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Opioid Requirements After Intercostal Cryoanalgesia in Thoracic Surgery

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ABSTRACT

Introduction: The optimal approach to pain management after thoracic surgery remains poorly defined. The purpose of this study was to examine the association between intercostal nerve cryoanalgesia and postoperative opioid requirements after thoracic surgery.
Methods: We conducted a single-center retrospective review of all patients who underwent unilateral thoracic surgery for pulmonary pathology from June 2017 to August 2019. Patients receiving intercostal nerve cryoanalgesia were compared with standard analgesia. The primary outcome was total oral morphine equivalent consumption during hospitalization, at discharge, and 90 d postoperatively. Secondary outcomes included pain scores and pulmonary function measured on postoperative days 1 and 3, at discharge, and postoperative complications. Planned subgroup analysis by opioid exposure and surgical approach was performed.
Results: The Wilcoxon rank-sum test demonstrated significantly less inpatient opioid use for cryoanalgesia patients (45 *versus* 305 mg, $P < 0.001$), regardless of opioid history (naïve: 22.5 *versus* 209.8 mg, $P < 0.001$; tolerant: 159.5 *versus* 1043 mg, $P < 0.001$) and minimally invasive approach (opioid naïve: 26.2 *versus* 209.8 mg, $P < 0.001$; tolerant: 158.5 *versus* 1059 mg, $P < 0.001$). Opioid-naïve patients required fewer discharge opioids (50 *versus* 168 mg; $P < 0.05$). Cryoanalgesia lowered daily pain scores ($P < 0.001$) and showed a trend toward lower 90-d opioid prescriptions and higher pulmonary function scores. There was no difference in postoperative complications ($P = 0.31$).
Conclusions: Our results suggest an association between intercostal nerve cryoanalgesia and reduced inpatient opioid requirements and pain in opioid-naïve and tolerant patients. Pulmonary function, 90-d opioid prescriptions, and adverse events were no different between groups. It may serve as a useful adjunct for opioid-sparing pain management in thoracic surgery.

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Introduction

Thoracic surgical procedures are known to cause high levels of postoperative pain resulting from direct manipulation and inherent insult to the skeletal, muscular, and neuropathic systems.[1] Inadequate postoperative pain control can limit patients' mobility and pulmonary effort, increasing the potential risk for adverse events and opioid dependence.[2] This is compounded by the lack of consensus regarding a standardized pain management approach. Most patients are treated with traditional opioid analgesia.[2] Although effective for acute pain, opioids are also associated with serious side effects. Moreover, unregulated and generous opioid prescribing may result in abuse and potential dependency, contributing to our nation's opioid epidemic.[3]

Complete recovery after thoracic surgery generally takes several weeks to months. Prior research has demonstrated that inadequate treatment of acute pain may precipitate chronic pain,[4,5] which further highlights the importance of effective pain management. Strategies aimed at reducing opioid consumption and associated risk for the dependency include minimally invasive surgical (MIS) techniques[6] for limiting tissue trauma[2] and surgical stress.[7] In addition, various forms of regional analgesia are used, but despite demonstrating some efficacy, they are of short duration.

Cryoanalgesia is a peripheral nerve blocking technique resulting in extended pain control for approximately 2 mo,[8,9] allowing patients the necessary time to heal and recover after surgery. Pressurized nitrous oxide produces cold temperatures that injure the axon and myelin sheath and temporarily prevents the peripheral sensory nerves' ability to conduct pain signals. As the structural elements of the nerve bundle (endoneurium, perineurium, and epineurium) are preserved, complete nerve regeneration occurs at a rate of 1-2 mm/d with the recovery of nerve function.

Although several randomized studies have shown a reduction in postoperative pain after thoracotomy with cryoanalgesia,[8,10] others have demonstrated a greater incidence of postoperative neuropathic pain,[1,4,10,11] and few studies have included opioid-tolerant patients who comprise a growing proportion of the population.[12] Therefore, the purpose of this study was to examine the association between intercostal nerve cryoanalgesia during thoracic surgery and postoperative opioid requirements, pain scores, pulmonary function, and adverse events in both opioid-naïve and tolerant patients. We hypothesized that cryoanalgesia, when used as part of a multimodal strategy, would reduce opioid requirements, pain levels, and postoperative complications and improve pulmonary function regardless of patients' opioid exposure history or surgical approach.

Methods

Patient selection and data collection

A retrospective cohort study was performed on all consecutive patients from June 2017 to August 2019 undergoing unilateral thoracic surgery for benign and malignant lung pathology via MIS (robotic-assisted thoracoscopic surgery and video-assisted thoracoscopic surgery) or muscle-sparing thoracotomy at a large, single institution.

A historical control group of patients (who preceded the introduction of cryoanalgesia) was used for comparison. They were managed with standard analgesic treatment (SAT) consisting of opioid and nonopioid medications from June 19, 2017, to July 10, 2018. The treatment group, termed CRYO, included patients who received intraoperative intercostal cryoanalgesia nerve block from July 17, 2018, to August 30, 2019.

Patient data were abstracted from the electronic medical record (EMR). Collected demographic information included patient age, sex, body mass index (BMI), and opioid exposure (patient prescribed opioids for chronic pain or reported current illicit drug use constituted tolerant classification). Operative, hospital, and outpatient follow-up data included surgical approach, procedure type, selection of nerve block, gabapentin use, length of stay (LOS), opioid consumption, pulmonary function, pain scores, and complications. Patients aged <18 y, pregnant, left the hospital against medical advice, underwent other procedures (rib stabilization, cardiac, and mediastinal) or whose status changed to hospice were excluded. This study was approved by the institutional review board, and the requirement of informed consent was waived.

Outcomes

The primary outcome was total opioid consumption in opioid-naïve and tolerant patients during hospitalization, at discharge, and within 90 d after discharge. Total opioid consumption was measured in milligrams of oral morphine equivalents (OME) and was calculated using standard conversion factors.[13] Opioids received preoperatively and in the postanesthesia care unit were not included for eliminating variations in anesthesia provider's management. Outpatient opioid use was assessed using the New Hampshire Controlled Drug Prescription Health and Safety Program, which logs all prescribed controlled substances, including those from neighboring states (https://newhampshirepdmp.com).

Secondary outcomes included pain scores, pulmonary function obtained on postoperative days 1 and 3, on discharge, and postoperative complications. A validated 11-point numeric rating scale was used for measuring patient self-reported pain scores ranging from 0 to 10 (0 = no pain and 10 = excruciating pain).[14] Incentive Spirometry (IS) effort (in milliliter) reflecting the patient's pulmonary vital capacity was recorded. Pain scores and IS values were entered into the patient's EMR by nursing staff at every shift during routine clinical care. According to our standard practice, postoperative follow-up was scheduled at 2, 4, 8, and 12 wk. Patients were monitored for wound healing, pulmonary complications, and neuralgia. Reported or observed complications were documented in the EMR.

Pain management

SAT pain management regimen (Table 1) consisted of oral and intravenous opioid medications with escalating doses as

Table 1 – SAT regimen.

Medication	Dose and frequency
Acetaminophen	500 mg po every 6 h
Diazepam	2 mg po every 8 h as needed for muscle spasm
Gabapentin	100-300 mg po three times a day
Ketorolac *or*	15 mg IV every 6 h
Ibuprofen	800 mg po every 8 h
Morphine *or*	1-2 mg IV every 2 h as needed for severe pain (8-10)*
Hydromorphone	0.2-1 mg IV every 2 h as needed for severe pain (8-10)*
Oxycodone *or*	5-10 mg po every 4-6 h as needed for moderate pain (5-7)*
Tramadol	50 mg po Q 6 h as needed for mild pain (3-5)*

IV = intravenous; PO = by mouth.
*Numerical Rating Scale (0 = no pain to 10 = excruciating pain).

needed at the discretion of the provider. Nonsteroidal anti-inflammatory drugs, acetaminophen, and gabapentin were scheduled when not contraindicated. Diazepam was used for muscle spasms as needed. Nerve block selection was determined by the operating surgeon and included local wound and intercostal space infiltration performed at the beginning of the operation with 0.5% bupivacaine with epinephrine or 1.3% liposomal bupivacaine when it became available for use at our hospital in March 2018. Consequently, all CRYO patients and only the last third of the SAT group received liposomal bupivacaine. Thoracic epidurals were rarely used. CRYO patients also followed SAT regimen. Only a portion of the patients in the SAT group received gabapentin. All patients in the CRYO group received gabapentin during their hospitalization and at discharge for approximately 6-8 wk. Generally, opioids prescribed at discharge were based on the patient's age and opioid requirement over the prior 24 h with the following suggested guidelines: 0 opioid pills, 0 opioids prescribed; 1-3 pills, 15 pills prescribed; ≥4 pills, 30 pills prescribed.[15] Patients on preexisting opioid medication resumed their home regimen. All opioid-tolerant patients were offered a referral to a pain center or rehabilitation services.

Surgical technique

Cryoanalgesia was applied under direct visualization using AtriCure's cryoSPHERE probe (AtriCure, Inc, Mason, OH) specifically designed for thoracic procedures with a bendable shaft and an 8-mm ball tip. Axonotmesis (disruption of axon and myelin with preservation of surrounding connective tissue) and subsequent Wallerian degeneration[11] occurs as a direct result of an ice ball creation because of pressurized nitrous oxide. The protocol includes an application time of 120 s, temperature between −50°C and −70°C, at least 4 cm from the base of the spine, an average number of five ablations between intercostal space three to nine (typically two intercostal spaces above, two below, and one at the incision level), followed by active defrost, which facilitates probe removal and avoids potential inadvertent damage to the nerve tubule structures. Muscle-sparing thoracotomy incisions were made at the fourth or fifth intercostal space, and MIS ports were placed in the sixth to eighth intercostal space, depending on the type of procedure, with an assistant port in the tenth intercostal space for robotic cases.

Statistical methods

Data analysis was performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC) and R version 3.2.3 (R Core Team [2015] Vienna, Austria). Categorical variables were expressed as counts and percentages and compared with Pearson's chi-squared or Fisher's exact test. Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) and compared with the two-sample t-test or Wilcoxon rank-sum test depending on the distribution of the data.

An analysis of covariance (ANCOVA) model was used to examine the association between the exposure of interest, cryoanalgesia, and the primary outcome of postoperative opioid consumption during hospitalization adjusting for the following covariates: sex, age, LOS, BMI, preoperative opioid exposure status, administration of liposomal bupivacaine, and use of gabapentin. As the model assumptions concerning normal distribution of the residuals could not be met, a transformation of the dependent variable was required. Rank transformation of the dependent variable was chosen because of its properties of robustness and power in both regression and analysis of variance,[16] and this transformation allowed for nonrejection of the normality assumption. To handle the case that the administration of liposomal bupivacaine and gabapentin was unbalanced between groups and our inability to evaluate for interactions related to this, we performed subgroup analyses restricted to patients who all received these medications. Initially, the differences were compared using the Wilcoxon rank-sum test followed by a rank-transformed ANCOVA model, adjusting for the same covariates. The variance inflation factor test did not demonstrate multicollinearity. To further examine the influence of these medications, another subgroup analysis examined opioid consumption of patients within the SAT group by comparing those who received liposomal bupivacaine to those who did not, thereby eliminating the influence of cryoanalgesia. We repeated the same analysis for gabapentin.

Planned subgroup analysis of inpatient opioid consumption using opioid exposure history and surgical approach was performed. Statistical significance was defined as a P value of <0.05.

Results

Patients' characteristics

Overall, 137 patients underwent a unilateral thoracic surgical procedure between June 19, 2017, and August 30, 2019, and were included in this study. The CRYO treatment group was comprised of 80 patients and the SAT cohort 57 patients. Two opioid-tolerant SAT patients were lost to follow-up after

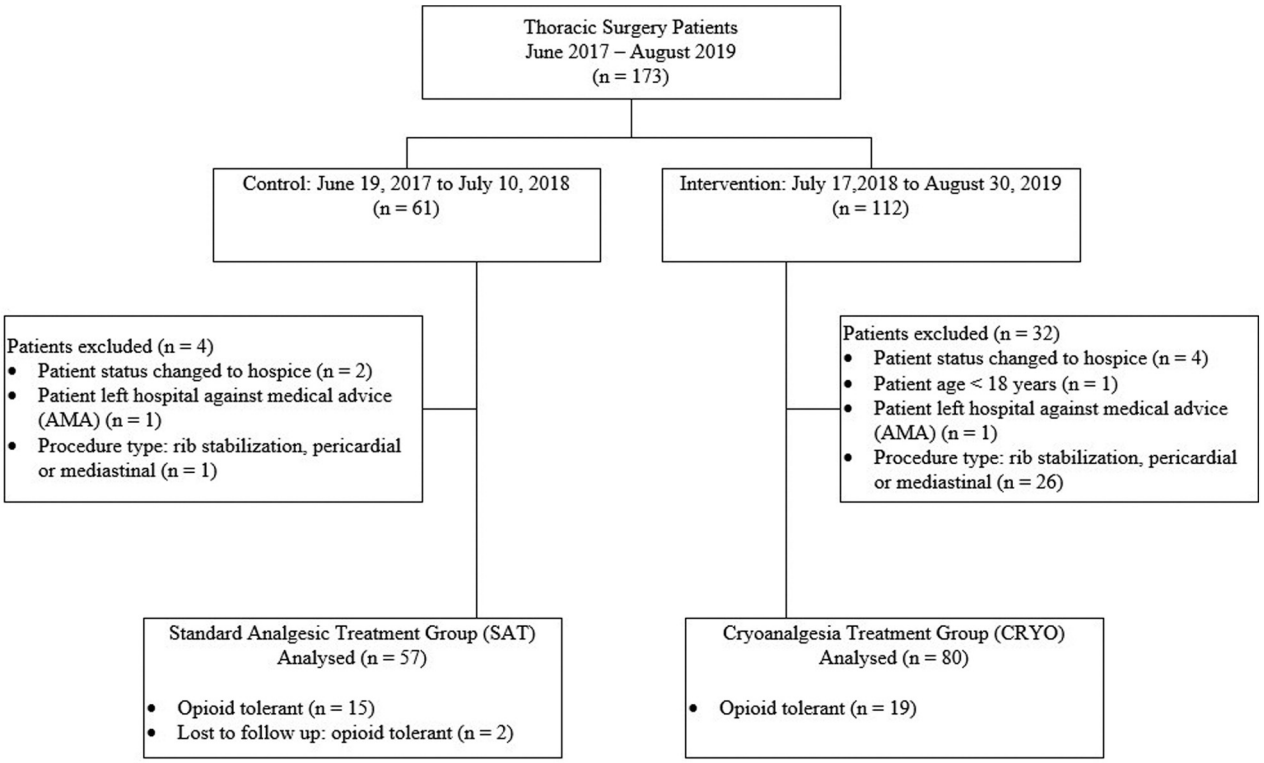

Fig. 1 – Flow diagram describing patient population and exclusions.

discharge, and consequently, the 90-d opioid prescription status and presence of complications for these patients were not analyzed (Fig. 1).

Patients' demographics for each group are depicted in Table 2; no statistically significant difference in age, sex, or BMI was observed. Opioid-tolerant patients comprised approximately 26% of both groups. The operative characteristics for both the CRYO and SAT groups demonstrating similar proportions for the surgical procedure type and approach, with most patients undergoing surgery for wedge resection (43.7% *versus* 47.4%, $P = 0.88$) and using minimally invasive techniques (77.5% *versus* 86%, $P = 0.21$; Table 3).

The groups were not balanced for nerve block selection (Table 5). All CRYO patients received liposomal bupivacaine injection *versus* 19 (33%) of SAT patients. Epidurals were only used in the SAT group ($n = 5$). In addition, gabapentin was not consistently prescribed in the SAT group (43.9%).

Table 2 – Patient demographics.

Characteristic	CRYO ($n = 80$)	SAT ($n = 57$)	P value
Age in years, mean (SD)	61.1 (15.1)	61.3 (16)	0.93
Sex, male, *n* (%)	46 (57.5)	33 (57.8)	0.96
BMI (kg/m^2), mean (SD)	28.64 (8.4)	28.53 (8.1)	0.94
Opioid tolerant			0.73
Total, *n* (%)	19 (23.8)	15 (26.3)	
Male, *n* (%)	9 (47.4)	8 (53.3)	

CRYO = cryoanalgesia.

Primary outcome

The results for Wilcoxon rank-sum test on inpatient opioid consumption for both the groups are presented in Figure 2. CRYO patients consumed significantly fewer opioids than SAT patients during hospitalization (median [IQR], 45 [130] mg *versus* 305 [633] mg, $P < 0.001$) and regardless of patients' prior opioid exposure (naïve: 22.5 [67.3] mg *versus* 209.8 [337.9] mg, $P < 0.001$; tolerant: 159.5 [480] mg *versus* 1043 [1655] mg, $P < 0.001$). Sixteen (26%) opioid-naïve CRYO patients and three (7%) SAT patients consumed 0 mg opioids while in the hospital ($P = 0.02$). For both groups, MIS approach was associated with lower median opioid consumption for opioid-naïve and tolerant patients, with CRYO patients consuming the least (opioid naïve: 26.2 [57.5] mg *versus* 209.8 [389.5] mg, $P < 0.001$; tolerant:158.5 [362.5] mg *versus* 1059 [2414] mg, $P = 0.001$).

Patients who underwent a thoracotomy with cryoanalgesia required fewer opioids regardless of opioid exposure; however, the result was not statistically significant (opioid naïve: 22.5 [165] mg *versus* 206.3 [187.1] mg; $P = 0.15$; tolerant: 452.5 [1136] mg *versus* 864 mg, $P = 0.33$).

Both untransformed and rank-transformed ANCOVA models were used for determining the association of cryoanalgesia with opioid consumption, adjusting for sex, age, LOS, BMI, preoperative opioid exposure status, administration of liposomal bupivacaine, and use of gabapentin. Epidural use was

Table 3 – Operative characteristics and postoperative outcomes.

Characteristic/ Outcomes	CRYO ($n = 80$)	SAT ($n = 57$)	P value
Surgical procedure, *n* (%)			0.88
Wedge resection	35 (43.7)	27 (47.4)	
Lobectomy	27 (33.8)	17 (29.8)	
Decortication	18 (22.5)	13 (22.8)	
Surgical approach (all patients), *n* (%)			0.21
MIS (RATS, VATS)	62 (77.5)	49 (86.0)	
Open thoracotomy	18 (22.5)	8 (14.0)	
(Opioid naïve), *n* (%)			0.37
MIS (RATS, VATS)	48 (78.7)	36 (85.7)	
Open thoracotomy	13 (21.3)	6 (14.3)	
(Opioid tolerant), *n* (%)			0.43
MIS (RATS, VATS)	14 (73.6)	13 (86.6)	
Open thoracotomy	5 (26.4)	2 (13.4)	
Received liposomal bupivacaine injection, *n* (%)	80 (100)	19 (33.3)	<0.001
Epidural use, *n* (%)	0 (0)	5 (8.8)	0.01
Received gabapentin, *n* (%)	80 (100)	25 (43.9)	<0.001
LOS (d)			0.27
Mean (SD)	7.06 (2.9)	7.83 (6.2)	
Median [IQR]	7 [3]	5 [6]	
Incentive spirometry effort (mL), mean (SD)			
POD#1	1386.7 (737.9)	1141 (634)	0.052
POD#2	1381.5 (709.1)	1169 (646)	0.07
Day of discharge	1518.9 (714.5)	1300 (609.4)	0.06
Discharge prescription OME (mg), mean (SD), ($n = 61$)*	49.7 (60.3)	168.6 (345)	0.03
90-d refill prescription OME (mg), mean (SD), ($n = 42$)*	42.3 (115)	130.4 (434)	0.22

CRYO = cryoanalgesia; IQR = interquartile range; MIS = minimally invasive surgery; OME = oral morphine equivalent; POD = postoperative day; RATS = robotic-assisted thoracoscopic surgery; VATS = video-assisted thoracoscopic surgery.
*Opioid-naïve patients.

excluded due to limited sample size ($n = 5$) and nonuse within the intervention group. Cryoanalgesia was associated with total hospital opioid consumption after adjusting for covariates in both untransformed ($P = 0.03$) and transformed data ($P < 0.0001$; Table 4). While controlling for the same covariates, gabapentin was not significant in both models (untransformed: $P = 0.73$ and transformed: $P = 0.12$), whereas liposomal bupivacaine association became significant in the transformed model (untransformed: $P = 0.15$ and transformed: $P = 0.02$; Table 4).

We were unable to assess for any interactions regarding liposomal bupivacaine, given its use in all patients who received cryoanalgesia. To examine the relationship for opioid reduction attributed to liposomal bupivacaine and to clarify the effect of cryoanalgesia, we performed a subgroup analysis restricted to patients who received this medication. Wilcoxon rank-sum demonstrated significantly lower opioid consumption in the CRYO group (CRYO: 45 [130] mg *versus* SAT 202.5 [375] mg, $P = 0.002$). The treatment effect of cryoanalgesia remained significant with rank-transformed ANCOVA when adjusting for other covariates ($P < 0.001$; Supplemental Table 1). To further assess liposomal bupivacaine's impact on opioid needs, while eliminating the influence of cryoanalgesia, we compared SAT patients with and without liposomal bupivacaine and found no statistically significant difference in opioid consumption ($P = 0.22$; Supplemental Table 1).

The influence of gabapentin on opioid consumption was approached similarly with the Wilcoxon rank-sum test demonstrating significantly lower opioid consumption in the CRYO group (CRYO: 45 [130] mg *versus* SAT 360.5 [749] mg, $P < 0.001$). The treatment effect remained significant with rank-transformed ANCOVA when adjusting for other covariates ($P < 0.001$; Supplemental Table 1). A comparison of SAT patients with and without gabapentin revealed a statistically significant difference with greater consumption of opioids in those who received gabapentin (360.5 [749] mg *versus* 194.3 [548] mg, $P = 0.02$).

As depicted in Table 3, the mean OME discharge prescription for opioid-naïve patients was lower in CRYO patients than in SAT patients. Of these, 28 (46%) CRYO *versus* 11 (26%) SAT patients ($P = 0.04$) did not require an opioid prescription. Opioid-naïve CRYO patients required fewer opioid refill prescriptions within 90 d after discharge but did not reach statistical significance (Table 3). Each group had two opioid-tolerant patients who required additional opioids beyond their baseline prescription (CRYO, 90 and 150 mg; SAT, 90 and 225 mg).

Secondary outcome

The median pain scores, presented in Figure 3, were consistently lower in CRYO patients on all days. Pulmonary function status, represented by the mean IS effort, did not achieve statistical significance (Table 3). However, at each time point, the CRYO group had higher pulmonary function volumes of >200 mL.

There was no difference in the proportion of complications between the groups (Table 5). However, the incidence of pneumonia was only observed in the SAT group ($n = 3$). All CRYO patients reported expected numbness immediately after surgery, which lasted approximately 6-8 wk. One CRYO patient required admission for pain control but showed no chest wall paresthesia at 90 d after discharge. Cryoanalgesia added approximately 15-20 min to the total surgical time.

Discussion

Our primary outcome suggests a favorable association between cryoanalgesia and inpatient opioid consumption. Despite controversies in published literature, numerous studies have reported that patients receiving intercostal cryoanalgesia have a reduced need for additional opioid medications.[1,6] Our study substantiates these findings, as approximately one-fourth of these patients did not require

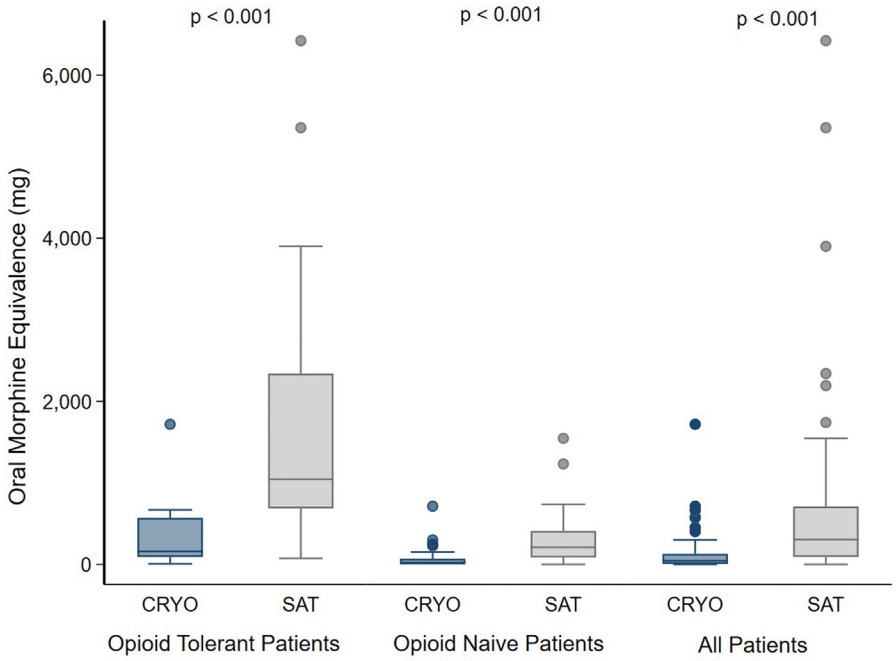

Fig. 2 – Box plot of total median inpatient opioid consumption by patient's opioid exposure history. CRYO, cryoanalgesia treatment group.

any opioids while hospitalized. Relying on opioids as the mainstay of treatment may contribute to persistent opioid use with an increased risk of becoming dependent and possible subsequent addiction.[17] Brescia *et al.*[17,18] reported that one in seven (14%) opioid-naïve patients who underwent lung resection became new persistent opioid users. Furthermore, a recent study linked discharge opioid prescriptions over 300 mg OME with opioid dependency.[19] In the present study, opioid-naïve patients who underwent cryoanalgesia required lower opioid prescriptions at discharge. Additional opioid prescriptions were not required for 77% of CRYO patients and 67% of SAT patients after discharge. Given the extended period of pain relief associated with cryoanalgesia, we had expected a more impressive difference between the groups. Nonetheless, opioid refill prescriptions for CRYO patients were lower by an average of 88 mg OME. Pain control after thoracic surgery is challenging, especially in opioid-tolerant patients.[12,20] In our study, cryoanalgesia was associated with almost a sevenfold reduction in opioid requirements. This is an important benefit for patients already dependent on opioids and may possibly minimize future increases in their baseline home regimen.

Table 4 – Multivariable regression models.

Variable	Untransformed data: estimate (95% CI)	Untransformed data: F statistic	Untransformed data: P value	Rank transformed data: F statistic	Rank transformed Data: P value
Treatment arm: cryoanalgesia	−726.13, −36.96	4.80	0.03	19.61	<0.0001
Liposomal bupivacaine	−583.59, 91.99	2.07	0.15	5.64	0.02
Gabapentin use	−267.29, 382.54	0.12	0.73	2.41	0.12
Opioid exposure history	311.95, 814.61	19.66	<0.0001	34.52	<0.0001
Age	−21.01, −7.10	16.01	0.0001	5.18	0.02
LOS	70.95, 118.04	63.07	<0.0001	15.45	0.0001
Sex (male)	−36.14, 381.43	2.67	0.10	0.17	0.68
BMI	−3.10, 21.82	2.21	0.14	0.75	0.38

Rank transformation was used on continuous variables before fitting the ANCOVA model because of the nonnormal residuals. Variables including liposomal bupivacaine injection, gabapentin use, opioid exposure history, age, LOS, sex, and BMI were adjusted in the model. The effect of treatment on ranked data is still significant ($P < 0.0001$) after adjusting for covariates. The effect of liposomal bupivacaine use ($P = 0.02$), opioid exposure history ($P < 0.0001$), age, ($P = 0.02$), and LOS ($P = 0.0001$) on ranked data are also significant.

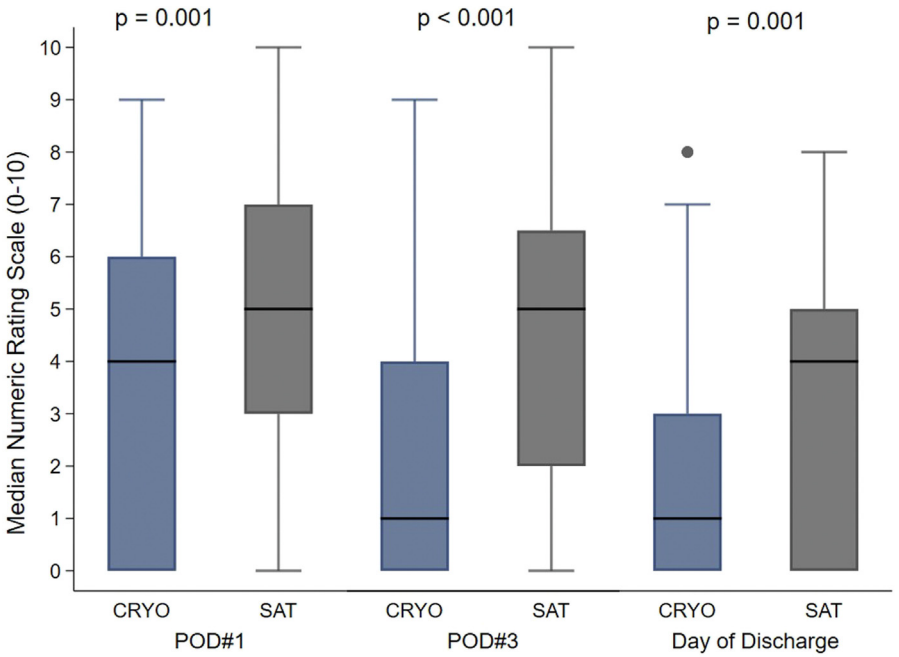

Fig. 3 – Box plot of postoperative median pain scores. An 11-point numeric rating scale (0-10 points) was obtained on the first and third day after surgery and at discharge. CRYO, cryoanalgesia treatment group; POD, postoperative day.

A recent study showed that opioid-naïve patients who undergo MIS have a 9% risk of possible opioid dependence *versus* 17% after thoracotomy.[17] We observed that both opioid-naïve and tolerant MIS CRYO patients required fewer inpatient opioids. Thoracotomy patients demonstrated a fourfold reduction in opioid requirements for all patients, ninefold for opioid naïve, and twofold for opioid-tolerant patients, although never achieving statistical significance. These findings may be attributed to surgical-related intercostal nerve injury associated with thoracotomy,[9,21] pain in areas excluded from cryoanalgesia "freeze zone," and the small sample size of thoracotomy patients, which limits the power of this subgroup analysis.

Table 5 – Postoperative complications.

Outcomes	CRYO ($n = 80$)	SAT ($n = 55$)*	P value
Any complication	4 (5.2%)	6 (10.9%)	0.31
Pneumonia	0	3 (5.5%)	0.06
Pleural effusion	1 (1.3%)	1 (1.8%)	1
Pneumothorax	1 (1.3%)	1 (1.8%)	1
COPD exacerbation	1 (1.3%)	1 (1.8%)	1
Uncontrolled pain requiring hospital admission	1 (1.3%)	0	1
Surgical site infection	0	0	-

COPD = chronic obstructive pulmonary disease; CRYO = cryoanalgesia.
*Two patients lost to follow-up.

Consistent with the findings of Khanbhai *et al.*'s[1] systematic review, postoperative pulmonary function changes were found to be equivocal in our study. Nonetheless, cryoanalgesia patients had higher initial volumes. This may be clinically important considering that thoracic surgery patients often have limited pulmonary reserves, and the respiratory depressive effects from opioids may exacerbate any pulmonary complications.

It is essential to note that cryoanalgesia creates numbness[22] in addition to pain relief.[23] Numbness is often confused for pain, causing distress in patients at this odd sensation.[23] However, the use of opioids will not affect numbness. Moreover, a multimodal approach that includes the use of chemically induced intercostal nerve blocks during surgery is important to bridge the gap as the axon degenerates and the full effect of cryoanalgesia becomes apparent.[24] Patients' pain scores support this concept, as CRYO patients experienced a decrease in pain from postoperative day 1-3 in contrast to the gradual decrease observed in SAT patients.

Cryoanalgesia works by ablating peripheral sensory nerves most often involved with incisional pain after thoracic surgery. This allows for a pain-free period promoting rapid recovery and reduces the risk for pain-related complications. However, two systematic reviews[1,4] expressed concerns for permanent nerve injury and variations in outcomes associated with cryoanalgesia. These concerns were generally based on probe setting parameters related to temperature, gas source, and duration of application. Subsequent research elucidated effective parameters for promoting safe and consistent pain relief with cryoanalgesia[9]; its success is directly related to accurate probe placement and post-procedure rehabilitation plan.[23]

Neuropathic-type pain after thoracotomy is not unique to cryotherapy,[25] with a reported incidence of 30%-60%.[5,25] Complications of hypersensitivity are possible[11]; however, the impact tends to be short termed and resolves as the nerve heals and sensation returns.[11] We found the use of gabapentin in patients receiving cryoanalgesia as an important empiric agent for counteracting anticipated transient degrees of dysesthesias as the nerve regenerates.[3,24] Patients with these complaints were often noncompliant with gabapentin dosing instructions, and symptoms improved once taken as directed. Successful outcomes are dependent on informing patients that they are trading pain for numbness. Education concerning realistic expectations after cryoanalgesia is imperative.

One patient in the CRYO group had postoperative pain and hypersensitivity, requiring inpatient admission for pain control within 2 wk after discharge, but the symptoms resolved by 3 mo. This is consistent with the findings of several recent trials demonstrating full resolution of neuropathic pain by 3-6 mo.[3,9,26] The potential for long-term hypoesthesia is possible but has not been reported as disabling[27,28] or significantly bothersome.[3,4] In our experience, these patients frequently had a greater amount of intercostal fat and muscle. Despite being easily visualized with a well-described anatomic location, the degree of intercostal muscle and pleural thickening may prevent sufficient nerve contact and pressure, resulting in variable outcomes. It has been postulated that incomplete cold thermal injury to the axon may cause electrical signal errors during axonal regeneration.[29] Intraoperative electromyography may be a useful addition for confirming nerve contact.[9,26] Our study had no patients with hypersensitivity or hypoesthesia beyond 90 d.

Historically, epidurals have been the standard modality for pain relief in thoracic surgery.[7] Although effective, several limitations exist, including reduced mobility, urinary retention, inability to use anticoagulants, limited duration of efficacy, and addition of 20-30 min operative time,[7] with an average cost of $1500.[30] A cryoablation probe costs approximately $2500 (personal communication; AtriCure), but the potential benefits for hospital cost savings may be realized when evaluating expenses for other pain control modalities, including drug delivery supplies, opioid drug costs, nursing time, operating room efficiency, and those associated with adverse events because of poor pain control. In addition, the potential benefits for mitigating patients' risk for opioid dependency and limiting the influx of circulating opioids within communities should be considered. Cryoanalgesia may serve as a beneficial alternative, given fewer contraindications, technical ease, longer duration of pain control, fewer mobility restrictions, and minimal risk.[11]

Limitations

Our study has several limitations. First, the retrospective nature of our study has inherent weaknesses, including the lack of blinding, thus potentially biasing results, which limits the ability to generalize our findings. Furthermore, the data were abstracted from the medical records and were dependent on accurate documentation of pain and IS values by nursing staff. Second, we did not analyze the potential contribution of comorbidities (smoking, alcohol use, and psychological issues), which was previously identified as predictors for new persistent opioid use after thoracic surgery.[17,20] Third, although the control group frequently had lower opioid amounts prescribed compared with published data for patients undergoing thoracic surgery,[19] we must consider the possibility of more liberal prescribing habits within this group, given only the recent shift in culture, centered on opioid-associated risks. Furthermore, analysis of opioid use after discharge would have been strengthened if we compared the actual number of tablets taken rather than the amount prescribed. Finally, there was variation in the administration of both gabapentin and liposomal bupivacaine as well as the use of epidurals between the groups, which complicates the interpretation of our results. Our findings would be stronger with greater consistency of medication administration between the groups. However, there is much debate regarding the efficacy of liposomal bupivacaine in significantly reducing opioid consumption after thoracic surgery. Presently, there is no consensus to preferentially recommend its use based on the current literature.[7,31-36] In addition, several studies have failed to demonstrate gabapentin's efficacy in reducing acute or chronic pain after thoracic surgery.[37-39] Although these variations were taken into consideration with statistical analysis, it is important to acknowledge the possibility for residual cofounding of unmeasured variables, which may reflect observed differences in outcomes. Furthermore, sensitivity analyses carry a greater chance for type II errors, given smaller sample sizes and the potential for lower power to detect a difference. Consequently, the results of these analyses should be interpreted with this in mind. Future large prospective randomized trials, inclusive of the previously mentioned limitations, are needed for demonstrating the promising benefits of cryoanalgesia in both opioid-naïve and tolerant patients undergoing thoracic surgery.

Conclusion

Our results suggest that cryoanalgesia during thoracic surgery is associated with lower inpatient opioid requirements and postoperative pain for both opioid-naïve and tolerant patients. Favorable trends for improved pulmonary function and reduced opioid requirements after hospital discharge are benefits not easily achieved using other strategies. The refinement of technique and equipment warrants consideration as an important adjunct within a multimodal approach for achieving opioid-sparing pain management.

Author Contributions

L.O., C.Q., and L.H. formulated the conceptual framework and methodology, participated in data collection, and were in charge with overall planning and supervision. C.Q. and L.H. preformed the clinical procedures. L.O. wrote the initial draft with support from A.D., C.Q., L.H., and V.O. who assisted with review and editing. A.D. and V.O. aided in interpretation of results and final edits of completed manuscript. L.O. and V.O. performed the data review, validated statistical analysis, and preparation of data figures.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2022.01.009.

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