Efficacy of Thoracic Epidural Analgesia With or Without Intercostal Nerve Cryoanalgesia for Postthoracotomy Pain

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GENERAL THORACIC

Background. We evaluated effects of thoracic epidural analgesia combined with intercostal nerve cryoanalgesia or epidural analgesia alone on acute and long-term pain after posterolateral thoracotomy.

Methods. Forty-two elective thoracotomy patients were randomly assigned to two groups, epidural combined with cryoanalgesia or epidural alone. A thoracic epidural catheter was inserted before induction of anesthesia. At the end of the operation, cryoanalgesia was performed to 3 intercostals nerves: 1 at the level of the incision, 1 caudal, and 1 cranial. Cryoanalgesia was blinded to the investigating anesthetists and patients. To avoid impingement of intercostal nerves, chest closure in all patients was performed using intracostal sutures through drilled holes in adjacent ribs. In the postanesthesia care unit, epidural infusion of ropivacaine (1 mg/mL) with fentanyl (5 μg/mL) was started and continued 3 days. Thereafter, pain was treated with oral strong or weak opioids combined with nonsteroidal antiinflammatory drugs or acetaminophen. Pain was assessed with the verbal pain scale or visual analog scale. Patients visited a local pain clinic at 8 weeks and at 6 months postoperatively.

Results. The cryoanalgesia group had more neuropathic-type pain compared with the epidural-alone group 8 weeks after operation ($p < 0.05$). The cryoanalgesia group had also more pain on normal daily activities 8 weeks after the operation ($p < 0.05$). After 6 months, there were no statistically significant differences between groups.

Conclusions. Intercostal cryoanalgesia seems to increase the incidence of long-term pain after thoracotomy.

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Long-term pain after surgery is a very common complaint. Especially after thoracotomy, the incidence of chronic pain is very high [1, 2]. Management of pain after thoracotomy can be difficult, but the benefits of effective pain control are significant, particularly regarding chronic pain [3, 4]. A variety of treatments for postthoracotomy pain are available, including epidural and regional analgesia, systemic or intrathecal opioids, and other oral or parenteral agents [2, 5–7]. Studies have shown that chronic postthoracotomy pain can be neuropathic or nociceptive [8–11].

Cryoanalgesia has been used in the treatment of postthoracotomy pain, and there are studies in which it has been effective, especially in acute pain [12–14], and some studies claim that it has been effective even in chronic pain [15]. However, Miguel and Hubbell [16] reported that cryoanalgesia was effective neither in acute nor in chronic pain after thoracotomy.

The incidence of chronic postthoracotomy pain can be decreased by thoracic epidural analgesia [4] and by a technique that uses drilled holes in adjacent ribs during chest closure [17]. We used the "drilled holes" technique to minimize postthoracotomy pain and to see more clearly the effects of intercostal nerve cryoanalgesia. Recently Ju and colleagues [18] reported that intercostal nerve cryoanalgesia may increase the incidence of chronic neuropathic pain but had satisfactory acute pain control after thoracotomy.

The purposes of this randomized and blinded study were, first, to evaluate the role of intercostal nerve cryoanalgesia on neuropathic pain after thoracotomy, and second, to investigate acute and prolonged postthoracotomy pain when postoperative pain is controlled with thoracic epidural analgesia alone or combined with intercostal nerve cryoanalgesia.

Patients and Methods

This study was approved by the institutional Ethics Committee of South Carelia Central Hospital. Forty-two patients (American Society of Anesthesiology I to III) scheduled for elective posterolateral thoracotomy gave informed written consent to participate. Of these, 21 were randomly allocated to a group that received thoracic epidural analgesia combined with cryoanalgesia (EC) and 21 to a group that received the epidural without cryoanalgesia (E). We excluded patients who required chronic opioid therapy and patients with moderate or severe pain—verbal pain scale (VPS) of 2 or more —at the

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operation site before the operation. Pain was evaluated by VPS or the visual analog scale (VAS).

The electrocardiogram, noninvasive or invasive blood pressure, heart rate, end-tidal carbon dioxide, end-tidal isoflurane concentration, peripheral oxygen saturation, and train-of-four were monitored using an S/5 monitor (GE Healthcare Finland Oy, Helsinki, Finland). Thoracic epidural catheters were inserted through the T5 to T6, T6 to T7, or T7 to T8 interspaces before induction of anesthesia.

Patients were premedicated with diazepam (0.1 mg/kg, adjusted to the nearest 2.5 mg) and received fentanyl (0.1 to 0.2 mg) and thiopental (3 to 5 mg/kg) for induction of anesthesia. Rocuronium was used for neuromuscular blockade. One-lung ventilation was used during the operation, and anesthesia was maintained with isoflurane (1% to 3% in 40% to 100% oxygen) and fentanyl boluses (0.05 to 0.1 mg) as needed.

At the end of the operation, the surgeon gave 60 seconds of cryoanalgesia at –70°C (140 Cryo Unit, Spembly Medical, Hampshire, UK) to 3 intercostal nerves: 1 at the level of the incision, 1 caudal, and 1 cranial. Cryoanalgesia was performed on the intercostal nerves about 10 cm from the nerve root. The investigating anesthetists (S.M., J.L.) and patients were blinded to whether cryoanalgesia was performed.

Intracostal sutures, USP 0 Maxon (Davis & Geck, Davis, NJ) through drilled (Mini Air Drill, Synthes, Oberdorf, Switzerland) 2-mm holes in adjacent ribs, were used during chest closure to avoid the impingement of intercostal nerves (Fig 1). Before the end of anesthesia, a 0.1-mg fentanyl bolus with physiologic saline (5 mL) was given to the epidural catheter.

In the postanesthesia care unit, an epidural infusion of ropivacaine (1 mg/mL) plus fentanyl (5 μg/mL) was started at a rate was of 3 to 10 mL/h, and 4-mL boluses were given as needed. Epidural infusion was continued for 3 days on the ward, and the rate was adjusted according to VAS (0 to 100 mm), with the goal of maintaining the VAS at 30 or less at rest and at 40 or less while walking.

The epidural infusion was stopped after 3 days, and pain was treated with oral strong (oxycodone) or weak

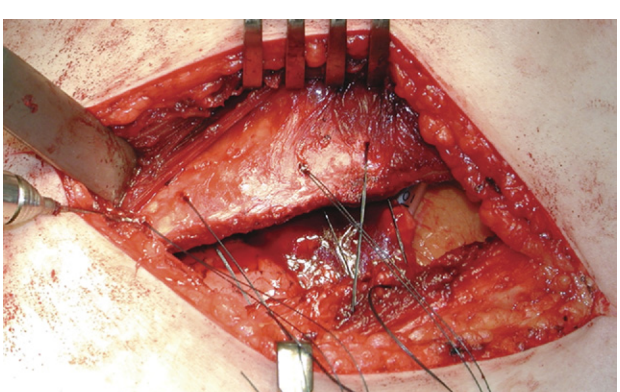

Fig 1. Intraoperative photograph shows the drilled holes technique in adjacent ribs during chest closure.

(tramadol or codeine) opioids combined with nonsteroidal antiinflammatory drugs or acetaminophen, as needed. VPS (0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and VAS were used for all patients at all points except for patients at home. At home, patients used VPS once a week for 6 weeks after the operation.

During first 12 hours, pain was evaluated only at rest because patients did not move a lot during that time. After that, pain was evaluated at rest, normal daily activities (during movement on the ward), and in exercise. Patients visited a local pain clinic for an evaluation of VPS and VAS at 8 weeks and at 6 months after their operation. Overall pain, tactile sensation (especially hypoesthesia), mechanical (dynamic or static) allodynia, hyperalgesia, and dysesthesia were tested around the operation site. Allodynia, hyperalgesia, and dysesthesia were combined and designated as neuropathic-type pain.

The primary outcome was the incidence of neuropathic-type pain. The secondary outcome was the intensity of acute and long-term pain after thoracotomy. Power analysis gave us 20 patients in each group with 80% power and a 35% difference between groups in neuropathic-type pain. The statistical analysis was performed with the Instat 3.06 program (GraphPad Software Inc, San Diego, CA). The Fisher exact test was used to compare differences in neuropathic-type pain and hypoesthesia between groups. For VAS and VPS, Wilcoxon ranked sign test was used to compare differences between groups in different points. A value of $p < 0.05$ was considered statistically significant. Values are mean ± standard deviation, unless otherwise specified.

Results

Patient characteristics are presented in Table 1. One patient in both groups was omitted from further analysis because of missing data. All patients visited the local pain clinic 8 weeks after operation, but 3 patients in the EC group and 2 in E group did not visit the local pain clinic at 6 months and were interviewed by telephone. They all stated that they had no pain at the operation site. At 8 weeks, 11 patients in the EC group had neuropathic-type pain (mostly allodynia) compared with 4 patients in the E group ($p = 0.048$; Table 2). Postoperatively, patients in the EC group had significantly more pain than E patients at rest at 12 hours ($p = 0.021$) and at 2 days ($p = 0.017$) and during normal daily activities at 8 weeks ($p = 0.041$; Table 3).

At 6 months postoperatively, there were no statistically significant differences between groups, but 5 EC group patients had moderate or severe pain during exercise compared with 2 E group patients. No patients had moderate or severe pain at rest, and only 1 patient in both groups had moderate pain at normal daily activities 6 months after the operation. Patients had more hypoesthesia (numbness) at the operation site (20 of 20) in the EC group compared with the E group (10 of 20) at 8 weeks ($p = 0.0004$). Hypoesthesia rates at 6 months were 8 of 20 in the EC group and 6 of 20 in the E group ($p = 0.715$).

Table 1. Patient Characteristics and Diagnoses

	Epidural and Cryoanalgesia	Epidural Alone
Variable	No. or Mean ± SD	No. or Mean ± SD
Total patients	21	21
Sex		
Male	13	15
Female	8	6
ASA score		
I	0	2
II	10	9
III	11	10
Age, years	64.6 ± 11.1	59.5 ± 14.9
Weight, kg	73.7 ± 13.8	74.9 ± 12.1
Height, cm	170.2 ± 10.5	171.7 ± 7.6
Diagnosis		
Infection	7	5
Malign tumor	9	11
Benign tumor	5	5

ASA = American Society of Anesthesiology; SD = standard deviation.

During the 3 days after the operation in the ward, there were no differences between EC and E groups, respectively, in epidural infusion rates (4.7 ± 0.6 vs 5.1 ± 0.5 mL/t) or number of boluses (6.2 ± 4.9 vs 5.8 ± 4.7). No differences were observed between groups in oxycodone requirements after epidural infusion was stopped: 23.1 ± 27.1 mg/3 d in EC and 38.4 ± 66.9 mg/3 d in E groups. At home, 14 patients in the EC group and 15 in the E group received capsules of tramadol (50 mg) or codeine (30 mg) and acetaminophen (500 mg), whereas others needed only nonsteroidal antiinflammatory drugs or acetaminophen. The groups were similar in patient satisfaction: 18 of 20 patients in both groups considered pain management as good or excellent.

Comment

Postthoracotomy pain has a complex etiology. It can be partly nociceptive, including stretching of thorax, manipulation of lungs and pleura, and fracture or displacement of ribs or small joints; and partly neuropathic, consisting mostly of stretching or impingement of the intercostal nerves. In the present study, we tried to avoid impingement of intercostal nerves by using the drilled holes technique in adjacent ribs during chest closure. The drilled holes technique has been reported to decrease postthoracotomy pain [17]. On the other hand, thoracic epidural analgesia has also been shown to decrease postthoracotomy pain [4]. We combined these and also used cryoanalgesia, which is supposed to decrease especially acute postthoracotomy pain [13, 14].

Several studies have suggested that cryoanalgesia is useful for the treatment of acute postthoracotomy pain [12, 13, 18, 19], and some have also suggested cryoanalgesia is a valuable method to prevent chronic pain [15]. But some studies have reported that cryoanalgesia can increase the incidence of long-term neuropathic pain [14, 18, 20]. The present study confirmed that cryoanalgesia could cause more long-term neuropathic-type pain. Furthermore, according to our study, cryoanalgesia does not seem to be very valuable in acute pain control after posterolateral thoracotomy, at least not in combination with epidural analgesia. In fact, our study favored the plain epidural group after 12 hours, 2 days (pain scores were rather low), and a nearly significant difference 1 day after the operation (Table 3). These findings are in accordance with the study of Miguel and Hubbell [16] who reported that cryoanalgesia offered no advantages over epidural morphine in the treatment of postthoracotomy acute pain. One reason not to notice advances of cryoanalgesia in the present study is that the acute pain in both groups was controlled with epidural analgesic infusion, which is very effective in acute postoperative pain.

Yang and colleagues [14] reported that the combination of cryoanalgesia and epidural analgesia failed to decrease the incidence of long-term postthoracotomy pain. Cryoanalgesia combined with thoracic epidural analgesia was associated with earlier recovery in pulmonary function, less pain during movement, and a lower daily requirement for rescue analgesics 1 week after the operation [14]. We did not measure postoperative pulmonary function, however. Yang and colleagues [14] used telephone contact during the postoperative months, whereas our patients visited a local pain clinic and completed a VPS every week for up to 6 weeks. Yang and colleagues [14] also reported that the incidence of numbness at the incision scar during their 6-month follow-up was similar in the two groups, indicating the possibility that the cryoanalgesia was not sufficient.

All cryoanalgesia patients in the present study had numbness around the incision scar 8 weeks after the operation, indicating that the cryoanalgesia was sufficient in our patients. On the other hand, the present study documented no differences in numbness after 6 months between groups, indicating recovery of the intercostal nerves from cryoanalgesia. Yang and colleagues [14] performed cryotherapy at –20°C for 90 seconds, Ju and colleagues [18] used –70°C for 90 seconds, and we used –70°C for 60 seconds. These differences can partly explain the differences in the frequency of numbness.

Table 2. Incidences of Hypoesthesia, Allodynia, Hyperalgesia, and Dysesthesia at 8 Weeks and 6 Months After Operation

	Cryoanalgesia Group, No.		Epidural Group, No.	
Variable	8 Weeks	6 Months	8 Weeks	6 Months
Hypoesthesia	20	8	10	6
Allodynia	9[a]	5	3	2
Hyperalgesia	2	1	0	0
Dysesthesia	1[b]	0	1	1

[a] One patient had both allodynia and hyperalgesia. [b] Patient had also allodynia.

Table 3. Pain Scores at Different Times Postoperatively at Rest or in Movement in Cryoanalgesia and Plain Epidural Groups

			Cryoanalgesia Group (n = 20)		Epidural Group (n = 20)		
Time	Pain	Variable	Mean ± SD	95% CI	Mean ± SD	95% CI	*p*-Value[a]
1 hour	VPS	RE	0.95 ± 1.10	0.46 to 1.44	1.19 ± 1.54	0.49 to 1.89	0.876
	VAS	RE	22.4 ± 26.5	10.3 to 34.4	28.6 ± 36.5	12.0 to 45.2	0.879
6 hours	VPS	RE	0.57 ± 0.68	0.26 to 0.88	0.76 ± 0.62	0.48 to 1.05	0.339
	VAS	RE	11.2 ± 14.9	4.4 to 18.0	11.3 ± 13.1	5.4 to 17.3	0.732
12 hours	VPS	RE	0.95 ± 0.86	0.56 to 1.35	0.45 ± 0.60	0.20 to 0.75	0.068
	VAS	RE	18.6 ± 17.8	10.5 to 26.7	6.4 ± 9.8	2.0 to 10.9	0.021
1 day	VPS	RE	0.81 ± 0.68	0.51 to 1.11	0.45 ± 0.60	0.18 to 0.72	0.065
		MO	2.14 ± 0.91	1.73 to 2.56	1.62 ± 0.92	1.20 to 2.04	0.051
	VAS	RE	13.8 ± 13.9	7.7 to 19.9	8.6 ± 12.3	3.2 to 14.0	0.21
		MO	45.9 ± 21.5	36.2 to 55.7	31.7 ± 17.6	23.6 to 39.7	0.052
2 days	VPS	RE	0.70 ± 0.66	0.41 to 0.99	0.15 ± 0.37	−0.01 to 0.31	0.017
		MO	1.57 ± 0.81	1.20 to 1.94	1.52 ± 0.87	1.13 to 1.92	0.899
	VAS	RE	12.8 ± 13.7	6.8 to 18.8	3.5 ± 8.7	−0.3 to 7.2	0.057
		MO	36.0 ± 20.0	26.8 to 45.1	29.5 ± 22.4	19.3 to 39.7	0.332
3 days	VPS	RE	0.50 ± 0.51	0.28 to 0.72	0.30 ± 0.57	0.05 to 0.55	0.259
		MO	1.57 ± 0.93	1.15 to 1.99	1.33 ± 0.80	0.97 to 1.70	0.415
	VAS	RE	8.1 ± 12.1	2.8 to 13.4	5.3 ± 11.1	0.5 to 10.1	0.54
		MO	32.6 ± 22.1	22.6 to 42.7	27.9 ± 19.4	19.0 to 36.7	0.597
1 week	VPS	RE	0.65 ± 0.59	0.39 to 0.91	0.70 ± 0.92	0.30 to 1.10	0.833
		MO	1.48 ± 0.60	1.20 to 1.75	1.19 ± 0.75	0.85 to 1.53	0.225
	VAS	RE	9.4 ± 11.6	4.3 to 14.5	5.8 ± 9.9	1.5 to 10.1	0.328
		MO	26.7 ± 16.2	19.3 to 34.1	19.8 ± 15.7	12.6 to 26.9	0.24
4 weeks	VPS	RE	0.59 ± 0.62	0.32 to 0.86	0.44 ± 0.62	0.17 to 0.71	0.581
		MO	1.24 ± 1.00	0.79 to 1.69	0.86 ± 0.73	0.53 to 1.19	0.233
	VAS	...	...	...	...	...	...
8 weeks	VPS	RE	0.35 ± 0.49	0.14 to 0.56	0.19 ± 0.40	0.02 to 0.36	0.423
		MO	1.10 ± 1.04	0.68 to 1.71	0.48 ± 0.60	0.20 to 0.75	0.048
	VAS	RE	7.1 ± 11.3	2.1 to 12.1	3.8 ± 8.1	0.3 to 7.2	0.188
		MO	22.1 ± 25.0	10.8 to 33.5	8.1 ± 12.1	2.6 to 13.6	0.041
6 months	VPS	RE	0.21 ± 0.42	0.03 to 0.39	0.11 ± 0.31	−0.02 to 0.24	0.432
		MO	0.90 ± 1.18	0.37 to 1.44	0.38 ± 0.67	0.08 to 0.69	0.237
	VAS	RE	6.3 ± 11.5	1.3 to 11.3	2.2 ± 6.5	−0.6 to 5.0	0.291
		MO	19.3 ± 27.2	6.9 to 31.7	7.6 ± 16.1	0.3 to 14.9	0.281

[a] Wilcoxon ranked sign test.

CI = confidence interval; MO = movement on the ward or at home; RE = rest; VAS = visual analog scale; VPS = verbal pain scale; SD = standard deviation.

We believe that because our patients visited a pain clinic, we could make more precise clinical examination, find more exactly the neuropathic-type pain areas, and test numbness compared with the studies of Yang and colleagues [14] and Ju and colleagues [18] because they interviewed patients by telephone.

One drawback of our study was that we did not have very many patients, but we think there were enough patients to show clinically significant findings. Pain scores tended to be higher in the cryoanalgesia group at many of the other evaluation times, but scores were significantly different only at three points (Table 3). Perhaps with a sufficiently large number of patients, there would also have been statistically significant differences at other times.

Tiippana and colleagues [4] showed that the incidence of chronic postthoracotomy pain was 11% to 12% when acute pain was controlled by thoracic epidural analgesia. Bong and colleagues [21] reported that thoracic epidural analgesia reduced the severity of acute pain but had no effect on the incidence of chronic pain. Others have reported much higher incidences of postthoracotomy pain (40% to 80%) without thoracic epidural analgesia [1, 2, 18, 21, 22]. In the present study only 2 of 40 patients had significant pain (moderate) in normal daily activities 6 months after the operation. This is very low incidence of clinically significant chronic pain and supports the theory that thoracic epidural analgesia or the drilled holes technique in adjacent ribs during the closure of chest, or both, can decrease the risk of chronic postthoracotomy pain.

Recovery of the intercostal nerves after cryoanalgesia has been reported to occur after 1 month [15]. In the present study, numbness was still present around operation area after 6 months in 14 of 40 patients, indicating that the operation itself can cause damage to the intercostal nerves. Cryotherapy has been used as an analgesic method in humans, but it has also been used as a neuropathic pain model in animals [23, 24]. These findings support the role of cryotherapy in increasing neuropathic-type pain after thoracotomy.

In conclusion, the findings of the present study are in accordance with previous studies where intercostal nerve cryoanalgesia increased the risk of long-term and neuropathic-type pain after thoracotomy. Furthermore, thoracic epidural analgesia combined with the drilled holes technique can decrease the risk of chronic postthoracotomy pain. Cryoanalgesia is not recommended for the treatment of postthoracotomy pain.

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