Intraoperative Intercostal Nerve Cryoanalgesia Improves Pain Control After Descending and Thoracoabdominal Aortic Aneurysm Repairs

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Background. **We reviewed the efficacy of intraoperative intercostal nerve cryoanalgesia for pain control in patients undergoing descending and thoracoabdominal aortic aneurysm repairs.**

Methods. **During 2013 and 2017, 241 patients underwent descending and thoracoabdominal aortic aneurysm repair. Of those, 38 patients were treated with intraoperative cryoanalgesia to the intercostal nerves at the level of 4th to 10th under electromyography guidance and were compared with patients who did not receive cryoanalgesia. Both groups received multilevel paravertebral block and local infiltration with liposomal bupivacaine. Numerical pain scale scores and amount of opioid usage in morphine milligram equivalences on the first to fourth and eighth postoperative days were collected. We excluded patients from the study who were extubated after the third postoperative day or who were reintubated.**

Results. **One hundred twenty-six patients met the inclusion criteria: 28 in the cryoanalgesia group and 98 in the control group. Preoperative patient demographics were similar in both groups, except for more frequent chronic dissection in patients with cryoanalgesia (93% vs 65%, $P = .004$). Postoperative major complications, length of stay, and discharge to home were not significantly different in either group. However, median ventilation hours were significantly shorter in the cryoanalgesia group (5 vs 12 hours, $P < .001$). Opioid use was significantly less in the cryoanalgesia group after postoperative day 4. Indexed morphine milligram equivalences, adjusted with body surface area, and numerical pain scale scores were significantly lower in the cryoanalgesia group throughout the postoperative course.**

Conclusions. **Intercostal nerve cryoanalgesia under electromyography guidance provided improved pain control and reduced narcotic use after descending and thoracoabdominal aortic aneurysm repairs compared with those who only received paravertebral block.**

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Pain is an expected byproduct after any surgical procedure. Successful postoperative pain management allows early patient mobilization and may contribute to shorter hospital length of stay and less healthcare costs. However, uncontrolled acute pain not only leads to poor short-term outcomes but may also lead to chronic pain[1,2] and persistent opioid use.[3]

A number of drugs are available for postoperative pain control, such as opioids, nonsteroidal antiinflammatory drugs (NSAIDs), central desensitizing analgesics (eg, gabapentin), local anesthetic agents, and combined regimens and protocols.[4] Opioid use is the backbone of postoperative pain control but comes with risks. Side effects of opioid use, including respiratory, central nervous system, and bowel function depression, are not uncommon. Acetaminophen is generally safe, but high doses can cause hepatic toxicity and may not be sufficient to control strong pains. NSAIDs need to be used with caution because of renal toxicity and bleeding complications.

Pain control after descending thoracic and thoracoabdominal aortic repairs carries a challenge because

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of extensive incisions. Epidural analgesia is the standard method for postthoracotomy pain control. However, it is not available for descending thoracic and thoracoabdominal aneurysm aortic aneurysm repairs because cerebrospinal fluid drainage is performed during the perioperative period for spinal cord protection, and its common side effect of hypotension is also not ideal during perioperative care, because it may trigger spinal cord injuries.[5] Intraoperative multilevel paravertebral block with a liposomal bupivacaine injection has been reported to be as effective as epidural anesthesia after thoracotomy,[6,7] but the effect of liposomal bupivacaine lasts only 48 to 72 hours.

CryoICE (AtriCure, Inc, Mason, OH) nitrous oxide cryoablation probe is a malleable device. Its original indication was cryoablation of the heart for arrhythmias and was approved for intercostal nerve cryoanalgesia by the US Food and Drug Administration in 2015. Cryoanalgesia induces Wallerian degeneration of the axons within the intercostal nerve with expected temporary pain relief for more than 30 days.[8,9] We hypothesized that intraoperative multilevel cryoablagesia block would provide better postoperative outcomes because of extended pain control after descending thoracic and thoracoabdominal aortic aneurysm repair. Thus, in the current study we reviewed the intraoperative and postoperative outcomes in patients undergoing descending thoracic and thoracoabdominal aortic aneurysm repairs with and without cryoanalgesia to evaluate for its efficacy and feasibility.

Patients and Methods

The Committee for Protection of Human Subjects, the local institutional review board, approved this study. During 2013 and 2017, 241 patients underwent descending or thoracoabdominal aortic aneurysm repair, and 38 patients were treated with intraoperative multilevel cryoanalgesia to intercostal nerves using CryoICE CRYO2 cryoablation probe (AtriCure) (Supplemental Figure 1). Intraoperative cryoanalgesia was applied to the 4th to 8th intercostal nerve in patients undergoing descending thoracic aortic aneurysm repair and 4th to 10th in patients receiving thoracoabdominal aortic aneurysm repairs, accordingly to the extent of incisions (Figure 1). These patients were compared with control patients who did not receive intraoperative cryoanalgesia. Both patient groups received liposomal bupivacaine paravertebral blocks from the fourth to eighth intercostal spaces, 2 intercostal spaces above and below the pleural cavity entry through the sixth intercostal space.

Numerical pain scores consisting of an 11-point scale (0-10 points)[10] were obtained at 7 a.m. and 7 p.m. ($\pm$2 hours) on the first to fourth and eighth postoperative days and then averaged for the day. Total amount of opioid usage was also collected on the first to fourth and eighth postoperative days. The amount of opioids was converted to morphine milligram equivalence (MME) using a conversion equation.[11] Perioperative data were retrospectively collected from the research database and patient chart.

Surgical Technique

Our operative technique for open surgical repair of the descending and thoracoabdominal aortic pathologies have been previously reported.[12] After induction of general anesthesia the patient was intubated with a double-lumen endotracheal tube and placed in the right lateral decubitus position. Thoracoabdominal incisions were used in all descending and thoracoabdominal aortic aneurysm repairs. The incision started from the back, between the scapula and thoracic spine, which extends near or down to the naval, depending on the extent of the aneurysm repairs. The sixth intercostal space was entered to expose the thoracic aorta, and the retroperitoneal space was entered to expose the thoracoabdominal aorta after partially separating the left diaphragm. After routine entrance to the chest, 10 mL diluted liposomal bupivacaine (20 mL liposomal bupivacaine with 50 mL normal saline, total of 70 mL) was injected to perform paravertebral block to each intercostal space from the fourth to eighth, and the remaining 20 mL was given at skin incisions and chest tube insertion sites at the completion of the procedure. Chest tubes were placed before chest closure. We routinely use 3 silicone, Argyle type, thoracic chest tubes (2 straight tubes in the anterior and posterior left pleural cavity and 1 angled tube on the diaphragm).

Cryoanalgesia with the CryoICE CRYO2 cryoablation probe (–60°C, 120 seconds) was applied to the 4th to 8th or 10th intercostal nerves, depending on the caudal extent of the incision. This was performed after obtaining hemostasis. Electromyography was used during cryoanalgesia to accurately locate the intercostal nerves and ensure the completeness of the cryoablation nerve block by confirming the disappearance of contractions of the corresponding intercostal nerve (Figure 1). If intercostal muscle contraction was present after the procedure, additional cryoablation was performed. Thus, an additional 20 to 25 minutes were required for the procedure when performing intercostal nerve cryoanalgesia.

Postoperative Management

Postoperative pain regimens were at the discretion of caretaking intensivists, surgeons, nurse practitioners, and physician assistants, including as-needed pain medications consisting of narcotics and nonnarcotics. Nonopiates, such as acetaminophens (given intravenously for the first 24 hours and then switched to oral) and gabapentinoids were usually prescribed as scheduled pain medications. NSAIDs were not routinely used because of concern for renal injuries. Patient-controlled analgesia was not uniformly prescribed during the early period of the study but was ordered to every patient after 2015 as part of the postoperative management protocol. It was the patient's decision to choose patient-controlled analgesia or not. The patient-controlled analgesia drug was hydromorphone, and dosing followed our hospital protocol: 0.2-mg demand dose, 10-minute lockout, 2 mg/hour maximum, and 0.4-mg rescue dose.

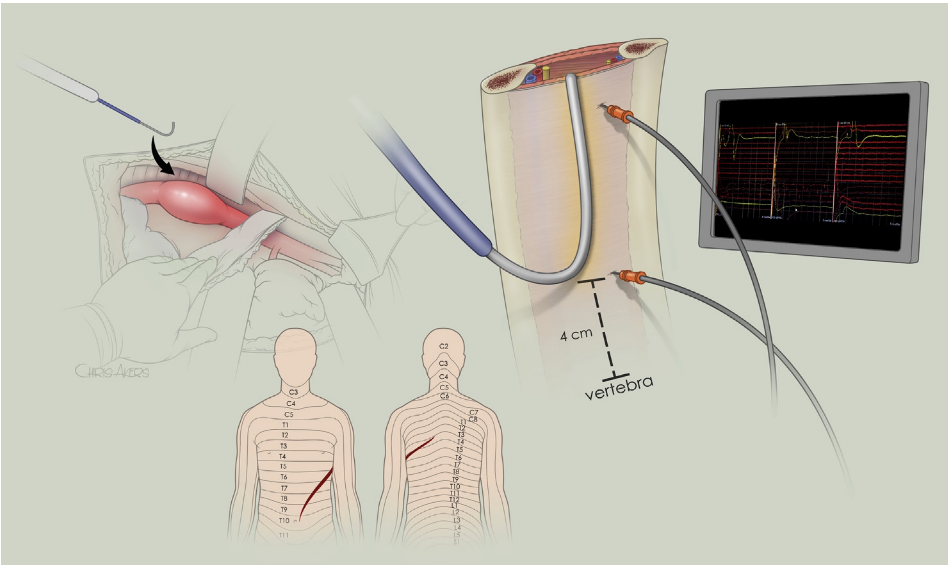

Figure 1. *Intraoperative intercostal nerve cryoanalgesia. The cryoablation probe was applied after locating the nerve with electromyography, because sometimes the nerves are not easily visible. The cryoablation probe was applied to the 4th to 8th or 10th intercostal nerves, depending on the caudal extent of the incision. Cryoanalgesia was repeated until the contraction of corresponding intercostal muscles disappeared.*

Statistical Methods

Continuous data are reported as mean $\pm$ 1 SD for normally distributed data or median plus interquartile range (IQR) for skewed data. Categorical variables are expressed as number and percentages. Univariate data analyses were conducted by contingency table methods for categorical variables and by unpaired *t* test or Wilcoxon rank-sum test for continuous variables, depending on the distribution of the data. Multiple general linear model analysis was used to adjust for preoperative narcotics use on the numerical pain scale.

The main analysis was focused on comparing the postoperative pain scores and MME between the cryoanalgesia group and the control group; thus, we excluded patients who were extubated after the third postoperative day or who were reintubated, because pain scales in these patients were difficult to evaluate due to sedation and intubation and the amount of narcotics use would be significantly increased while intubated regardless of pain levels. If a patient was discharged before postoperative day 8, data from the day of discharge were used for numerical pain scale and MMEs. The MMEs were further adjusted by the body surface area (m^2) for indexed MME.

A subanalysis was conducted in all patients to further evaluate the safety and efficacy of the cryoanalgesia by comparing postoperative outcomes. All data were analyzed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Main Analysis

Preoperative patient characteristics are summarized in Table 1. One hundred twenty-six patients met the inclusion criteria (extubated within 2 postoperative days without reintubation): 28 patients in the cryoanalgesia group and 98 patients in the control group. There was significantly more chronic aortic dissection in the cryoanalgesia group compared with the control group. Median body weight was significantly higher in the cryoanalgesia group. Patients in the cryoanalgesia group had significantly more frequent chronic aortic dissection and prior proximal aortic repairs. Other preoperative demographics were similar in the 2 groups, including median age, sex, preoperative narcotics use, and comorbidities.

Intraoperative and postoperative outcomes are shown in Table 2. The amount of intraoperative transfusions was similar in both groups. Postoperative median ventilation hours were significantly shorter in the cryoanalgesia group compared with the control group. Time to chest tube removal was similar in both groups. Incidence of other major postoperative complications were similar in both groups.

The numerical pain scale scores were significantly less in the cryoanalgesia group throughout the postoperative course (day 1: 1 [0-2.3] vs 4.5 [2.5-6.5], $P < .001$; day 2: 0.5 [0-1.3] vs 4 [2-5.5], $P < .001$; day 3: 3 [0.3-4.3] vs 4 [2-5], $P < .001$; day 4: 0 [0-2] vs 4 [1-6], $P < .001$; day 8: 3 [0-4] vs 4 [0-6], $P = .018$) (Figure 2). Adjusting the numerical pain score by multiple general linear model analysis with preoperative narcotic by cryoanalgesia treatment interaction did not affect our results.

Postoperative opioid usage (MMEs) was significantly less in the cryoanalgesia group after postoperative day 4 (day 1: 57.3 [15-93.5] vs 72 [36-120], $P = .122$; day 2: 48.1 [21.9-91.7] vs 48 [20-96], $P = .847$; day 3: 30 [5-53.1] vs 47.5 [20-86.8], $P = .058$; day 4: 15 [5-37] vs 35 [15-60.5], $P = .006$; day 8: 0 [0-11.3] vs 32.5 [14-63], $P < .001$) (Figure 3). When these values were adjusted by body surface area (m^2) (ie, indexed MME), the cryoanalgesia group had significantly less opioid usage throughout the postoperative course (day 1: 27.5 [7.0-93.5] vs 33.5 [18.5-54.3], $P = .001$; day 2: 21.9 [10.9-45.2] vs 25.7 [11.9-44.6], $P = .004$;

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Table 1. Preoperative Patient Demographics

Patient Variables	Cryoanalgesia (n = 28)	Control (n = 98)	*P*
Age, y	61 (44-70)	59 (45-78)	.456
Male	21 (75)	63 (66)	.378
Body weight, kg	93 (77-110)	83 (70-96)	.036
Estimated glomerular filtration rate (Cockcroft-Gault equation), mL/min	114 (77-127)	93 (63-120)	.083
Coronary artery disease	4 (16)	19 (20)	.781
Chronic obstructive pulmonary disease	7 (25)	30 (32)	.499
History of stroke	1 (4)	8 (8)	.683
Marfan syndrome	4 (14)	13 (14)	1.000
Prior proximal aortic repair[a]	13 (46)	25 (26)	.048
Prior distal aortic repair[b]	4 (14)	13 (14)	1.000
Descending aortic aneurysm	12 (43)	40 (43)	.082
Thoracoabdominal aortic aneurysm			
Extent I	8 (29)	16 (16)	
Extent II	4 (14)	5 (5)	
Extent III	1 (4)	11 (12)	
Extent IV	2 (7)	20 (21)	
Extent V	1 (4)	6 (6)	
Acute aortic dissection	3 (10)[c]	6 (6)	.424
Chronic aortic dissection	26 (93)[c]	62 (65)	.004
Preoperative narcotics use	6 (5)[d]	10 (8)[d]	.111

[a]Proximal aortic repair includes ascending or aortic arch repair; [b]Distal aortic repair includes descending thoracic and thoracoabdominal aortic repair; [c]One case was acute on chronic dissection; [d]Data were unavailable in 2 patients in the cryoanalgesia group and in 4 patients in the control group.

Continuous variables are median (interquartile range); categorical variables are number (%).

day 3: 14.4 [2.9-25.8] vs 22.7 [9.2-45.0], $P < .001$; day 4: 7.0 [2.1-17.2] vs 16.4 [8.5-31.8], $P < .001$; day 8: 0 [0-5.5] vs 16.5 [6.9-32.1], $P < .001$). On postoperative day 4, 6 patients (21%) in the cryoanalgesia group and 12 (12%) in the control group did not use any opioids ($P = .230$). On postoperative day 8, 15 patients (54%) in the cryoanalgesia group and 16 (16%) in the control group were opioid-free ($P < .001$). Gabapentinoid and acetaminophen usages were similar in both groups (cryoanalgesia vs control: gabapentinoid, 25% vs 21%, $P = .688$; acetaminophen, 61% vs 41%, $P = .062$). Only 2 of 98 patients (2%) in the control group used NSAIDS.

Subanalysis

When all patients were included in the study, preoperative characteristics were similar in the 2 groups, except for more frequent chronic aortic dissection in the cryoanalgesia group (Supplemental Table 1). Intraoperative and postoperative outcomes are summarized in Supplemental Table 2. The cryoanalgesia group received less intraoperative blood transfusion. Mechanical ventilation hours were significantly shorter in the cryoanalgesia group compared with the control group (7 hours vs 22 hours, $P < .001$). However, incidence of pneumonia and atelectasis were similar between the

Table 2. Intraoperative and Postoperative Outcomes

Patient Variables	Cryoanalgesia (n = 28)	Control (n = 98)	*P*
Cell saver, unit	31 (20-42)	27 (17-40)	.216
Packed red blood cells, unit	1 (0-3)	2 (0-3)	.557
Fresh frozen plasma, unit	0 (0-2)	1 (0-4)	.342
Chest tube usage, day	5 (3-7)	4 (3-6)	.630
Mechanical ventilation, h	5 (3-15)	12 (4-21)	.016
Atelectasis (requiring bronchoscopy)	0 (0)	5 (5)	.588
Pneumonia	1 (4)	0 (0)	.228
Atrial fibrillation	6 (21)	39 (32)	.288
Renal failure	4 (14)	8 (8)	.267
Gastrointestinal complications (ileus and bleeding)	1 (4)	9 (9)	.456
Length of stay, day	11 (8-14)	12 (8-17)	.148
Discharge to home	26 (93)	80 (84)	.355

Continuous variables are median (interquartile range); categorical variables are number (%).

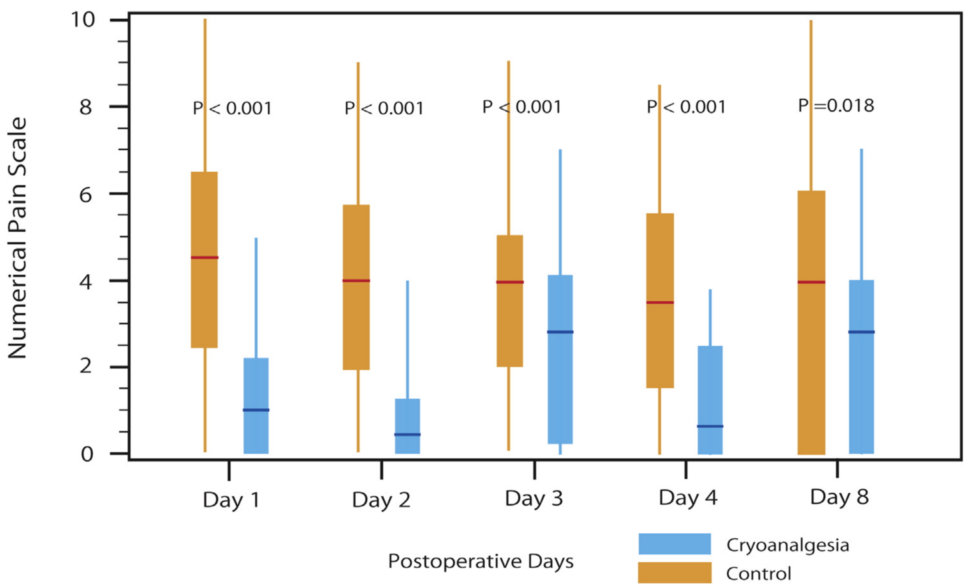

Figure 2. Numerical pain scale scores consisting of an 11-point scale (0-10 points) were obtained at 7 a.m. and 7 p.m. (±2 hours) on the first to fourth and eighth postoperative days and averaged for the day. Note that the cryoanalgesia group had significantly lower scores compared with the control group throughout the postoperative course.

2 groups. Gastrointestinal complications (ileus, bleeding, etc) were significantly less in the cryoanalgesia group (8% vs 30%, $P = .004$). Patients who had cryoanalgesia were more frequently discharged to home when compared with the control group (76% vs 57%, $P = .023$).

Comment

In 1974 Nelson and colleagues[8] described cryoanalgesia using a cryosurgery probe to prevent postthoracotomy pain. In their report of 38 patients, they monitored patients up to 24 months and had no neuromas or neuritis formation, and the effect of the procedure lasted 6 to 8 months. Sensation returned to near normal by 12 months. Ju and colleagues[13] also reported that pain control after intercostal cryoanalgesia (n = 53) and epidural analgesia (n = 54) were equivalent in the acute phase. Similarly we demonstrated that intraoperative intercostal nerve cryoanalgesia provided sufficient relief in patients undergoing descending thoracic and thoracoabdominal aortic aneurysms without procedure-related complications. One of the limitations of local anesthetic infiltration is that the effect may only last for hours to a few days. On the contrary cryoanalgesia nerve block may be effective for more than 1 month. As hypothesized we also showed that cryoanalgesia provided superior pain control over paravertebral nerve blocks with local liposomal bupivacaine injection throughout the postoperative course, with reduced use of opioids.

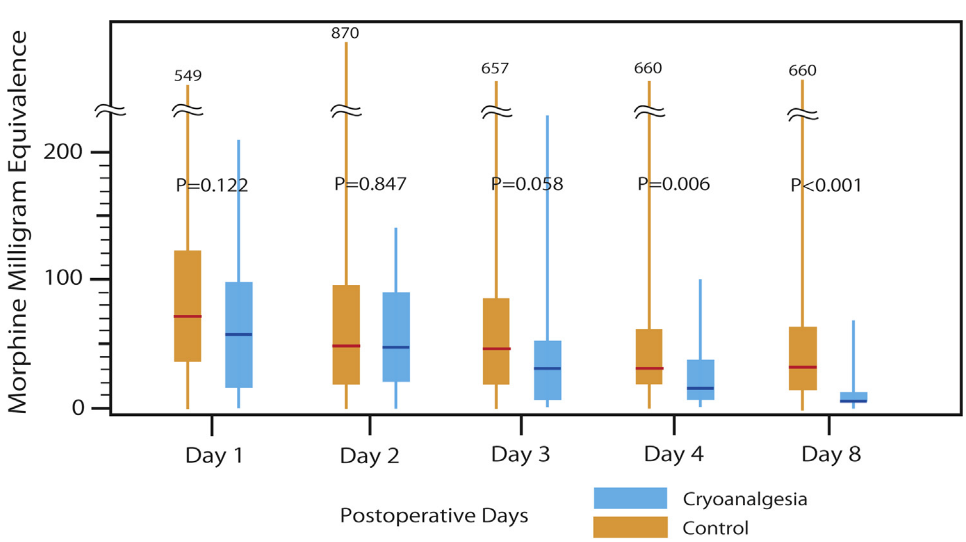

Figure 3. Total amount of opioid use in morphine milligram equivalence was collected on the first to fourth and eighth postoperative days. The amount of opioids was converted to morphine milligram equivalence using a conversion equation.[11] Note that the amount of opioid use was significantly less in the cryoanalgesia group compared with the control group after postoperative day 4.

The use of electromyography to confirm the completeness of the cryoanalgesia has never been reported previously. Identifying the intercostal nerves from the intrathoracic space was not as easy as expected, based on our experience: Not all the intercostal nerves were visible, especially in patients with obesity. Of note in the last case in which we performed intercostal nerve cryoanalgesia, we mislocated 2 of 7 intercostal nerves without the guide of electromyography and 1 of 7 cryoanalgesia was incomplete and required re-cryoablation. Thus, we recommend the adjunct of electromyography during the procedure for the accurate detection of the nerves and effective blocks.

Poor pain management may cause sequelae of undesired postoperative events, such as deep vein thrombosis, cardiac ischemia, and insomnia. Especially after thoracotomies, postoperative pain leads to pulmonary complications, such as atelectasis and infections.[2] We were unable to detect a significant difference in postoperative outcomes with and without cryoanalgesia other than mechanical ventilation hours in the main cohort. This may be partly due to the small sample size and exclusion of patients who were intubated for more than 3 days or had reintubation, which were patients with definite pulmonary complications (we excluded 10 patients from the cryoanalgesia cohort and 105 patients from the control group). However, when all patients were included to the analysis (ie, subanalysis in the current study), we found less pulmonary complications (a composite of prolonged intubation, atelectasis, pneumonia, and reintubation) with the use of cryoanalgesia. Nonetheless although the use of cryoanalgesia added extra minutes to the operative procedure, up to 25 minutes, it did not increase postoperative complications in the main and subanalyses.

The economic load of chronic pain that develops from an acute episode of pain in a 30-year-old patient may be as much as $1 million over a lifetime.[1] Persistent pain is experienced in 50% to 60% of patients who undergo thoracotomy,[2,14] and new persistent opioid usage is reported in 14%.[3] In the current study the amount of narcotic use was significantly less with application of intercostal nerve cryoanalgesia after postoperative day 4, and by postoperative day 8 more than half of the patients in the cryoanalgesia group did not require opioids for pain control and 16% in the control group were opioid-free. Thus, cryoanalgesia may potentially reduce future opioid abuse and save healthcare costs in patients undergoing descending thoracic and thoracoabdominal aortic surgery.

This study should be viewed with limitations. First, this is a retrospective, nonrandomized, single-center study. The retrospective design of the current analysis restricts the generalizability of our findings. Second, we had a limited sample size, especially in the cryoanalgesia group, and some of our results may not have significant differences because of power limitations. Third, because most patients were prescribed medications outside our institution, the prescription data for pain medications were not available for the study, which did not allow us to perform a cost-effectiveness analysis. Last, allodynia-like pain, which is pain induced by nonpainful stimuli, such as gentle touching by hand or clothing, has been reported after 12 months.[13] This type of pain could become chronic and very bothersome once it happens. Our cryoanalgesia group has been followed for a median of 529 days (IQR, 268-637) and we have not seen these complications. Further follow-up is mandatory to confirm the safety and cost-effectiveness of intercostal nerve cryoanalgesia.

In conclusion, intraoperative intercostal nerve cryoanalgesia under electromyography guidance provided superior acute pain control after descending thoracic and thoracoabdominal aortic repairs compared with multilevel paravertebral block by local liposomal bupivacaine injection. It also contributed to a decreased requirement for opioid use.

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