our study aimed to assess whether the type of regional anesthesia influenced the incidence of chronic postthoracotomy pain syndrome (CPTPS).
Methods: This was a prospective, randomized study that included 300 patients undergoing lung cancer resection using thoracotomy. They were randomized into three groups: paravertebral nerve block (PVB), thoracic epidural anesthesia (TEA), and intercostal nerve block (INB). General anesthesia was similar in the groups. A horizontal visual analogue scale (VAS) was used to assess the intensity of the pain syndrome. It was assessed and recorded 7 days, 1 month, and 6 months after surgery.
Results: At 6 months after surgery, the incidence ($p < 0.05$) of the CPTPS was higher in the INB group (40%) than in the TEA group (23%). The CPTPS frequency in the PVB group did not differ from the other groups (34%).
Conclusion: The use of the TEA in patients who underwent open lung cancer surgery contributed to a significant decline in the CPTPS frequency compared to patients who were administered INB. Using PVB did not decrease the CPTPS frequency.

Keywords: regional anesthesia, postthoracotomy pain, lung cancer

Introduction

Despite the development of videothoracoscopy, thoracotomy is still commonly used in lung cancer resection as in surgical treatment of esophageal cancer.[1–4] In patients undergoing thoracotomy, the postoperative period can be the source of acute postthoracotomy pain syndrome (APTPS). From 38% to 63% of patients report acute pain, with intensity ranging from moderate to severe (numeric rating scale ≥3).[1] The development of APTPS results in impaired breathing. This impairment can generate hypoventilation, which can cause lung infection.[4,5] In addition, these patients have disturbed sleep, loss of appetite, and a significant decline in their quality of life.[6]

According to the available literature, about 40% of patients with APTPS subsequently develop chronic postthoracotomy pain syndrome (CPTPS).[7] CPTPS is defined as pain that develops after surgical intervention and lasts for at least 2 months (International Association for the Study of Pain).[8] The mechanism of CPTPS is long-lasting, non-curable, acute surgical pain associated with surgical trauma and inflammation of the chest wall, lungs, and pleural parenchyma.[9] For this reason, APTPS should be prevented and effectively treated as soon as possible.[10] In addition, the presence of a neuropathic component due

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to injury or irritation of the intercostal nerves has been reported as a mechanism of pain chronicization.[11,12] The emergence of a neuropathic pain component is critical for thoracotomy and thoracoscopy because of surgical techniques and the innervation of the chest wall.[11] In published research, only combined methods (including non-steroidal anti-inflammatory drugs [NSAIDs], anticonvulsants, NMDA-antagonists, and regional anesthesia) affected the incidence of APTPS and CPTPS.[13–15] Data show that, in patients undergoing open thoracic surgery, paravertebral nerve block (PVB), thoracic epidural anesthesia (TEA), and intercostal nerve block (INB) are equally used.[16] Several investigations showed TEA to be superior to PVB in relieving APTPS.[5,17] However, authors reported some advantages of PVB.[18,19] Despite these conflicting findings, most relevant studies found no significant differences between TEA and PVB in analgesic efficacy against APTPS.[20–22] Interestingly, some studies also found INB to be as effective as other methods.[21,23]

Studies reporting incidences of CPTPS, however, are small[5,18] and present insufficient data for statistical analysis.[15] Our study aimed to assess the influence of PVB, TEA, and INB on the incidence of CPTPS.

Materials and Methods

The study protocol was approved by the Institutional Review Board of the P.A. Herzen Moscow Cancer Research Institute (No. 12-09). All patients provided written informed consent. Patients were enrolled from January 2012 until December 2016. The study was registered ISRCTN12472990. All consecutive patients scheduled for thoracotomy were screened for study inclusion using the following eligibility criteria: adult patients and American Society of Anesthesiologists (ASA) physical status from I to III. Exclusion criteria were general anesthesia within 7 days before study inclusion, administration of an experimental drug within 30 days before surgery, preoperative pain syndrome, or use of analgesics, acute unstable angina, acute myocardial infarction documented by laboratory findings within the past 6 weeks, heart rate (HR) <50 beats per minute (bpm), systolic blood pressure (SBP) <100 mmHg, heart block, and preoperative vasopressor administration. In all, 300 patients with non-small-cell lung cancer were included in the study. All patients were operated on at the lateral decubitus position via standard posterolateral thoracotomy in the 5th intercostal space without any rib resection, trying to preserve latissimus dorsal muscle whenever possible. Two retractors were used for rib spreading. Patients were randomly assigned to three groups using Research Randomizer (http://www.graphpad.com): 1) TEA; 2) PVB; or 3) INB.

Intraoperative monitoring included three-lead electrocardiography, non-invasive blood pressure (BP), pulse oximetry, bispectral index monitoring (BIS), train-of-four (TOF), expired carbon dioxide (CO_2), and urine output. The BIS value was maintained between 50 and 60. The TOF was maintained at 0 counts (post-tetanic count: 6–10). BP and BIS values were measured every 5 minutes, and TOF was measured every minute. Crystalloids were infused at 9 mL/kg/h during surgery. If bleeding occurred, 6% hydroxyethylstarch of the same volume as blood loss was infused. The trigger hemoglobin level for packed red blood cells transfusion was 85 g/L. Atropine 1% (1 ml) was administered intravenously (IV) if the HR was lower than 45 bpm. An IV infusion of norepinephrine was started if the SBP was lower than 90 mmHg.

In the TEA group, an epidural catheter was placed at the T_4–T_6 interspace before induction. Then, an intraepidural infusion of ropivacaine 0.3%, fentanyl (4 μg/mL), and epinephrine (2 μg/mL) was started at 5–15 mL/h. Postoperatively, this group received an anesthetic solution containing ropivacaine 0.3%, fentanyl (4 μg/mL), and epinephrine (2 μg/mL) for 2 days. After day 2, only ropivacaine 0.2% was infused until the 5th postoperative day.

In the PVB group, a paravertebral catheter was placed at the T_5–T_6 level using ultrasound. Before the induction of general anesthesia, the patients received a bolus (10 mL) of lidocaine 2% and the same anesthetic solution as the TEA group in a volume of 20 ml. At the end of surgery, a second bolus dose (20 ml) of the anesthetic solution was administered. Postoperatively, the patients received the same anesthetic solution as the TEA group with an infusion rate at 8–12 mL/h for the first 2 days. Then, this solution was changed to ropivacaine 0.2%, and the infusion was continued until the 5th postoperative day.

In the INB group, an INB was provided by the surgical team after the lung or lobe resection. A solution of ethanol 96% (30 mL) and novocaine 0.5% (30 mL) was mixed and injected into the intercostal space (subpleural and paravertebral) just below the intercostal nerve at three levels (20 mL of solution at each level) to provide the intercostal block at the level of thoracotomy and above and below the incision as described in the literature.[24] Postoperatively, additional injections of a local anesthetic were administered transdermally in patients with acute pain syndrome, defined by a visual analogue

score (VAS) above 50 mm. Those patients received a 0.5% solution of novocaine (20 mL) at the same levels. The needle was placed at an angle approximately 20° cephalad to the skin in the paravertebral line. The needle was kept away from the lower border of the rib as the skin returned to its initial position. Then, the needle was placed 3 mm below the inferior margin of the rib, with the goal of placing the tip in the space containing the neurovascular bundle (i.e., between the internal and innermost intercostal muscles).

Patients in all groups received oral pregabalin (75 mg twice a day) before surgery and once on the day of surgery, 2 hours before anesthesia induction. After surgery, pregabalin (75 mg twice a day) was continued until hospital discharge. Patients received lornoxicam (8 mg) preoperatively and twice a day after surgery. Nefopam (20 mg) was administered intramuscularly 40 minutes before the end of the surgery to prevent hyperalgesia and continued from the onset of initial pain syndrome for 5 days (20 mg twice a day). In the case of persistent pain syndrome, morphine (10 mg) was also prescribed upon patient request or if the VAS was >50 mm.

General anesthesia was similar in the three groups. Propofol (2 mg/kg), fentanyl (0.002 mg/kg), ketamine (25 mg), and rocuronium (0.6 mg/kg) were administered for induction. Ventilation was mechanically controlled and adjusted to maintain end-tidal CO_2 at 30–35 mmHg and inspired fraction of O_2 at 35%. After endotracheal intubation, anesthesia was maintained with sevoflurane (0.8–1 MAC), fentanyl (0.05–0.1 mg IV every 15–30 minutes when the SBP increased by more than 15% from the baseline value or was >140 mmHg). Rocuronium was administered for muscle relaxation, based on TOF response.

Horizontal VAS was used to assess the intensity of the pain syndrome. Patients were requested to mark their pain intensity on the following scale: 0 = no pain and 100 mm = worst possible pain. Static and dynamic pain components were assessed 7 days, 1 month, and 6 months after surgery. The static pain component was measured at rest. The dynamic pain component was defined as the highest intensity of pain during normal daily activity, deep breathing, and maximal coughing. On the 7th day after surgery, the intensity of pain was assessed during a consultation in the patient's room. On discharge, patients received a VAS and then were interviewed by telephone 1 month and 6 months after surgery. An intensity of pain syndrome 1–30 mm was considered mild, 31–70 mm was deemed moderate, and over 70 mm was classified severe. The pain syndromes (VAS ≥1 mm) 7 days and 1 month after surgery were classified as APTPS, and the pain syndrome 6 months after surgery was considered CPTPS.

Our primary objectives were to compare i) the frequency of CPTPS between the TEA and PVB groups and ii) the effectiveness of TEA and PVB with INB in CPTPS prevention. The secondary objectives were i) to compare the intensity of APTPS and CPTPS between the groups and ii) to evaluate the changes in pain intensity during the study period.

Data are presented as means ± standard deviation or absolute values. Statistica 10 software (StatSoft Inc., USA) was used for the statistical analysis. The Mann–Whitney U test was performed to compare age, weight, duration of surgery, blood loss, and pain intensity between independent samples. For the multiple sample analysis, a Kruskal–Wallis test was used. The pain intensity between dependent samples was compared through Friedman analysis of variance (ANOVA; multiple samples) and the Wilcoxon test (two samples). A chi-square test was used to compare ASA physical status, gender, and type of surgery. We assessed pain syndrome frequency using chi-square and Fisher tests for independent samples and Cochran's Q test for dependent samples.

To calculate the required sample size, we considered the study results of Richardson et al.[18] We aimed to show a 13.8% reduction of CPTPS incidence in the PVB group compared with the TEA group. However, we expected a possible reduction in two directions, resulting in a two-tailed test calculation for the sample size. We chose a group size of 90 to detect the planned CPTPS reduction with a power of 80% and a significance level of 0.05. Of note, 100 patients were included in each group because we expected to lose 10% of patients due to personal reasons, comorbidity, or death.

Results

During the study period, 347 patients were screened. Of those screened, 47 met the exclusion criteria: 17 patients suffered from an atrioventricular block I–II, 23 patients had a HR less than 50 bpm, and seven patients had preoperative hypotension with SBP less than 100 mmHg. Each group included 100 patients. The groups were comparable regarding demographic features, blood loss, and type and duration of surgery (**Table 1**).

During the postoperative period, the three groups did not differ in the frequency of APTPS and CPTPS at rest. Dynamic pain component analysis showed that, in the TEA group, the rate of APTPS was lower by day 7

Table 1 Demographic characteristics and surgery duration

	TEA (n = 100)	PVB (n = 100)	INB (n = 100)
Age (years)	55 ± 9	58 ± 9	55 ± 10
Gender (m/f)	74/26	77/23	76/24
BMI (kg/m2)	27 ± 1	27 ± 4	27 ± 4
ASA physical status (I/II/III)	11/55/34	9/53/38	10/54/36
Pneumonectomy/lobectomy	22/78	19/81	18/82
Duration of surgery (h)	3.50 ± 0.95	3.30 ± 1.03	3.40 ± 1.00
Blood loss (ml)	380 ± 106	354 ± 114	339 ± 145

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Table 2 Frequency of postoperative pain syndrome in study groups

End points	TEA (n = 100)		PVB (n = 100)		INB (n = 100)		p value		
							Dynamic pain		
	Static pain	Dynamic pain	Static pain	Dynamic pain	Static pain	Dynamic pain	TEA/ PVB	TEA/ INB	PVB/ INB
7 Days n (%)	14 (14)	32 (32)	24 (24)	46 (46)	18 (18)	50 (50)	0.04	0.01	0.6
1 Month n (%)	12 (12)	24 (24)	22 (22)	32 (32)	16 (16)	44 (44)	0.2	0.03	0.08
6 Months n (%)	10 (10)	23 (23)	16 (16)	34 (34)	14 (14)	40 (40)	0.08	0.01	0.4
p value									
d.7/m.1	0.16	0.005	0.16	0.001	0.16	0.01			
d.7/m.6	0.046	0.003	0.005	0.003	0.16	0.002			
m.1/m.6	0.16	0.3	0.01	0.16	0.41	0.046			

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compared to the INB and PVB groups (p = 0.01 and p = 0.04, respectively), and after 1 month compared to the INB group (p = 0.03). The rate of CPTPS was higher in the INB group than in the TEA group (p = 0.01) (**Table 2**). At rest, the rate of APTPS did not differ between 7 days and 1 month after surgery for all groups. The CPTPS rate was lower than the APTPS rate after 7 days in the TEA and PVB groups (p = 0.046, p = 0.005, respectively) and after 1 month in the PVB group (p = 0.01). The APTPS rate while moving was higher 7 days after surgery than 1 month after surgery in all groups (p <0.02). A similar finding was reported for the CPTPS incidence while moving; and it was lower than the APTPS incidence in the INB group on day 7 (p <0.01) and after 1 month (p = 0.046).

During the postoperative period, the APTPS and CPTPS intensities at rest were similar between groups. Dynamic pain analysis showed that the intensity of APTPS in the TEA group was lower than that of the INB (p = 0.04) and PVB (p = 0.04) groups on day 7 and that of the INB group after 1 month (p = 0.006). The CPTPS intensity was higher in the INB group than in the TEA group (p = 0.006) (**Table 3**). At rest, the intensity of APTPS decreased from day 7 to 1 month only in the PVB group (p = 0.008). The dynamic pain component assessment showed that the intensity of APTPS declined from day 7 to 1 month postoperatively in all groups (p <0.01). When moving, CPTPS intensity was lower than that of the APTPS on day 7 in all groups (p <0.02), but it did not differ after 1 month.

Dynamic pain component analysis showed that the rate of moderate pain syndrome differed among the groups. On day 7, the patients in the INB (5/100) group reported moderate APTPS more often than those in the PVB (0/100) and TEA (0/100) groups (p = 0.02). After 1 month, this rate was still higher in the INB group (4/100) than in the TEA group (0/100, p = 0.04) although

Table 3 Intensity of postoperative pain syndrome in study groups

End points	TEA (n = 100)		PVB (n = 100)		INB (n = 100)		p value		
							Dynamic pain		
	Static pain	Dynamic pain	Static pain	Dynamic pain	Static pain	Dynamic pain	TEA/PVB	TEA/INB	PVB/INB
7 Days n (%)	0.17 ± 0.45	0.63 ± 0.98	0.36 ± 0.69	0.92 ± 1.04	0.24 ± 0.56	1.18 ± 1.36	0.04	0.04	0.3
1 Month n (%)	0.12 ± 0.33	0.44 ± 0.83	0.23 ± 0.45	0.65 ± 1.08	0.23 ± 0.57	0.78 ± 1.21	0.2	0.006	0.2
6 Months n (%)	0.10 ± 0.30	0.38 ± 0.79	0.16 ± 0.39	0.59 ± 0.98	0.18 ± 0.48	0.73 ± 1.11	0.06	0.006	0.4
p value									
d.7/m.1	0.1	0.001	0.008	0.001	0.8	<0.001			
d.7/m.6	0.08	0.01	0.001	0.0005	0.09	<0.001			
m.1/m.6	0.5	0.4	0.02	0.3	0.08	0.61			

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it did not differ from the PVB group (2/100, p = 0.4). After 6 months, no significant differences in the rate of moderate CPTPS were observed between the three groups (TEA 0/100; PVB 3/100; INB 3/100).

Discussion

In our study, open lung cancer resection patients who received TEA showed less incidence and intensity of CPTPS. The incidence of CPTPS decreased by 23% in the TEA group. The patients receiving PVB did not display decreased levels of CPTPS. The use of INB was less effective at reducing CPTPS than that of TEA. Six months after surgery, the rate of CPTPS in patients receiving INB was 40%. Most of these findings were previously published in Russian.[25)]

Several investigators have reported the effectiveness of TEA in preventing CPTPS. At the 6 months follow-up, the frequency of CPTPS in TEA group was 33% in Kampe et al.'s study,[26)] 39% in Sentürk et al.'s study,[27)] and 45% in Bayman et al.'s study.[28)] Matsutani et al. showed that the supplementation of pregabalin to TEA decreased CPTPS incidence at 2-month follow-up, it was 18%.[13)]

Only a few studies have described the effect of PVB on the incidence of CPTPS,[5,18)] making it challenging to discuss this end point.[15)] These studies provided insufficient data for highlighting a statistical difference in incidence of CPTPS between TEA and PVB. The frequency of CPTPS at 6-month follow-up was 20.4% in the TEA group and 6.6% in the PVB group,[18)] and at 12-month follow-up, 14.9% in the TEA group and 8.7% in the PVB group.[5)] In our study, the incidence of CPTPS in the PVB group did not differ from other groups.

Cancer lung surgery is associated with extensive interventions, resulting in injuries to the intercostal nerves and massive afferent visceral inflows and local inflammation. In such conditions, a unilateral PVB probably cannot provide antinociceptive protection comparable to TEA. In our study 7 days after surgery, the patients in the PVB group suffered from APTPS more frequently than in the TEA group and had greater pain intensity. Perhaps using the multiple-injection technique would improve the efficacy of PVB. Casati et al.[20)] showed that continuous PVB analgesia through the three-injection technique is as effective as an epidural blockade in controlling APTPS. The authors relied on a previous finding that the single bolus technique produced a safe, but unpredictable, block.[29)]

In our study, the rate of moderate APTPS was higher in the INB group than in the TEA group on day 7 and

1 month after surgery. We did not find a difference in the rate of moderate CPTPS between groups. Nevertheless, the rate of CPTPS (mild–severe) tended to be lower in the TEA group than in the INB group. Katz et al. reported the rate of CPTPS more than 1.5 years after surgery. They differentiated the pain-free counterparts by the intensity of pain experienced as early as 6 hours, and up to 2 days, after surgery.[10)]

In the literature, the timing of the adequate sensitive block initiation is one of the most important determinants in comparing regional and local anesthesia methods.[4,27)] In our study, TEA and PVB were initiated prior to incision, whereas INB was performed at the end of the surgery. This fact may explain INB's disappointing performance. Rice et al.[23)] showed a five-level posterior INB with liposomal bupivacaine that was performed percutaneously before the thoracotomy. The authors concluded that INB with liposomal bupivacaine provides a safe and effective alternative to TEA. Unfortunately, we did not find studies assessing the impact of INB on CPTPS frequency.

When paravertebral or epidural catheter placement is unsuccessful, undesirable, or not possible for technical, medical, or other reasons, our clinic's described regimen routinely provides INB. In our institution, we used the supplementation of alcohol to local anesthetic for partial neurolysis of intercostal nerves to prolong the analgesic effect.[24)]

In many studies, the first time long-term pain could be assessed was 2 months after discharge.[5,14,21)] It was interesting to assess pain syndrome intensity 1 month after surgery. Bendixen et al. assessed pain syndrome from 1 day to 52 weeks after a thoracotomy. The difference in the frequency of pain syndrome at week 4 and week 52 was 16.5% and 11.8%, respectively.[1)] Also, numerous researchers have identified chronic pain syndrome as pain persisting for at least 6 months.[8)]

The rate of the APTPS dynamic pain component in all groups was higher on day 7 than at 1 month and the rate of the CPTPS at 6 months. The rate after 1 month remained stable, except for the INB group. When moving, CPTPS intensity was lower than that of the APTPS on day 7 in all groups, but it did not differ after 1 month. This finding is critical because motor activity is a priority for full physiological, psychological, and social adaptation. Relief from dynamic pain contributes to return to normal daily life.

Our results suggest that TEA remains the gold standard for thoracotomy, but new comparative studies of TEA and PVB in light of the CPTPS prevention have to be provided, due to the heterogeneity of available studies.

Conclusion

Patients who were administered TEA had less incidence and reduced intensity of CPTPS when compared with INB. Six months after surgery, the incidences of CPTPS were 23%, 34%, and 40% in the TEA, PVB, and INB groups, respectively. We did not find differences in CPTPS frequency and intensity between PVB and other groups. A pain syndrome that persists more than 1 month after surgery should be considered a predictor of pain syndrome chronicity.

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Disclosure Statement

All authors, and our spouse and other immediate family have no any financial relationship with a biotechnology manufacturer, a pharmaceutical company, and other commercial entity that has an interest in the subject matter or materials discussed in the manuscript, within the period of 24 months prior to the submission. All authors have no conflict of interest.

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