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ORIGINAL RESEARCH

Intercostal Nerve Cryoanalgesia Versus Thoracic Epidural Analgesia in Lung Transplantation: A Retrospective Single-Center Study

Erin Isaza · Jesse Santos · Greg J. Haro · Joy Chen · Daniel J. Weber · Tobias Deuse · Jonathan P. Singer · Jeffrey A. Golden · Steven Hays · Binh N. Trinh · Marek Brzezinski · Jasleen Kukreja

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ABSTRACT

Introduction: The optimal pain management strategy after lung transplantation is unknown. This study compared analgesic outcomes of intercostal nerve blockade by cryoanalgesia (Cryo) versus thoracic epidural analgesia (TEA).
Methods: Seventy-two patients who underwent bilateral lung transplantation via clamshell incision at our center from 2016 to 2018 were managed with TEA ($N = 43$) or Cryo ($N = 29$). We evaluated analgesic-specific complications, opioid use in oral morphine equivalents (OME), and pain scores (0–10) through postoperative day 7. Adjusted linear regression was used to assess for non-inferiority of Cryo to TEA.
Results: The overall mean pain scores (Cryo 3.2 vs TEA 3.8, $P = 0.21$), maximum mean pain scores (Cryo 4.7 vs TEA 5.5, $P = 0.16$), and the total opioid use (Cryo 484 vs TEA 705 OME, $P = 0.12$) were similar in both groups, while the utilization of postoperative opioid-sparing analgesia, measured as use of lidocaine patches, was lower in the Cryo group (Cryo 21% vs TEA 84%, $P < 0.001$). Analgesic outcomes remained similar between the cohorts after adjustment for pertinent patient and analgesic characteristics ($P = 0.26$), as well as after exclusion of Cryo patients requiring rescue TEA ($P = 0.32$). There were no Cryo complications, with four patients requiring subsequent TEA for pain control. Two TEA patients experienced hemodynamic instability following a test TEA bolus requiring code measures. Additionally, TEA placement was

Erin Isaza and Jesse Santos contributed equally.

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E. Isaza
School of Medicine, University of California, San Francisco, San Francisco, USA

J. Santos
Department of Surgery, University of California, San Francisco, East Bay, San Francisco, USA

G. J. Haro · J. Chen · D. J. Weber · T. Deuse · B. N. Trinh · J. Kukreja (✉)
Division of Cardiothoracic Surgery, Department of Surgery, University of California, San Francisco, 500 Parnassus Ave, Suite MUW-405, San Francisco, CA 94143-0118, USA
e-mail: jasleen.kukreja@ucsf.edu

J. P. Singer · J. A. Golden · S. Hays
Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine, University of California, San Francisco, San Francisco, USA

M. Brzezinski
Department of Anesthesia, University of California, San Francisco, San Francisco, USA

delayed beyond postoperative day 1 in 33% owing to need for anticoagulation or clinical instability.
Conclusions: In lung transplantation, Cryo was found to be safe with analgesic effectiveness similar to TEA. Cryo may be advantageous in this complex patient population, as it can be used in all clinical scenarios and eliminates risks and delays associated with TEA.

Keywords: Cryoablation; Lung trans plantation; Bilateral thoracotomy; Thoracic epidural analgesia; Pain management

Key Summary Points
The clamshell incision used in lung transplantation is associated with significant postoperative pain. Cryoablation for pain control, a recognized method of regional analgesia, has not been studied in the context of lung transplantation.
Cryoanalgesia was found to be safe with similar analgesic effectiveness to thoracic epidural analgesia.
Cryoanalgesia offers multiple clinical advantages over the thoracic epidural analgesia, including one-time application without further monitoring and intervention in nearly all clinical scenarios.
Cryoanalgesia may be a useful alternative to thoracic epidural analgesia in lung transplant recipients.

INTRODUCTION

The clamshell incision used in lung transplantation is associated with substantial postoperative pain and requires multimodal analgesia to expedite patient recovery. Yet, the optimal pain management strategy in this patient population is still unknown. Thoracic epidural analgesia (TEA) can provide appropriate pain relief but has several limitations, including insertion site complications, hypotension, relative contraindication with anticoagulation, 24-h monitoring, and potential for pharmacy error [1–6]. Regional analgesia is an alternative to TEA and comes in the form of intercostal nerve blockade via liposomal bupivacaine injections and a more novel approach using cryoanalgesia (Cryo). Regional analgesia mitigates many of the limitations of TEA as it is done during the procedure under direct visualization, has decreased hypotension risk, and can be administered to most patients regardless of clinical condition. Additionally, it can optimize resource allocation, including pharmacy, pain specialists, and nursing, since preparation and continuous monitoring of TEA infusion is no longer needed.

Cryo is a mechanical analgesic technique that freezes the axons while leaving the structural sheath intact, allowing for regeneration of nerve function [7]. Cryo was first described in 1917 by Dr. Friedrich Trendelenburg [8], and while there has been a US Food and Drug Administration (FDA)-approved device since 2014 (cryoICE Cyroablation Probe, Atricure Inc; Mason, OH), the data in thoracic surgery is limited, with the use of Cryo confined to posterolateral thoracotomy [9–12]. Cryo has shown benefit in pediatric patients with pectus excavatum undergoing minimally invasive Nuss procedure [13–15].

Historically, our recipients were treated with postoperative TEA following lung transplantation. In July 2017 we transitioned to Cryo because of the aforementioned limitations of TEA. The purpose of this manuscript is to evaluate the safety and effectiveness of Cryo versus TEA in patients undergoing lung transplantation.

METHODS

Study Design

We retrospectively identified a series of 72 consecutive patients who underwent bilateral lung transplantation via clamshell incision and

who were managed with TEA (N = 43) or Cryo (N = 29) at our institution between May 2016 and August 2018. Prior to July 2017, TEA placement at level T4–6 was attempted on postoperative day 1 (POD 1) prior to extubation if clinically feasible, and infusion of 0.0625–1% ropivacaine was initiated. Eight patients from the TEA era did not have a TEA placed and were excluded from analysis. The study design is summarized in Fig. 1. After July 2017, intraoperative Cryo was performed on subsequent patients, with application to bilateral interspaces 3–7 under direct visualization during surgery. Each nerve bundle was cooled to − 60 °C with the cyroSphere probe (AtriCure Inc; Mason, OH) (Fig. 2). Patients undergoing re-transplantation or requiring extracorporeal membrane oxygenation prior to transplantation were excluded as they were considered to have differing postoperative recoveries that would hinder comparison.

The main outcomes included analgesic-specific complications, pain scores (mean and maximum) through POD7 by visual analogue scale (0–10), and total opioid use (primarily oxycodone and to a lesser degree fentanyl and hydromorphone) through POD7 measured in oral morphine equivalents (OME) [16–18]. Pain scores and opioid use were only assessed through POD7 as by that time, most patients have had all chest tubes removed and are transitioned to an oral pain regimen. Postoperative pain scores were gathered by UCSF nursing staff at predetermined intervals (every 4 h), per standard protocol at our institution. Of note, our program policy emphasizes rehabilitation of

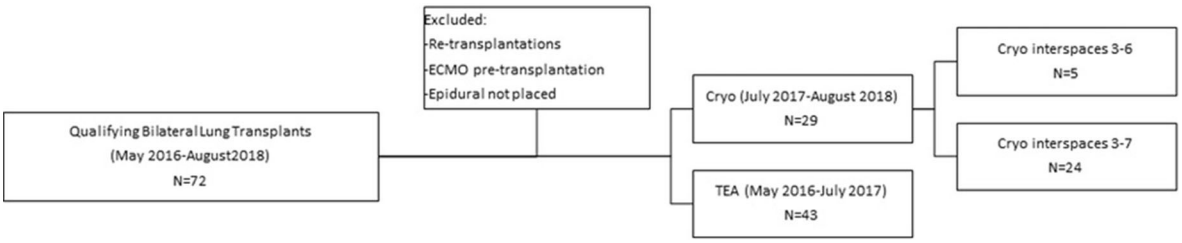

Fig. 1 Outline of study design, including exclusion criteria. All patients receiving any Cryo were analyzed as part of the Cryo cohort

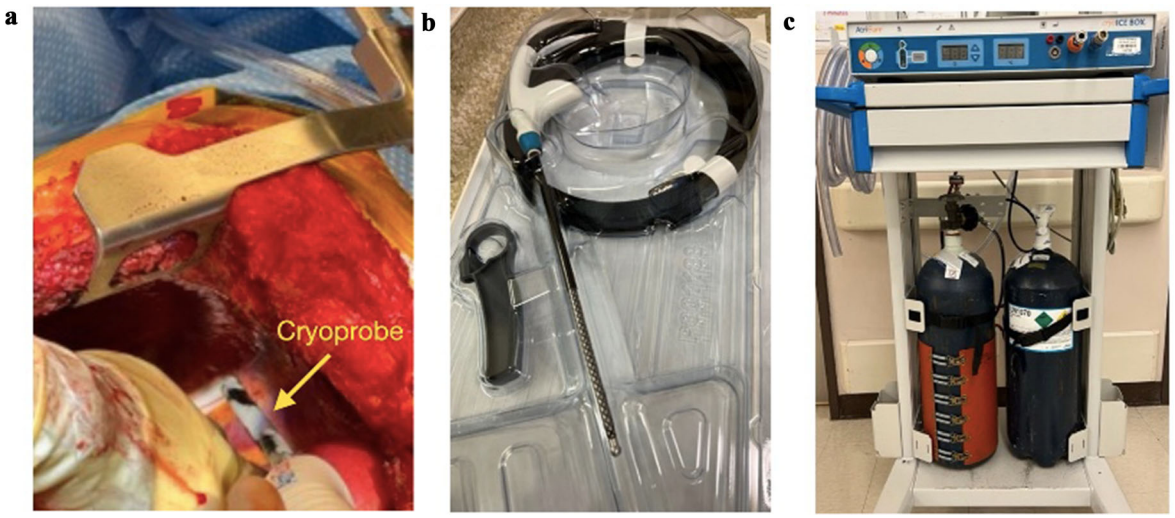

Fig. 2 **a** Intercostal nerve blockade by cryoprobe for lung transplant clamshell incision. **b** Packaged CryoSphere. **c** CryoICE box setup

intubated patients; intubated patients are not kept sedated and paralyzed and are able to provide pain scores. Postoperative multimodal analgesia consisting of acetaminophen, lidocaine patches, and opioid analgesics as needed was performed per standard of care regardless of treatment modality. Patients were followed until their first postoperative clinic visit.

The University of California, San Francisco Institutional Review Board approved the study and informed consent was waived as de-identified data were collected by chart review (Protocol 17-23961, Expiration December 25, 2019). This study was not supported by an external funding source. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Statistical Analysis

Descriptive statistics were used to evaluate baseline patient characteristics. Categorical outcomes were assessed with Fisher's exact test, and continuous outcomes were assessed with Student's *t* test for parametric distributions and Mann–Whitney *U* test for nonparametric distributions.

Linear regression models based upon a priori covariates were utilized to examine the outcomes. As a result of the sample size, the number of covariates that could be used was limited. Propensity scores [19] based upon baseline patient characteristics, including sex, diagnosis (restrictive vs obstructive lung disease), lung allocation score, and preoperative ICU admission, were utilized to overcome this limitation and to reduce the ability of these characteristics to predict the TEA and Cryo cohorts. The linear regression models were adjusted for these propensity scores in addition to pertinent analgesic covariates, including outpatient opioid history, postoperative opioid-sparing analgesia (acetaminophen, gabapentin, lidocaine patch), postoperative extracorporeal membrane oxygenation (ECMO), and postoperative tracheostomy. Nonparametric outcomes were log-transformed, and the β coefficients presented were exponentiated. Overall, the propensity scores and linear regression models did not violate model assumptions (Supplementary material—Evaluation of Linear Regression Models).

Missing data were found to be missing at random and no deletion or imputation methods were used. A predetermined two-sided alpha of 0.05 was considered statistically significant. All analyses were performed in Stata 15.1 (StataCorp LP; College Station, TX) using the following packages: pscore, psmatch2, pstest, and pbalchk.

RESULTS

Patient Characteristics

Twenty-nine Cryo and 43 TEA patients were identified from 2016 to 2018 (Table 1). There were substantial differences in baseline patient characteristics between the cohorts. Cryo patients were older (66 years vs 58 years, $P < 0.001$), had higher lung allocation scores (49 vs 44, $P = 0.002$), and required more pretransplant ICU admissions (38% vs 9%, $P = 0.006$) and intubations (24% vs 5%, $P = 0.026$). These differences not unexpectedly corresponded to Cryo patients demonstrating increased need for postoperative tracheostomy (42% vs 12%, $P = 0.006$) and increased length of stay (22 days vs 14 days, $P < 0.001$).

Analgesic Characteristics

An epidural was successfully placed in 67% of TEA cohort by POD1. TEA placement was delayed beyond POD1 in 33% owing to need for anticoagulation or clinical instability, and the last TEA was placed on POD4. Thirty-three percent of TEA patients required an increased dose of ropivacaine from 0.0625% to 1%, and 35% of patients required the addition of fentanyl to the infusion. The median epidural duration was 10 days [IQR 8–12] dictated primarily by the duration of indwelling chest tube.

In the Cryo cohort, four patients (14%) required rescue TEA for breakthrough pain. Three of these four patients were from our first five cases of early Cryo experience. In these first

Table 1 Patient and analgesic characteristics

Characteristics[a]	Cryo (N = 29)	TEA (N = 43)	p value
Age (years)	66 [63–69]	58 [49–65]	< 0.001
Male	19 (65.5)	24 (55.8)	0.41
White	18 (62.1)	29 (67.4)	0.639
Restrictive lung disease	24 (82.8)	31 (72.1)	0.3
Lung allocation score	49 [42–75]	44 [38–56]	0.002
Outpatient opioid use	2 (6.9)	8 (18.6)	0.175
Pre-transplant			
ICU admission	11 (37.9)	4 (9.3)	0.006
Intubated	7 (24.1)	2 (4.7)	0.026
Post-transplant			
ECMO	5 (17.2)	6 (14.0)	0.704
Time to extubation (days)	2.9 [1.6–11.4]	1.5 [0.8–2.7]	0.165
Tracheostomy	12 (41.7)	5 (11.6)	0.006
Length of stay (days)	21.5 [16.4–36.5]	13.8 [11.6–17.4]	< 0.001
Survival to discharge	27 (93.1)	42 (97.7)	0.363
Opioid-sparing analgesia			
Acetaminophen	26 (89.7)	43 (100.0)	0.111
Gabapentin	3 (10.3)	6 (14.0)	0.651
Lidocaine patch	6 (20.7)	36 (83.7)	< 0.001

Consecutive series of 72 patients who underwent bilateral lung transplantation via clamshell incision that was managed with cryoanalgesia (Cryo) or thoracic epidural analgesia (TEA) at our center from 2016 to 2018

Cryo cryoanalgesia, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *PGD* primary graft dysfunction, *TEA* thoracic epidural analgesia

[a]Continuous variables are presented as median [interquartile range]; categorical variables are presented as number (proportion)

five cases, we ablated four bilateral interspaces (interspaces 3–6). In all subsequent patients, we expanded Cryo to include five interspaces (3–7) to cover the chest tube insertion site. The fourth patient requiring subsequent TEA for pain control had a history of pre-transplant, outpatient opioid use and had the fifth highest opioid requirement of both cohorts.

Analgesic Effectiveness

Pain scores are summarized for both cohorts in Table 2 and Fig. 3. In the unadjusted analysis, Cryo and TEA had similar average pain scores through POD7 (3.2 vs 3.8, P = 0.21), maximum pain scores through POD7 (4.7 vs 5.5, P = 0.16), and total opioid doses through POD7 compared to TEA (484 vs 705 OME, P = 0.12) (Fig. 4).

Analgesic effectiveness remained similar between the two groups after adjustment for

Table 2 Unadjusted analgesic outcomes

Outcomes[a]	Cryo ($N = 29$)	TEA ($N = 43$)	*P* value
Analgesic-specific morbidity[b]	0 (0.0)	2 (4.7)	0.51
Pain score POD7 (0–10)[c]	3.2 ± 1.9	3.8 ± 1.6	0.21
Max pain score POD7 (0–10)[c]	4.7 ± 2.5	5.5 ± 1.8	0.16
Total opioid use POD7 (OME)[d]	484 ± 371	705 ± 582	0.12

Following clamshell incision for lung transplantation, cryoanalgesia (Cryo) was used to ablate bilateral interspaces 3–7, or thoracic epidural analgesia (TEA) was placed on the first postoperative day if clinically feasible

Cryo cryoanalgesia, *Pain Score POD7* overall pain score through postoperative day 7, *Max Pain Score POD7* overall maximum pain score through postoperative day 7, *TEA* thoracic epidural analgesia, *Total OME POD7* total oral morphine equivalent through postoperative day 7

[a]Continuous variables are presented as median [interquartile range] or mean ± SD; categorical variables are presented as number (proportion)

[b]Fisher's exact test

[c]Student's *t* test

[d]Mann–Whitney *U* test

pertinent patient and analgesic characteristics (Table 3), including average pain score through POD7 ($P = 0.31$), maximal pain score through POD7 ($P = 0.26$), and total opioid use through POD7 ($P = 0.42$).

A sub-analysis that excluded the four Cryo patients who required subsequent TEA did not alter the overall findings ($P > 0.32$).

The pre-transplant outpatient opioid use was similar in both groups (Cryo 7% vs TEA 19%, $P = 0.175$). While the post-transplant opioid use was similar in both groups (as noted above), the utilization of postoperative opioid-sparing analgesia, measured as use of lidocaine patches, was lower in the Cryo group (Cryo 21% vs TEA 84%, $P < 0.001$) (Table 1). As a result of concern for altered mental status, gabapentin was utilized postoperatively only in patients with prior preoperative use, and there was no substantial difference in use between the cohorts (10% vs 14%, $P = 0.651$).

Safety Profile

Regarding analgesic-specific morbidity (Table 2), there were no Cryo complications observed during the study period, while two TEA patients experienced hemodynamic instability following a test bolus of the local anesthetic after insertion requiring code measures. Both patients had a return of spontaneous

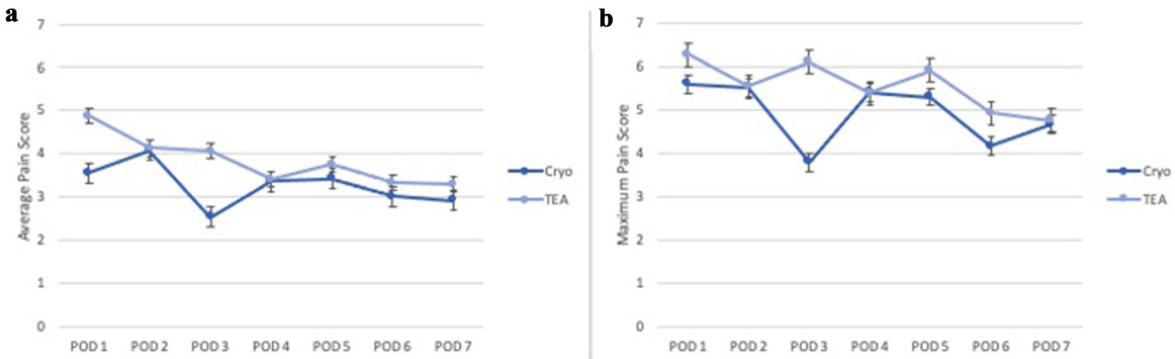

Fig. 3 Daily pain scores (0–10). Following clamshell incision for lung transplantation, cryoanalgesia (Cryo) or thoracic epidural analgesia (TEA) was utilized for pain management. In unadjusted analysis depicted in these figures, pain was overall well controlled. **a** Average pain score. Cryo and TEA had similar average pain scores through postoperative day 7 (POD7). **b** Maximum pain score. Maximum pain scores through POD7 were also similar between the cohorts. Data represent mean with standard deviation

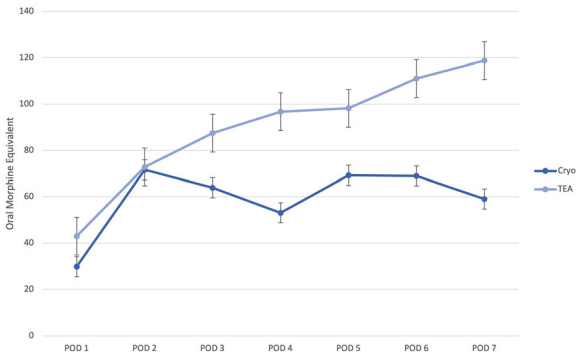

Fig. 4 Daily opioid use. Following clamshell incision for lung transplantation, cryoanalgesia (Cryo) or thoracic epidural analgesia (TEA) was utilized for pain management. In unadjusted analysis depicted in this figure, Cryo patients appeared to utilize fewer opioids through postoperative day 7 (POD7), and the difference in opioid use between cohorts appeared to increase over time. Data represent mean with standard deviation

circulation. There were no other complications associated with TEA.

DISCUSSION

Optimal pain control after a clamshell incision is an essential part of postoperative recovery. In this manuscript, we retrospectively reviewed a series of lung transplant patients who underwent either thoracic epidural placement or cryoanalgesia.

Our findings suggest that intercostal nerve blockade with cryoanalgesia in patients who undergo bilateral lung transplantation via clamshell incision is safe and has equivalent effectiveness compared to TEA. There was no statistically significant difference between the cohorts in pain score and total opioid use through POD7. While we did not measure pain scores or opioid use beyond POD7, it is notable that Cryo lasts much longer than 7 days (up to several months) and can provide postoperative pain control for the majority of a patient's recovery. In contrast, TEA is placed for a limited period only, and pain recurs after catheter removal.

We observed several potential advantages of Cryo over TEA in this patient population. For one, Cryo can be utilized in most (in this series in all) patients, with exceptions including patients with exposed intercostal nerves or thickened pleural scars. However, TEA is limited to those with "standard" postoperative recoveries. In fact, epidural placement in our study was delayed beyond POD1 in one-third of the

Table 3 Adjusted analgesic outcomes

Cryo vs TEA	β coefficient[c]	95% confidence interval	*P* value
All patients[a]			
Pain score POD7	0.68	− 0.67, 2.03	0.31
Max pain score POD7	0.97	− 0.73, 2.66	0.26
log total opioid use POD7	132%	67%, 261%	0.42
Excluding rescue TEA[b]			
Pain score POD7	0.63	− 0.81 2.07	0.38
Max pain score POD7	0.91	− 0.91, 2.73	0.32
log total opioid use POD7	120%	58%, 250%	0.62

Linear regression models that adjusted for pertinent patient and analgesic characteristics were utilized to assess differences in analgesic outcomes between cryoanalgesia (Cryo) and thoracic epidural analgesia (TEA). Covariates: propensity score (sex, diagnosis, lung allocation score, pre-transplant ICU admission), outpatient opioid history, postoperative opioid-sparing analgesia, postoperative ECMO, and postoperative tracheostomy

Cryo cryoanalgesia, *Pain Score POD7* overall pain score through postoperative day 7, *Max Pain Score POD7* overall maximum pain score through postoperative day 7, *TEA* thoracic epidural analgesia, *Total OME POD7* total oral morphine equivalent through postoperative day 7

[a]Analgesic outcomes were similar between Cryo and TEA following clamshell incision for lung transplantation

[b]Analgesic outcomes were not altered after exclusion of the four Cryo patients who required TEA

[c]β coefficient exponentiated for log outcomes

TEA subjects, which can translate into more systemic opioid use prior to epidural placement. The predominant reason for delay was need for postoperative ECMO, as the anticoagulation required for ECMO was a contraindication to epidural placement. Some degree of primary graft dysfunction occurs in about 80% of transplant recipients, with 16% having severe (grade 3) PGD [20]. Between 5% and 10% of patients with severe PGD will require ECMO as a bridge to recovery [21–23]; thus, a sizeable cohort of patients will have delayed epidural placement in anticipation of ECMO need in the near future. Other reasons for delay in placement included clinical instability unrelated to ECMO and unavailability of the pain specialist. Although there are centers that place TEA preoperatively [3], we utilize ECMO with anticoagulation intraoperatively on nearly all bilateral lung implantations, and it is our practice to place TEA postoperatively in the ICU prior to extubation. This practice allows for thorough post-transplant evaluation of the patient, including neurologic and hemodynamic status as well as risk of primary graft dysfunction. Cryo, in contrast, was successfully administered in all patients as it was independent of the clinical state and availability of the pain specialist to place the epidural. At our institution, it takes 20 min to ablate bilateral interspaces, and is performed either after native lung/hilar dissection while waiting for the arrival of the donor organs in the operating room or during ECMO wean post-implantation allowing controlled reperfusion of the allografts. As such, administration of cryoanalgesia does not prolong operative time. Second, TEA can be associated with analgesic-specific morbidity, defined as adverse events directly attributable to analgesia. While analgesic-specific morbidity was overall minimal in our study, two TEA patients experienced hemodynamic instability following a test bolus of ropivacaine requiring code measures. Of note, these patients had been clinically stable and received the standard dose and concentration of ropivacaine bolus. Life-threatening hemodynamic instability is rare, and TEA is more commonly associated with modest hypotension that can confound the clinical picture in these complex patients [2]. TEA can also be complicated by traumatic hematoma, infection with epidural abscess, and catheter migration necessitating replacement with repeat procedure [1–6]. TEA patients in our study did not experience any of these insertion site complications. In contrast to TEA, there were no observable complications associated with Cryo. While a possible association of Cryo with neuropathic pain has been previously reported [12], no Cryo patients in the study time period experienced neuropathic pain requiring pharmacologic intervention. It is possible that our findings are due to differing and improving equipment and techniques.

Beyond the aforementioned complications, TEA is labor intensive and detracts from managing more pertinent clinical issues. TEA requires 24-h monitoring and care by pain specialists, pharmacists, and nurses. In our study, over a third of the TEA patients required modification of the infusion to maintain adequate analgesia. In contrast, Cryo is an efficient analgesic method with a one-time application, which does not require further monitoring or care. While we were not able to perform direct cost comparison between TEA and Cryo, it is very likely that the costs of the drug (ropivacaine and/or fentanyl), its preparation by the pharmacist, and the need for daily monitoring by staff (both nursing and pain specialists) make TEA a much more costly venture than a single-use cryoablation probe and procedure.

Four Cryo patients did require TEA for pain control. Three of these patients were among our very first Cryo patients, and they received TEA out of concern for potential inadequacy of Cryo. In retrospect, these patients likely could have been maintained with Cryo alone. Regardless, we did alter our technique to ablate five interspaces as opposed to four on each side to cover the chest tube insertion site, and perhaps our improved subsequent outcomes were due to this modification. We found that the Cryo patients who required TEA did not influence the overall results of our study.

This retrospective study has several limitations. Over the 2 years of the study period, our lung transplantation program had a significant increase in emergency evaluation and transplantation of patients with acute on chronic

respiratory decompensation. In fact, prior to the institution of Cryo in July 2017, 29.7% of transplant patients were in the ICU prior to surgery, compared to 35.0% after July 2017 [24]. As such, the TEA and Cryo cohorts had substantial differences: Cryo patients were sicker, had higher lung allocation score, more tracheostomies, and longer hospital stays post-transplant. Although we adjusted for confounding characteristics, there may still be unmeasured variables that could alter the findings. Next, our database only contains opioid use and pain scores through POD7. As nerve regeneration after Cryo occurs over weeks to months, there may be differences in these outcomes that emerge with time between the techniques. We did not compare Cryo to other regional analgesics, such as liposomal bupivacaine injection, because of the latter's limited duration and potential altered pharmacokinectics in lung transplant recipients at risk of kidney and/or hepatic dysfunction from immunosuppressants and prophylactic antimicrobials. In addition, we recognize the inherent limitations given our small sample size. While we believe our data supports the conclusion that Cryo and TEA have equivalent postoperative analgesic effects, further studies are necessary prior to drawing definitive conclusions regarding differences in complications and long-term outcomes. Despite these limitations, this study represents the first evaluation of Cryo in patients undergoing lung transplantation via a clamshell incision and demonstrates its safety and effectiveness.

CONCLUSIONS

Intercostal nerve blockade by cryoablation in lung transplantation was found to be safe with analgesic effectiveness similar to TEA. Cryo may be particularly advantageous in the complex lung transplant patient population as it eliminates the inherent risks of TEA, can be used in all patients regardless of the clinical scenario, and does not require ongoing monitoring and care.

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Author Contributions. The study was conceptualized by Greg J. Haro, Marek Brzezinski, and Jasleen Kukreja. Material preparation, data collection and analysis were performed by Erin Isaza, Greg J. Haro, Daniel J. Weber, Joy Chen, Marek Brzezinski, and Jasleen Kukreja. The draft of the manuscript was written by Erin Isaza, Jesse Santos, and Greg J. Haro and all authors commented on previous versions of the manuscript. All authors read and reviewed the final manuscript.

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Golden, Steven Hays, and Binh N. Trinh have nothing to disclose.

Compliance with Ethics Guidelines. The University of California, San Francisco Institutional Review Board approved the study and informed consent was waived as de-identified data were collected by chart review (Protocol 17-23961, Expiration December 25, 2019). This study was performed in compliance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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