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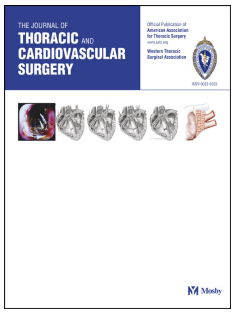

A Randomized Study of Cryoablation of Intercostal Nerves in Patients Undergoing Minimally Invasive Thoracic Surgery

Benny Weksler, MD, Conor Maxwell, DO, Lauren Drake, DO, Lawrence Crist, DO, Kara Specht, PA-C, Pamela Kuchta, CRNP, Kurt DeHaven, CRNP, Isabella Weksler, BA, Brent A. Williams, PhD, Hiran C. Fernando, MD

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Division of Thoracic and Esophageal Surgery, Cardiovascular Institute, Allegheny Health Network, Pittsburgh, PA

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Corresponding author:

Benny Weksler, MBA, MD
Cardiovascular Institute
Allegheny General Hospital
320 E. North Ave
14th Fl South Tower
Pittsburgh, PA 15212
Email: benny.weksler@ahn.org

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Glossary of abbreviations:

MITS – Minimally invasive thoracic surgery

MME – Morphine milligrams equivalent

IS – Incentive spirometry

POD – postoperative day

PCA – Patient controlled analgesia

LANSS – Leeds assessment of neuropathy symptoms and signs

IQR – Interquartile range

LOS – Length of stay

Keywords:

Minimally Invasive Thoracic Surgery

Pain management

Cryo-analgesia

Intercostal nerve block

Central Message:

In a randomized study, cryo-analgesia did not decrease pain or narcotic consumption, but it did increase neuropathic pain.

Perspective Statement:

Cryo-analgesia is an attractive method for decreasing postoperative pain, but it has not been tested in minimally invasive thoracic surgery (MITS). In a randomized study of patients undergoing MITS, we examined the standard of care with and without cryo-analgesia and found no difference in pain or narcotic consumption. Cryo-analgesia caused more postoperative neuropathic pain.

Central picture:

Postoperative morphine milligram equivalent (MME)

Abstract

Objectives: Minimally invasive thoracic surgery can cause significant pain, and optimizing pain control after surgery is highly desirable. We examined pain control after intercostal nerve block with or without cryo-ablation of the intercostal nerves.

Methods: This was a randomized study (NCT05348447) of adults scheduled for a minimally invasive thoracic procedure. Each intercostal space near the incision site was injected with lidocaine and bupivacaine with epinephrine (standard-of-care). The cryo-analgesia group also had 5-6 intercostal nerves ablated. The primary outcome was the amount of narcotics (in morphine mg equivalent, MME) taken during the postoperative hospital stay and the first two weeks post-discharge. Secondary outcomes were incentive spirometry (IS) volume and pain scores in the hospital and pain and neuropathy scores at two weeks.

Results: Our final cohort contained 103 patients (52 standard-of-care; 51 cryo-analgesia). There were no differences between the treatment groups in MMEs administered during the hospital stay (44.9 mg standard of care vs. 38.4 mg cryo-analgesia), total MME at two weeks (108.8 vs. 95.2 mg), or pain assessed on postoperative day (POD) 1 (3.8 and 3.3), POD2 (2 and 3.5), or two weeks (2 and 3.5). The decrease in IS in the postoperative period was not significantly different between the two groups. Patients in the cryo-analgesia group had higher neuropathy scores (8 vs. 13, p=0.019) two weeks after surgery.

Conclusions: In this randomized study, cryo-analgesia did not decrease postoperative pain or narcotic requirements. Cryo-analgesia increased neuropathic pain two weeks after surgery.

Introduction

Minimally invasive thoracic surgery is associated with less narcotic use as compared with open thoracotomy, but it is still associated with significant pain. [1] Over 10% of patients who undergo minimally invasive surgery have symptoms of chronic pain. [2] In the VIOLET trial,[3] patients undergoing minimally invasive lobectomy had improved physical function compared to those undergoing thoracotomies. However, close to 60% of patients experienced prolonged incisional pain in the minimally invasive group. There are several strategies for pain management after minimally invasive thoracic surgery, including epidural analgesia, paravertebral block, and intercostal nerve block. Our thoracic surgery group usually relies on intercostal nerve block with bupivacaine and epinephrine. Intercostal nerve block during surgery decreases opioid consumption in the postoperative period and is widely used by thoracic surgeons. [4] Unfortunately, it lasts only 6-8 hours. We previously studied a liposomal bupivacaine formulation, which allowed continuous steady release of the drug for up to 96 hours. We did not see any benefits of liposomal bupivacaine in a randomized study of patients undergoing minimally invasive thoracic surgery. [5]

Cryo-ablation of intercostal nerves is not new and has been tried since the 1970s in patients undergoing thoracotomy. [6] Applying a cryoprobe to the intercostal nerves causes an axonal injury followed by degeneration that is usually reversible with time. [7] There have been multiple randomized studies comparing cryo-analgesia with epidural analgesia, intravenous analgesia, or bupivacaine nerve block[8-13] in patients undergoing open thoracotomy.[8-13] Benefits of cryo-analgesia have been suggested in studies that did not employ epidural analgesia. Cryo-analgesia also benefits patients undergoing minimally invasive pectus excavatum repair [14] or

minimally invasive cardiac surgery. [15] Our retrospective study showed cryo-analgesia's benefit in patients undergoing minimally invasive thoracic surgery. [16]

No randomized studies have been conducted on using cryo-analgesia in minimally invasive thoracic surgery. The present study examined the effectiveness of adding cryo-analgesia to intercostal nerve blocking with bupivacaine by comparing outcomes in patients undergoing minimally invasive thoracic surgery.

Methods

This was a prospective, randomized study registered in clinicaltrials.gov as NCT05349447. The trial opened in April 2022 and closed in January 2024. The Institutional Review Board of the Allegheny Health Network approved the study (IRB number 2021-238, approved on 11/9/2021), and all patients gave informed consent for the research. Atricure Inc. provided a research grant for this study. The investigators designed the trial and analyzed the results freely, without interference from the funding source.

Patients:

Eligible patients were 18 or older and scheduled for elective minimally invasive thoracic procedures. Procedures included robotic thoracic surgery and video-assisted thoracoscopic surgery (VATS). All robotic procedures were performed by one surgeon (BW), and all thoracoscopic procedures were performed by a different surgeon (HF). Initially, all patients undergoing any minimally invasive thoracic procedure were eligible. One month after the beginning of the trial, we limited enrollment to patients undergoing lung procedures: wedge resection, segmental resection, or lobectomy. Exclusion criteria included emergency or urgent surgery, chronic narcotic use, history of alcohol or drug abuse, diagnosis of fibromyalgia, use of

gabapentin for any reason, liver disease (Child-Pugh score B or C), renal failure requiring dialysis, and inability to understand the study.

Study Design:

Patients were recruited for the trial during their preoperative visit. Randomization was conducted using the envelope method. Forty-eight to 72 hours before surgery, our research coordinators opened the randomization envelope and communicated the group assignment to the surgical team. Patients remained unaware of their group assignment for the duration of the trial.

Patients were randomly assigned to receive either standard of care or standard of care plus cryo-ablation of 5-6 intercostal nerves. All patients received an internal intercostal block from the 2^{nd} intercostal nerve to the 10^{th} intercostal nerve using a mixture of 1:1 bupivacaine (0.5%) with epinephrine (1:200,000) and lidocaine (2%). Each port incision was infiltrated with 3-4 ml, and the access incision was infiltrated with up to 10 ml of the solution. In the study patients, cryoablation was performed after the intercostal block. Cryoablation was achieved using the Cryos-L CryoSphere probe and the CryoICE system (AtriCure, Mason, OH). The system delivers nitrous oxide to the probe's tip, cooling it to -80^{o}C. Five or six intercostal nerves were treated for 2 minutes each. The nerves above and below the intercostal space where the ports were located were always included in the 5-6 nerves ablated.

Pain Management Strategy:

Approximately 2 hours before surgery, all patients received 200 mg celecoxib, 300 mg gabapentin, 650 mg acetaminophen, and 50 mg tramadol. During surgery, bupivacaine with epinephrine and lidocaine was injected into the skin before all incisions. After entering the

pleural cavity, 1-2 ml of the bupivacaine-lidocaine solution was injected into each intercostal space, starting with the second or third spaces. After surgery, all patients received patient-controlled analgesia (PCA) preferentially with hydromorphone. Occasionally, morphine or fentanyl PCA was used. Patients received PCA until the chest tube was removed, but only for up to three days. After the PCA was discontinued, patients were transitioned to 50-100 mg tramadol every 6 hours. Breakthrough pain was treated with oxycodone. Patients also received ketorolac and acetaminophen in the postoperative period.

Surgical Procedure:

Robotic procedures were performed as previously described, with four working ports and one assistant port. [5] VATS was performed primarily using the uniportal technique [17], but an additional port was added in a few instances. Chest tubes were managed using a digital chest drainage system (Thopaz+, Medela AG, Baar, Switzerland). We removed the chest tube when drainage decreased to <400 ml of fluid per 24 hours and less than 20 ml/minute of air for 4 hours or more.

Anesthesia Management:

Each attending anesthesiologist could choose the anesthesia technique administered during the trial.

Study End Points and Assessment:

The primary endpoint was the amount of narcotics consumed by patients in the hospital and during the period from surgery to the first postoperative visit (usually two weeks after discharge). The total amount was converted to morphine equivalent dose (MED) in morphine milligrams equivalents (MME). The total narcotics administered included any narcotics received

in the post-anesthesia care unit, PCA, any narcotics for breakthrough pain, all oral narcotics received in the hospital, and oral narcotics consumed as an outpatient. The conversion factors to MME used were 6.7 for hydromorphone, 3 for intravenous morphine, 0.1 for fentanyl, 0.1 for oral tramadol, and 1.5 for oxycodone. All patients returned their medication bottles during the first postoperative visit, and our staff counted the remaining pills to determine each patient's total outpatient narcotic consumption.

Secondary endpoints included pain assessed using a visual analog scale (VAS) and lung function as determined using an incentive spirometer. The VAS is an easy-to-use and reproducible method to assess pain. [18] Patients estimated their pain level using an 11-number scale varying from 0 (no pain) to 10 (unbearable pain). Nurses recorded the pain score multiple times per shift (usually every two hours while the patient was awake). We used the average of all pain scores taken over 24 hours. The Incentive spirometer is an easy-to-use device that measures lung function well and can evaluate pulmonary recovery after surgery. [19] A baseline incentive spirometry measurement was taken at the preoperative visit, and starting on postoperative day (POD) 1, the best of 3 incentive spirometry attempts each morning was documented. Another secondary endpoint of the study was postoperative neuropathy two weeks 3, 6, and 12 months after surgery. This evaluation used the Leeds Assessment of Neuropathy Symptoms and Signs (LANSS). [20] LANSS assigns a score ranging from 0 to 20 points, and a score equal to or above 12 suggests pain of neuropathic origin. (Appendix 1) Numbness is given 3 points on the scale. The present report addresses the early postoperative period and does not include the 3, 6, and 12-month neuropathy scores, which will be reported separately.

Statistical Analysis:

Sample size:

Using the mean MME of 37 reported in our previous trial,[5] the current trial was designed with alpha equal to 0.05 and a 90% power to detect an expected minimum of 30% reduction in the total MME used. A sample size of 92 patients was needed, and we planned to recruit 100 patients for the trial. During the trial, seven patients did not complete all the data points for the first postoperative visit, including variables such as outpatient MME. To account for these missing variables, we received permission from our IRB to increase the number of patients recruited to 110.

Data analysis:

Continuous variables are reported as median and interquartile range (IQR, 25th-75th percentile). Categorical variables are reported as frequencies and percentages. Mann-Whitney U test was used to compare continuous variables, and the Chi-Square test was used to compare categorical variables. Significance was set at $p<0.05$, and all comparisons were two-tailed.

Results

We recruited 110 patients for the study. Before randomization, three patients decided to withdraw from the study. After randomization but before treatment, four patients (2 randomized to standard of care and 2 randomized to cryo-analgesia) were excluded because two decided not to pursue surgery, and 2 withdrew consent for the study. Our final cohort contained 103 patients (Figure 1). The study groups were similar in age, sex, body mass index, and preoperative lung function (Table 1). Most patients (76.7%) had robotic surgery, and 88.3% had an anatomic lung resection. One patient in the cryo-analgesia group had a conversion to

228 open surgery for bleeding during a VATS lobectomy and was not excluded from the analysis.
229 There were no conversions in patients undergoing robotic surgery.

230 The median hospital length of stay (LOS) was two days and was similar between the two
231 groups (Table 2). There were no differences in pulmonary complications or prolonged air leaks
232 between patients who received standard of care and patients who underwent cryo-analgesia.
233 Patients who received cryo-analgesia had higher incentive spirometry measurements on POD1
234 (1375 vs. 750 mL, $p<0.001$) and POD2 (1500 vs. 1000 mL, $p=0.012$) as compared with patients in
235 the standard-of-care group. However, the difference between the preoperative and
236 postoperative incentive spirometry was not statistically significant on postoperative days 1, 2,
237 and 3 (Table 2). There were no differences in the average pain VAS scores on POD 0, 1, 2, or 3
238 between the study groups (Table 2). The median pain score on POD1 was 3.6 and slowly
239 decreased to 2.2 on POD3. Narcotic use in the hospital, as measured by total MME, was also
240 similar between the two groups (44.9 mg vs 38.4 mg, $p=0.468$). We also looked at narcotics use
241 during the surgical procedure. Patients in the SOC group received 15 mg (10-20), and the CRYO
242 group also received 15 mg (10-20) MME, $p=0.903$. Ketorolac use in the hospital was also similar
243 between the two groups. The SOC group received 75 mg (45-120), while the CRYO group
244 received 75 mg (60-120), $p=0.60$.

245 Most patients were seen in the clinic for their first postoperative visit approximately two
246 weeks after surgery (Table 3). There was a trend towards less out-patient MME use in the
247 standard-of-care group (22.5 mg vs 32.5 mg, $p=0.117$). Still, no significant differences were
248 observed in total narcotic use since surgery or daily narcotic use since surgery (Table 3, Figure
249 2). The median pain score at the first postoperative visits was 2.0 in the standard-of-care group

and 3.5 in the cryo-analgesia group (p=0.249). The median LANSS neuropathy score was significantly lower in the standard-of-care group (8 vs 13, p=0.019). To assess the incidence of neuropathy, we compared the proportion of patients in each group with a LANSS score above 12. In the SOC group, 32% of patients had a LANSS score equal to or above 12 at two weeks of follow-up compared to 52% of patients in the CRYO group (p=0.045).

To better understand the relationship of MME to other variables, we conducted a univariate and multivariable analysis of factors associated with MME. For in-hospital MME, univariable associations were observed for age, robotic surgery, anatomic resection, and LOS. After including all 4 in a multivariable model, age (younger patients, higher MME), anatomic resection (higher MME), and LOS (higher LOS, higher MME) were significantly associated with in-hospital MME (p-values < 0.05). For total MME, univariable associations were observed for age and LOS. After including both in a multivariable model, age (younger, higher MME) and LOS (higher LOS, higher MME) were significantly associated with MME (p<0.05).

Discussion

In a randomized study comparing the combination of intercostal nerve block and cryo-analgesia with intercostal nerve block alone, we did not find significant differences in narcotic use or pain after minimally invasive thoracic surgery. As measured by the LANSS questionnaire, patients undergoing cryo-analgesia had significantly higher neuropathic pain scores compared to controls. Although the incentive spirometry on days 1 and 2 was higher in the experimental group, the difference between pre and postoperative spirometry was not statistically significant. This suggests no difference in pulmonary function between the two groups.

Cryo-analgesia is potentially an attractive method for achieving non-narcotic prolonged analgesia. Freezing the nerves causes axonal injury, axonotmesis, and distal Wallerian degeneration of the nerve, followed by slow regeneration and return of nerve function. [21] During the time it takes for the nerve to regenerate, the patient experiences prolonged numbness over the affected nerve's territory. Cryo-analgesia of sensory nerves in patients undergoing thoracic surgery has been studied since the 1970s. [6] Maiwand reported on 600 patients undergoing thoracotomy and cryo-analgesia in what is still the most extensive published experience to date. [22] Using a nitrous oxide probe, he treated five intercostal nerves (the thoracotomy space and two spaces above and one below) for 30 seconds per nerve. He applied the probe close to the neural foramina, which we avoided. Maiwand found that sensation returned 38 days after one freeze cycle vs. 91 days with two freeze cycles, yielding equivalent analgesia. His study is difficult to interpret by modern standards, as it lacked a standardized tool for assessing patient-reported pain and a measure of narcotic consumption, such as MME.

There are 22 published randomized studies comparing cryo-analgesia to other analgesic modalities. Most were in patients undergoing thoracotomy, two were in patients undergoing minimally invasive pectus repair, and one was in patients undergoing cardiac surgery through mini-thoracotomy. Lau and colleagues [15] reported the results of the FROST trial of patients undergoing minimally invasive cardiac surgery. Patients were randomized to receive either cryotherapy or standard of care with intravenous and oral opioids. Forced expiratory volume in 1 second (FEV1) 48 hours postoperatively, pain as measured by VAS, and the amount of narcotics administered were endpoints. Although FEV1 was higher in the cryotherapy group at

48 hours, it was not significantly different 72, 96, and 120 hours after surgery. Pain scores and narcotic use were not different between the two groups. There have been two small, randomized studies of cryotherapy vs. standard of care in patients undergoing minimally invasive pectus excavatum repair. In a study of 20 patients randomized to either cryo-analgesia or standard of care, the cryo-analgesia group consumed significantly fewer narcotics during hospitalization and had a shorter length of stay. Curiously, pain scores were similar between the 2 groups. [23] Rim and colleagues [14] randomized 48 patients to cryo-analgesia or standard of care. Pain scores were lower in the cryo-analgesia group during the first 72 hours, but narcotic consumption was similar between the groups.

Out of 19 randomized studies in patients undergoing thoracotomy for lung or esophageal surgery, seven showed reduced pain, and sometimes reduced narcotic usage in patients undergoing cryo-analgesia, [12,13,24-28] and 12 did not show any reduction with cryo-analgesia. [8-11,29-36] These randomized studies are very diverse and challenging to compare. Randomized studies that compared cryo-analgesia to epidural analgesia did not show the advantages of cryo-analgesia, [8-10,29,32,34,36] and there was no additive effect to epidural analgesia. [10,34,36] When cryo-analgesia was compared with non-steroidal analgesics, two studies showed improved pain with cryo-analgesia, and one did not. [30] Studies comparing cryo-analgesia to intercostal nerve blocks in patients undergoing thoracotomy showed advantages to using cryo-analgesia. Still, significant differences were not seen when directly comparing cryo-analgesia to intercostal nerve block plus intravenous analgesia. [35] Modern studies comparing cryo-analgesia to intravenous PCA also showed mixed results, with one positive [13] and one negative study. [11]

Notably, all these studies were performed in patients undergoing thoracotomy before the era of minimally invasive thoracic surgery. The present study is the first to compare cryo-analgesia to intercostal nerve block in patients undergoing minimally invasive thoracic surgery. Our study did not demonstrate decreasing pain and narcotic usage after adding cryo-ablation, and it is similar to previous studies that did not show that cryo-analgesia was added to intercostal nerve block and PCA.[35] There was no statistical difference in pulmonary complications (15.4% vs. 5.9%, p=0.201), but our study was not powered to detect differences in pulmonary complications.

When designing our trial, we made several choices that may have affected our results, particularly the number of intercostal nerves ablated with cryotherapy. We ablated 5-6 intercostal nerves based on previous studies in patients undergoing thoracotomy. In VATS cases, we ablated the nerve in the space used for the incision, and the nerves were two spaces below the incision and 2 to 3 spaces above the incision. In robotic cases, we ablated the nerve in the intercostal space used for our ports (usually the 8th space), one space below and 3-4 spaces above the incision. Many women develop numbness over the nipple area when the intercostal nerves are ablated above the 5th intercostal space, and several of our patients complained of loss of sensation or allodynia in the area. This was also seen in Maiwand's studies [22] and may have contributed to the significant difference in the incidence of neuropathy between the treatments in our trial. In future studies using this technology, we strongly suggest avoiding ablation above the 5th intercostal space.

Importantly, we observed higher neuropathy scores at the first postoperative visit in patients with cryo-analgesia. In the LANSS questionnaire, numbness at the incision is assigned 3

points, and we expected a 3-point difference between the two groups. However, the difference was a bit higher, at 4 points, which may suggest that patients undergoing cryotherapy have other neuropathic symptoms besides numbness. More patients in the CRYO group had scores at or above 12, suggesting pain of neuropathic origin. Long-term neuropathic pain was described in previous studies of cryoanalgesia [9,10,34,36] and should be a consideration when using cryo-analgesia.

Following current recommendations from AtriCure Inc., we ablated for 2 minutes at each level. Although the recovery of nerve function progresses at 1-3 mm per day, the duration of the nerve dysfunction is proportional to the duration of the cryoablation. [7] In our patients, this was reflected by a very long duration of nerve dysfunction. Some of our patients still had numbness in the surgical site one year after the procedure.

It's important to note that our study has several limitations. It is a single-center study, so the findings may not be widely applicable. Although patients were blinded to the study, our nurses who recorded the data were not technically blinded. The information on cryo-analgesia was available to the nurses in the patients' operative reports. While this is a limitation, we don't think it significantly affected our study. An additional issue is the lack of standardization of anesthesia procedures. Each anesthesiologist was free to use techniques they found appropriate, which may have resulted in varying amounts of narcotics being administered to patients. We did not account for intraoperative narcotics when calculating our MME (morphine milligram equivalent), however, we did not find differences in the amount of narcotics administered intraoperatively. Narcotic consumption was calculated from the patient's arrival in the recovery room. Furthermore, we did not adjust the dose of local anesthetic for each patient

based on their weight. All patients received a similar dose of local anesthetics, which may have affected the study since bupivacaine has a dose-response curve, and higher doses provide better analgesia. However, this procedure was consistent in both the control and experimental groups. Finally, we didn't assess dynamic pain scores. Patients may experience relatively low pain at rest, but severe pain when they move or cough. However, we believe that narcotics use (MME) is a better and more objective indicator of pain, so our results remain relevant.

In conclusion, in this randomized study of patients undergoing minimally invasive thoracic surgery, the use of cryo-analgesia with bupivacaine and lidocaine did not further decrease pain or reduce narcotic use in the early postoperative period. There was no change in respiratory function, but more neuropathy was reported at the first postoperative visit. We are currently investigating if ablating fewer intercostal nerves for less time may provide a decrease in narcotic use after MITS.

372 Table 1. Patient characteristics
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Characteristics [a]	Full cohort (n=103)	Control arm (standard-of care, n=52)	Experimental arm (+cryo-analgesia, n=51)	p-value
Age, years (IQR)	66.6 (62.7-73.5)	70.9 (63.1-75.5)	66.2 (61.2-71.6)	0.054
Female sex, n (%)	61 (59%)	32 (61.5%)	29 (56.9%)	0.691
BMI, kg/m^2 (IQR)	27.5 (23.3-32.4)	27 (23.2-32)	28.1 (23.6-32.7)	0.327
FEV1, % predicted (IQR)	88% (76-101)	88 (75-98.2)	88 (77.5-104)	0.589
DLCO, % predicted (median, IQR)	77% (61 -92)	78% (61-98.2)	74% (64-92)	0.636
Preoperative incentive spirometry, ml (IQR)	2000 (1500-2500)	1750 (1500-2488)	2000 (1500-3000)	0.186
Robotic surgery, n (%)	79 (76.7%)	38 (73.1%)	41 (80.4%)	0.260
Anatomic lung resection, n (%)	91 (88.3%)	46 (88.5%)	45 (88.2%)	1.000
Conversion to open surgery, n (%)	1 (1%)	0 (0%)	1 (2%)	0.495
Preoperative neoadjuvant therapy, n (%)	7 (6.8%)	4 (7.7%)	3 (5.9%)	1.000

375 [a] Median and interquartile range (IQR), unless otherwise specified. BMI, body mass index; DLCO,
376 diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1
377 second.
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380 Table 2. Postoperative characteristics and pain assessment
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Variable [a]	Full cohort (n=103)	Control arm (standard of care, n=52)	Experimental arm (+cryo-analgesia, n=51)	p-value
Length of stay, days (IQR)	2 (1-3)	2.5 (1-4.7)	2 (1-3)	0.515
Days with chest tube (IQR)	2 (1-3)	2 (1-4.7)	2 (1)	0.324
Pulmonary complication, n (%)	11 (10.7%)	8 (15.4%)	3 (5.9%)	0.120
Air leak > 5 days, n (%)	14 (13.6%)	9 (17.3%)	5 (9.8%)	0.270
Postoperative pain, VAS score (IQR)				
POD 0	3.8 (2-6)	4.0 (2.1-6)	3.8 (2-6)	0.533
POD 1	3.6 (2-5.5)	3.8 (2.2-5.6)	3.3 (2-5.3)	0.576
POD 2	2.3 (1-5.3)	2.0 (1-5.3)	3.5 (1-5.3)	0.695
POD 3	2.2 (0-4.9)	2.8 (0-5)	2.1 (0.2-4.6)	0.881
Incentive spirometry, ml (IQR)				
POD 1	1000 (750-1500)	1000 (750-1075)	1250 (1000-2000)	<0.001
POD 2	1000 (750-1625)	1000 (750-1500)	1500 (1000-2000)	0.012
POD 3	1075 (750-2000)	1000 (750-1712)	1500 (937-2000)	0.276
Incentive spirometry, ml (IQR)				
Preop to day 1	-750 (-1250, -500)	-875 (-1250, -500)	-750 (-1250, -500)	0.330
Preop to day 2	-500 (-1000, -250)	-500 (-1000, -250)	-500 (-1000, 0)	0.649
Preop to day 3	-500 (-825, 0)	-500 (-750, 0)	-375 (-1000, 0)	0.961
MME in-patient, mg (IQR)	41.5 (24-84)	44.9 (20.7-96.9)	38.4 (25.1-64.5)	0.468
MME in-patient per day, mg (IQR)	20.8 (9.6-36.8)	21.2 (10-37.1)	20.8 (9.3-33)	0.702

382 [a] Median and interquartile range (IQR) unless otherwise specified. MME, morphine milligrams
383 equivalents; POD, postoperative day; VAS, visual analog scale.
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386 Table 3. Outcomes at the first postoperative visit
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Variable [a]	Full cohort (n=103)	Control arm (standard of care, n=46)	Experimental arm (+cryo-analgesia, n=50)	p-value
Days since surgery (IQR)	15 (14-20)	15 (13.8-22)	15 (14-19.3)	0.431
Total out-patient MME, mg (IQR)	30 (0-113)	22.5 (0-91.3)	32.5 (5-136.3)	0.117
Total MME since surgery, mg (IQR)	96 (38.8-180.7)	105.8 (35.5-159.3)	94.5 (40-201.9)	0.625
Total MME per day since surgery, mg (IQR)	5.8 (2.4-11.2)	6.5 (1.8-10.4)	5.4 (2.7-12.7)	0.541
Pain score at visit, VAS (IQR)	2.0 (0-4)	2.0 (0-4)	3.5 (0-5)	0.249
LANSS neuropathy score (IQR)	11 (3-15)	8 (0-13)	13 (3.75-18)	0.019

389 [a] Median and interquartile range (IQR). LANSS, Leeds Assessment of Neuropathy Symptoms and
390 Signs; MME, morphine milligrams equivalents; POD, postoperative day; VAS, visual analog scale.
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500 Central Figure: Comparison of MME in the hospital, as outpatient and total

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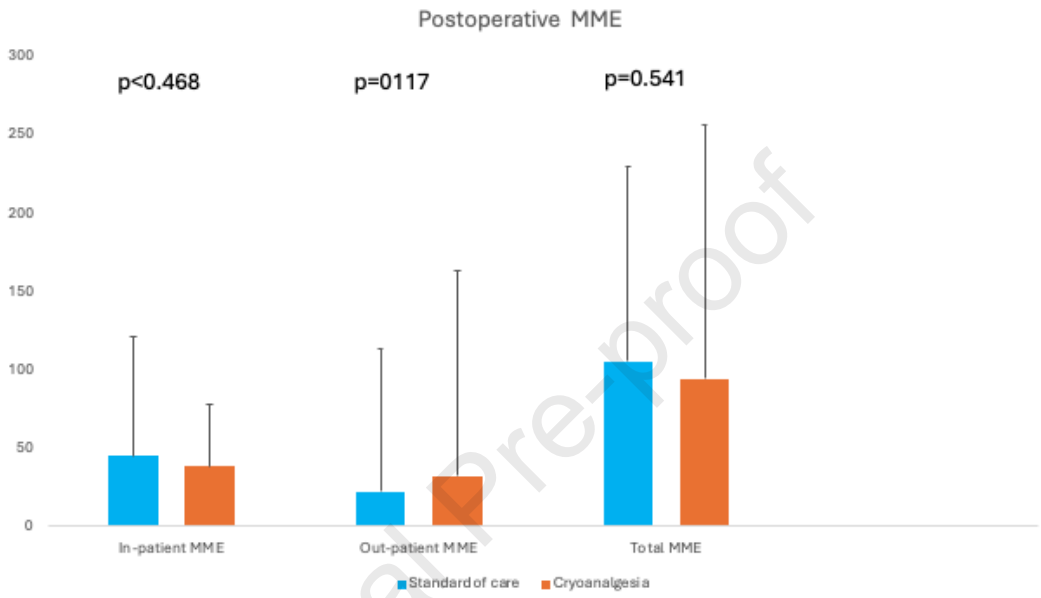

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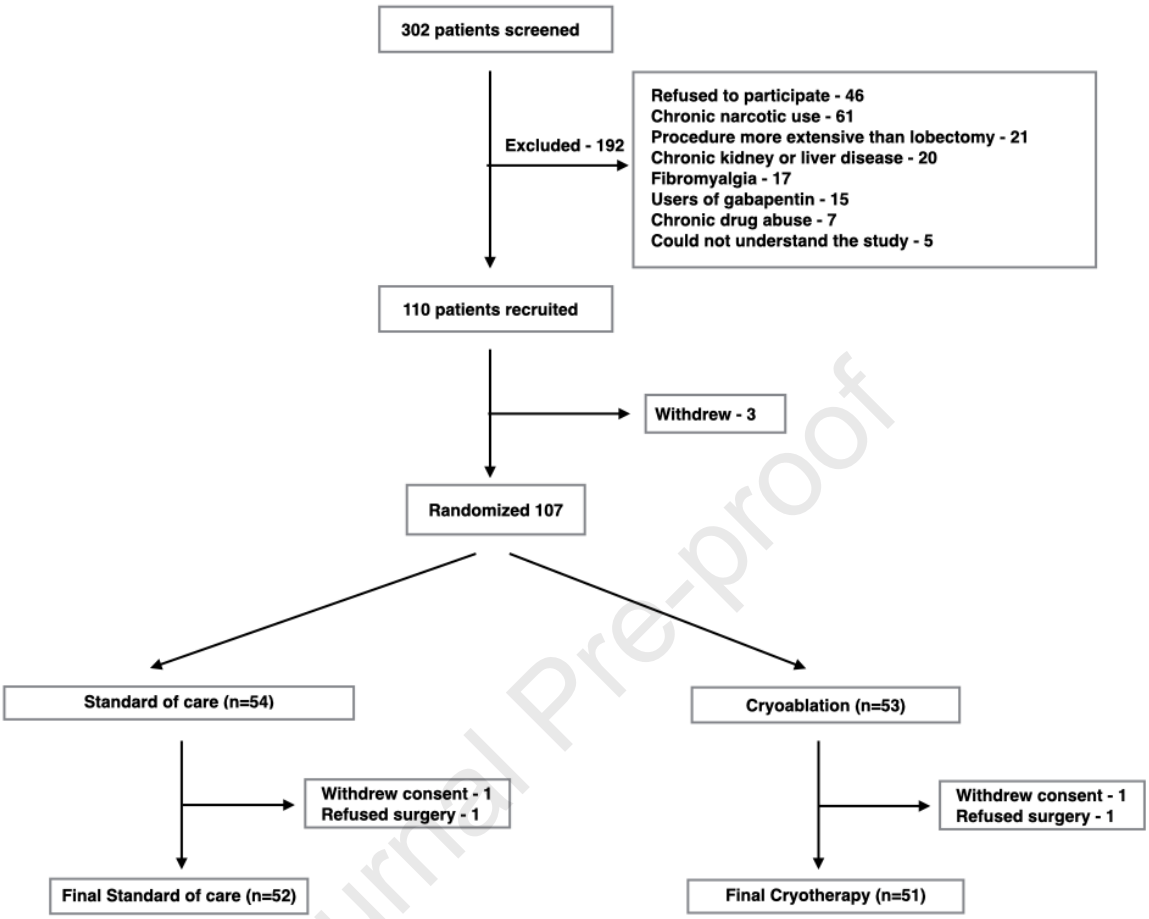
513 Figure 1. Consort diagram



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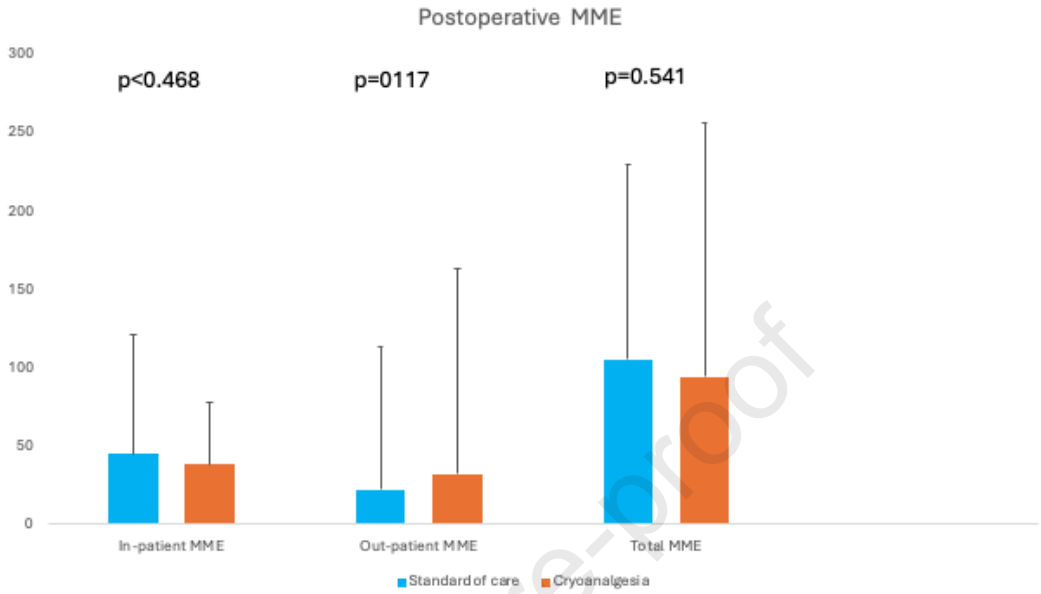
515 Figure 2: Comparison of MME in the hospital, as outpatient and total



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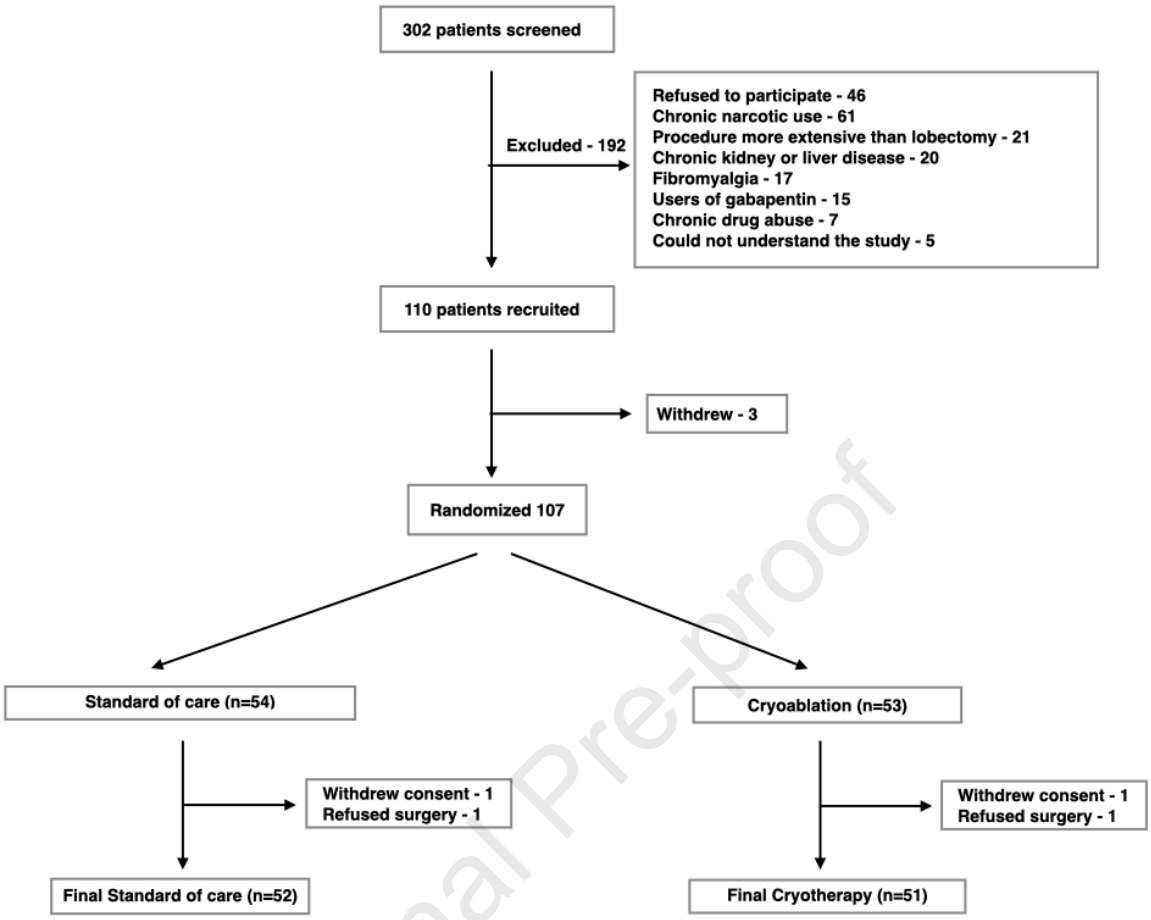

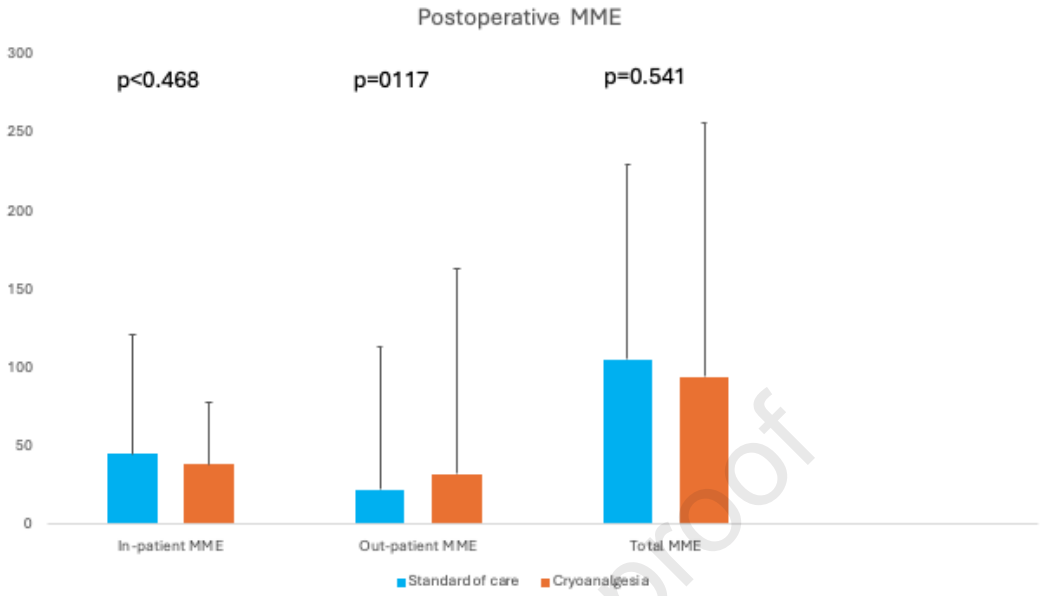

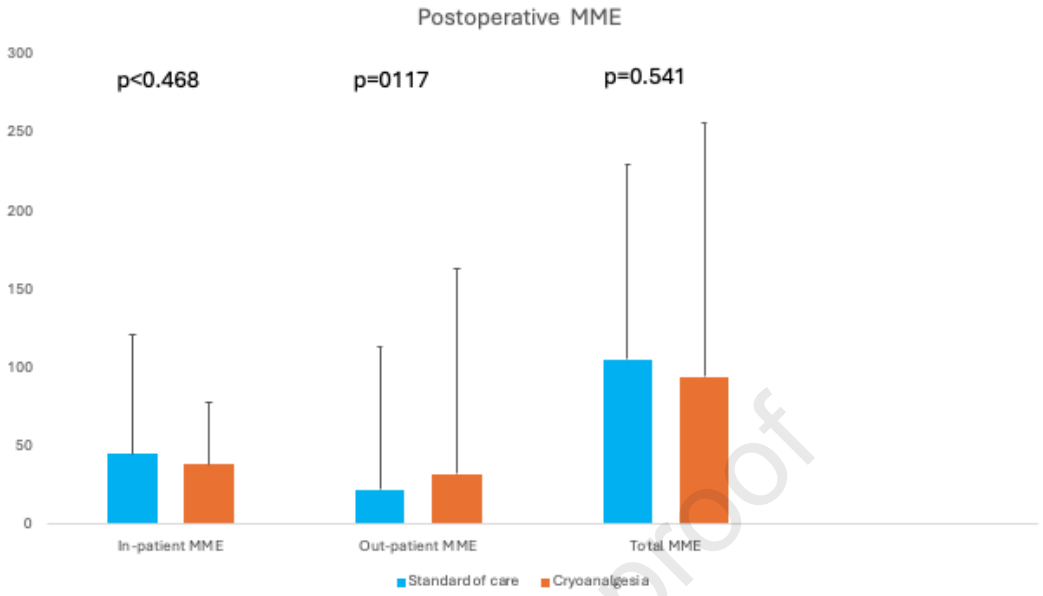

A Randomized Study of Cryoablation of Intercostal Nerves in Patients Undergoing Minimally Invasive Thoracic Surgery (NCT05349447)

Weksler B, Maxwell C, Crist L, Specht K, Kuchta P, DeHaven K, Williams B, Weksler I, Fernando HC.

Division of Thoracic and Esophageal Surgery, Cardiovascular Institute, Allegheny Health Network