Cryoablation in lung transplantation: Its impact on pain, opioid use, and outcomes

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ABSTRACT

Objective: To assess the effect of intraoperative cryoablation on postoperative patient-reported pain, opioid use, and clinical outcomes in lung transplantation.

Methods: We performed a single-center retrospective cohort study of adult lung transplant recipients from August 2017 to September 2018. We compared outcomes of patients who received intraoperative cryoablation of the intercostal nerves with those who did not. Primary outcomes were postoperative patient-reported pain scores and opioid use. Secondary outcomes included postoperative sedation and agitation levels and perioperative outcomes. Data were abstracted from patients' electronic health records.

Results: Of the 102 patients transplanted, 45 received intraoperative cryoablation (intervention group) and 57 received the standard of care, which did not include intercostal or serratus blocks or immediate postoperative epidural placement (control group). The intervention group had significantly lower median and maximum postoperative pain scores at days 3 and 7 and significantly lower oral opioid use at days 3, 7, and 14 compared with the control group. Chronic opioid use at 3 and 6 months' posttransplant was lower in the intervention group. Differences in perioperative outcomes, including length of mechanical ventilation, sedation and agitation levels, and hospital stay, were not clinically meaningful. Survival at 30 days and 1 year was superior in the intervention compared with the control group.

Conclusions: Findings suggest that use of intraoperative cryoablation is an effective approach for treating pain and reducing opioid use in patients who undergo lung transplant, but a randomized study across multiple institutions is needed to confirm these findings. (JTCVS Open 2023;13:444-56)

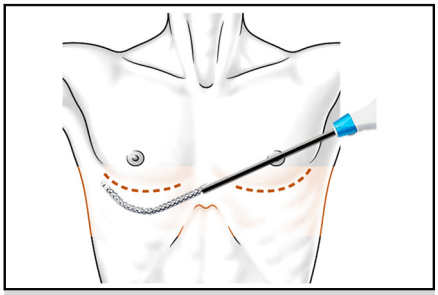

Figure depicts our study's intervention, cryoablation of the intercoastal nerves.

CENTRAL MESSAGE

Lung transplant recipients who received intraoperative cryoablation of the intercostal nerves had significant reduction in oral opioid use and postoperative pain scores compared with those who did not.

PERSPECTIVE

Identification of effective strategies to treat pain after lung transplant is critical for improved clinical outcomes and health-related quality of life. Our study presents an effective approach for treating pain using intraoperative cryoablation of the intercostal nerves.

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Abbreviations and Acronyms

EHR = electronic health record
FEV1 = forced expiratory volume at 1 second
HRQOL = health-related quality of life
ICU = intensive care unit
IV = intravenous
LAS = lung allocation score
RASS = Richmond Agitation-Sedation Scale

▶ Video clip is available online.

Pain following lung transplant is a major concern among patients, commonly occurs,[1,2] and is often poorly controlled.[2] Importantly, pain interferes with the goals of lung transplantation, contributing to adverse clinical outcomes[1,3] and decreased and health-related quality of life (HRQOL).[4,5] In addition, poorly controlled postoperative pain is a strong predictor of chronic pain,[3] a prevalent issue following lung transplantation, affecting 10% to 75% of recipients.[4,6-9] Identification of effective strategies to treat pain is critical for improved outcomes.

Current postoperative pain-management strategies for lung transplantation are not adequately effective.[2,5] Thoracic epidurals and paravertebral blocks are the first-line regional anesthetic strategies for thoracic surgical procedures.[10] However, anatomical abnormalities and concerns for coagulopathy, infection, and hemodynamic compromise limit their use in patients who undergo lung transplant.[11-15] Opioids are commonly administered postoperatively but often do not adequately control pain. Many recipients of lung transplants are discharged with opioid prescriptions and up to one-third become chronic opioid users.[1,4] Chronic opioid use after lung transplant is associated with reduced lung function,[16] mortality,[16] and poor HRQOL.[6,8,16]

Few studies have focused on nonpharmacologic approaches to reduce postoperative pain after lung transplant. Cryoablation of nerves provides immediate and temporary pain relief for up to 60 days.[17] This approach has been effective at treating postoperative pain and reducing opioid use in other populations,[17-19] but its use remains understudied in lung transplantation.[20] The aim of this study was to assess the impact of intraoperative cryoablation on postoperative patient-reported pain, opioid use, and clinical outcomes in lung transplantation.

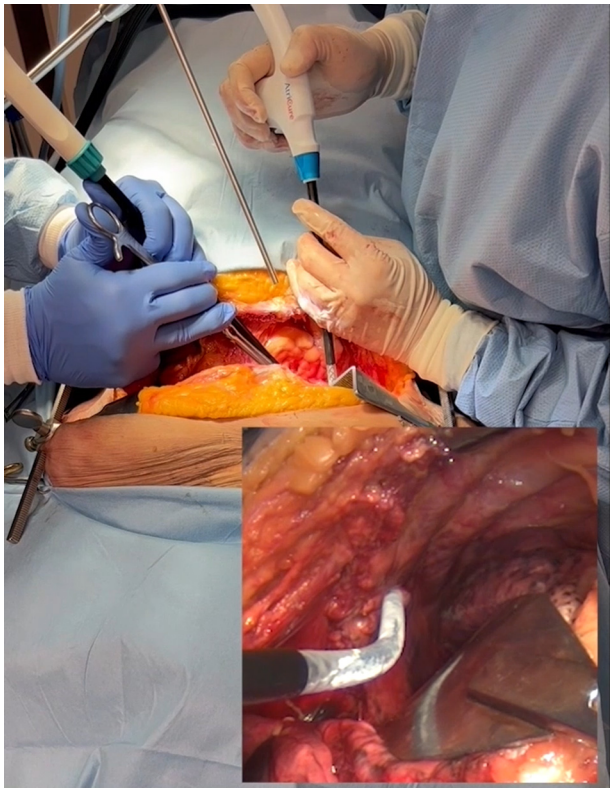
METHODS

Study Design

This was a single-center retrospective cohort study of adult (>18 years) single- and double-lung transplant recipients from August 2017 to September 2018. We excluded patients who underwent multiorgan and redo transplant surgeries. During our study period, our center was led by 2 lung transplant surgeons who worked collaboratively to determine transplant candidacy and donor acceptance and standardized their intraoperative and perioperative practice (ie, chest tube placement/management, postoperative pain management). In August 2017, one surgeon initiated the routine use of intraoperative cryoablation in an effort to better address postoperative pain, whereas the other surgeon maintained the standard of care. Patient assignment to either the surgeon performing cryoablation or the surgeon performing standard of care was determined by the date of transplant surgery and corresponding surgeon on call. The patient's date of transplant surgery is unpredictable and dependent on organ allocation, a random process based on organ availability, recipient medical urgency, and recipient and donor blood type, size, and antibody compatibility. Surgeon call schedule was randomly developed. We reviewed patients' charts and classified the transplanted cohort into 2 groups: patients who received intraoperative cryoablation (intervention group) and those who did not (control group). The study was approved by the Institutional Review Board of the University of Pennsylvania on July 17, 2018 (Protocol #831186). Patient written consent for the publication of the study data was waived by the Institutional Review Board because the mortality rate among patients who receive lung transplantation is high, it is not possible to obtain consent from deceased patients, and excluding patients who are deceased would introduce significant bias.

Procedures

Bilateral anterolateral sternal-sparing thoracotomy and bilateral thoracosternotomy are the preferred surgical approaches at our institution.



VIDEO 1. This video demonstrates the methods used to perform the study's intervention, intraoperative cryoablation of the intercostal nerve. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00383-7/fulltext.

Figure E1 presents our standardized intraoperative anesthesia and postoperative pain-management protocol for lung transplantation. All patients received standard posttransplant management. Neither cohort received local anesthetic for pain management. Mechanical ventilation was discontinued when patients were awake and demonstrated hemodynamic and respiratory stability on minimal ventilator settings. Patients worked with a physical therapist daily until hospital discharge. Patients were discharged from the intensive care unit (ICU) to our step-down unit when deemed safe and appropriate by our ICU team.

Patients in the intervention group underwent intraoperative cryoablation of the intercostal nerve (Video 1). Intraoperatively, the surgeon performed 1 session of cryoablation (–50 °C to –70 °C for 120 seconds) using the AtriCure *Cryo*ICE cryoablation system (AtriCure, Inc). Under direct visualization, the surgeon identified the intercostal nerves and ablated at 4 levels (intercostal space of entry, 1 space above and 2 spaces below) before lung implantation. These 4 spaces were selected to cover the pericostal suture area, the entry space, and 2 spaces below entry where chest tubes are placed. Total treatment time was 8 minutes for single and 16 minutes for bilateral lung transplants.

Data Collection

We abstracted data on patient demographic and clinical characteristics from the electronic health record (EHR). Demographic variables included age, sex, and race/ethnicity. Clinical variables included lung diagnostic group, body mass index, preoperative mechanical ventilation or extracorporeal membrane oxygenation, transplant type, and lung allocation score (LAS). We identified patients with pretransplant chronic pain syndrome, defined as patients with documented pain and pharmacologic treatment for at least 6 months.

Primary Outcomes

The primary outcomes of this study were group differences in postoperative patient-reported pain and opioid use. Bedside nurses (blinded to the study) assessed and documented patients' pain level at least every 4 hours (7 AM/PM, 11 AM/PM, 3 AM/PM, and as needed) according to our center's standardized pain assessment protocol. Nurses assessed pain using the Numeric Rating Scale; an 11-point scale ranging 0 ("no pain") to 10 ("worst pain imaginable").[21] We abstracted pain scores from the EHR. Pain scores can be confounded by the frequency of pain assessment or by heterogeneity in patient activity. For this reason, we examined differences among the intervention and control groups' expected values for median and maximum pain level per postoperative day. We defined the maximum pain level as the greatest patient-reported pain score per postoperative day. To assess oral opioid use, we obtained daily delivered doses of oral opioids from the patients' medication administration record in the EHR. We converted opioid doses to morphine milligram equivalents.[22] We also compared the intervention and control groups' total intravenous (IV) and oral opioid use by postoperative day. We focused on model-based estimates for days 3, 7, 14, and 21 because these days correspond to important clinical milestones. Days 0 to 3 are primarily ICU days. By day 3, most patients are extubated and transitioned to oral medications. Days 3 to 14, patients are typically transferred to the step-down unit and engaging in physical activity. By day 21, most patients are ready for discharge from the hospital.

Secondary Outcomes

Secondary outcomes included postoperative sedation and agitation levels and clinical outcomes including length of mechanical ventilation, length of hospital stay, 30-day and 1-year survival, forced expiratory volume at 1 second (FEV1), and chronic opioid use in the first postoperative year. We determined patients' sedation and agitation level using the Richmond Agitation-Sedation Scale (RASS). The RASS is a 10-point scale, with 4 levels of agitation (+1 "restless" to +4 "combative"), 1 level to denote a calm and alert state (0), and 5 levels of sedation (−1 "drowsy" to −5 "unarousable").[23] Bedside nurses assess and document the patient's RASS score in the EHR every 4 hours. We compared the 2 groups' expected average RASS score per postoperative day. The FEV1 was routinely performed after transplant in the outpatient clinic. We collected FEV1 tests from the EHR at 1, 3, 6, and 12 months' posttransplant. We restricted our analysis to bilateral recipients because native lung function can affect FEV1 values in unilateral recipients. We defined chronic opioid use at 3, 6, and 12 months' posttransplant by reviewing patients' medication list in the EHR, which is updated at each clinic visit.

Statistical Analysis

For patient-level analysis of the intervention's main effects, we implemented a 2-step approach to limit bias from confounding. Step 1 used model-based inverse probability weighting, a method based on propensity score modeling, to adjust for potential confounding arising from patient differences across groups. This approach modeled the combination of era (before and after the start of the treatment era) and actual treatment (intervention vs control), as 4-level outcomes in a regression model in which patient characteristics were the independent variables. Using multinomial logistic regression, with the 4 levels of outcome defined by intervention group (2) and period (2), we first modeled these 4 groupings as a function of patient characteristics: the a priori-defined confounders (age, diagnosis, transplant type, and LAS). Predicted values from this logistic regression resulted in a probability that each patient, with their characteristics, would be in each group. The inverse of this probability for the actual group to which the patient belonged was the weight assigned to that patient. When each patient's frequency is multiplied by their weight for his or her actual group, the result is groups with equal weighted totals, that total being the sample size for the entire study. When patients differ across groups, their weights differ, and these weights account for patient differences. By weighting each patient's observation, this approach produces groups of patients with similar characteristics to adjust for any differences and reduce confounding. In subsequent analyses, we assessed balance by comparing each covariate distribution across these weighted samples to show similarity.[24]

Lung transplant recipients who received intraoperative cryoablation of the intercostal nerves had significant reduction in oral opioid use and postoperative pain scores compared with those who did not. Step 2 used weighted random effects multivariate longitudinal response models with time from transplant modeled by day. To allow for nonlinear effects of time (days posttransplant), each analysis modeled time as a cubic spline with knots at days 3, 7, 14, and 21 days. Thus, we could estimate the daily expected values over time based on when the values were collected. These expected values were standardized using observation weights, from step 1, to adjust for patient differences.

In this model, we used both a random intercept and a random slope (for time) for each patient to accommodate random variation from the pain values in outcomes across patients over posttransplant follow-up and the correlations over time of these measures within patients. Based on the same type of model, we were also able to estimate the expected value over time for mean opioid requirement in morphine milligram equivalents for each postoperative day for each patient, standardized across (controlling for) patient characteristics. We displayed expected values, of pain, for example, over time by means of curves to trace pain levels and trajectories from transplant until the end of observation. Using the same method, we also estimated the differences in heights between the curves, representing differences between groups, at the prespecified days: 3, 7, 14, and 21. In all reports, statistical significance of results is reflected in the 95% confidence intervals reported for point estimates of these differences.

Secondary outcomes were analyzed using the Fisher exact test and the Kruskal–Wallis ranked test to compare differences in categorical variables and nonparametric variables respectively. The Kaplan–Meier method was used for survival analysis and the log-rank method for group comparisons. All analyses were performed using the programs "mixed," "mlogit," and "margins" within the Stata statistical package, versions 15.1, 16.0, and 17.0 (Stata Corp).

TABLE 1. Cohort characteristics

Patient characteristics	Total cohort (n = 102)	Intervention (n = 45)	Control (n = 57)
Age, y, median (IQR)	60.2 (52, 67)	65 (58, 67)	61.4 (49, 67)
Sex: male, n (%)	60 (58.8)	25 (55.6)	35 (61.4)
BMI, median (IQR)	25.0 (21.9, 28.7)	25.3 (22.7, 31.9)	24.8 (21.5, 27.8)
LAS, median (IQR)	44.9 (39.4, 84.0)	42.4 (37.4, 67.1)	48.3 (41.2, 87.6)
Hispanic/Latino, n (%) (n = 308)	4 (4.0)	2 (4.4)	2 (3.6)
Race			
Asian/Asian American	4 (3.9)	2 (4.4)	2 (3.5)
Black/African American	14 (13.7)	5 (11.1)	9 (15.8)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)
White	83 (81.4)	38 (84.4)	45 (79.0)
Other	1 (1.0)	0 (0)	1 (1.8)
Transplant type			
Single	23 (22.5)	11 (24.4)	12 (21.1)
Bilateral	79 (77.5)	34 (75.6)	45 (78.9)
ECMO bridge to transplant (n = 308)	6 (5.9)	2 (4.4)	4 (7.1)
Mechanical ventilation preoperative (n = 308)	7 (6.9)	2 (4.4)	5 (8.8)
Diagnostic group			
Obstructive	25 (24.5)	12 (26.7)	13 (22.8)
Pulmonary vascular	6 (5.9)	5 (11.1)	6 (10.5)
Infective	15 (14.7)	0 (0)	10 (17.5)
Restrictive	56 (54.9)	28 (62.2)	28 (49.1)
Chronic pain syndrome (n = 307)	26 (25.7)	12 (26.7)	14 (25.0)

IQR, Interquartile range; *BMI*, body mass index; *LAS*, lung allocation score; *ECMO*, extracorporeal membrane oxygenation.

RESULTS

Patient Characteristics

In total, 102 patients met inclusion criteria for this study (Figure E2). The cohort's median age was 60 years. A majority of the cohort was male (60%) and White (81%). More than one-half the cohort had restrictive lung disease (55%), and 25% had a previous history of chronic pain syndrome. A small proportion of patients were bridged to transplant with extracorporeal membrane oxygenation (6%) or mechanical ventilation (7%). The cohort's median LAS at time of transplant was 44.9, and most patients underwent bilateral lung transplant surgery (78%) (Table 1). Of the 102 lung transplant recipients, 45 patients received intraoperative cryoablation (intervention group) and 57 patients did not (control group). Our method of standardization using weights adjusted for differences in patient characteristics between groups.

Differences in Pain Scores

Among both the intervention and control groups, pain scores increased over the first 2 weeks following surgery and decreased thereafter (Figures 1 and 2). Compared with the control group, the intervention group consistently had lower median and maximum pain scores over time. The expected values for median pain scores at day 3 and day 7 were significantly reduced among the intervention group, whereas the difference attenuated slightly at day 14 and 21 (differences [95% CI]: day 3: 1.0 [0.4-1.8]; day 7: 1.0 [0.1-1.9]; day 14: 0.9 [–0.3 to +2.1]; day 21: 0.6 [–0.8, +1.9]) (Table E1). Similarly, the expected values for maximum pain scores at day 3 and day 7 were significantly lower and remained lower at days 14 and 21, although not at conventional levels of statistical significance (differences [95% CI]: day 3: 1.5 [0.2-2.5]; day 7: 1.3 [0.2-2.5]; day 14: 1.2 [–0.3, +2.6]; day 21: 0.7 [–1.0, +2.5]) (Table E2).

Differences in Opioid Use

In the first few postoperative days, oral opioid use was minimal, as patients' pain and sedation were managed by the ICU team with continuous IV medications. By day 3, patients were typically weaned from continuous IV medications and oral opioids were administered according to patient-reported pain levels. Oral opioid use for the cohort

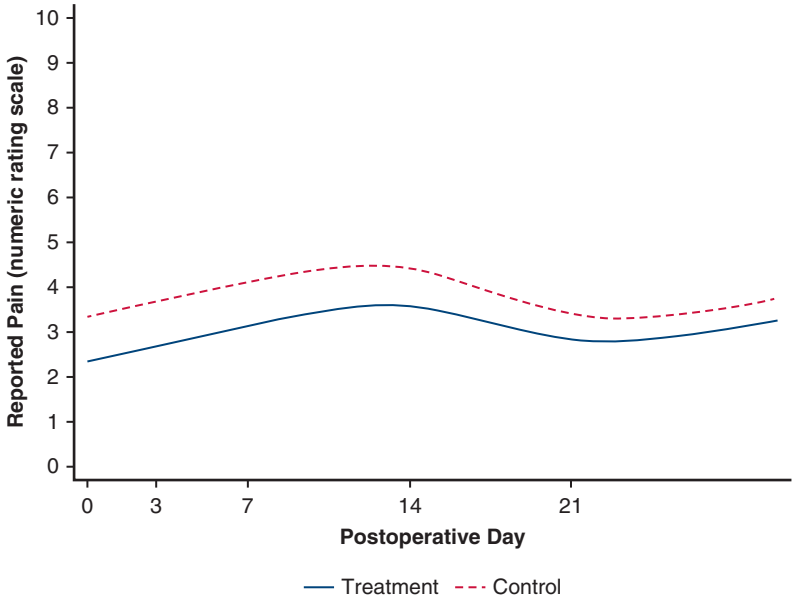


FIGURE 1. Median pain scores. Median pain score by postoperative day for intervention versus control groups. Greater values reflect greater pain.

sharply increased after day 3 until approximately day 14 and thereafter began to decline (Figure 3).

Oral opioid use was significantly lower in the intervention compared with the control group at days 3, 7, and 14 and remained lower at day 21 but not significantly (differences [95% CI]: day 3: –8.3 [–14.6, –1.9]; day 7: –16.5 [–28.6 to –4.3]; day 14: –19.1 [–34.3 to –4.0]; day 21: –12.9 [–30.4 to +4.5]) (Table E3). In addition, these reductions were not offset by increased IV opioids or epidural placements (8.9% intervention vs 12.3% control group).

Secondary Outcomes

Overall, the trend over time for RASS scores for the entire cohort shifted from light sedation on postoperative day 0 to drowsy on day 7 and then to alert and calm by day 14. Differences in RASS scores between the intervention and control groups were not statistically significant (differences [95% CI]: day 3: 0.10 [–0.30 to +0.51]; day 7: 0.06 [–0.25 to +0.37]; day 14: 0.0 [–0.26 to +0.26]; day 21: 0.0 [–0.17 to +0.18]) (Table E4). A graphical depiction of daily group comparisons is presented in Figure 4.

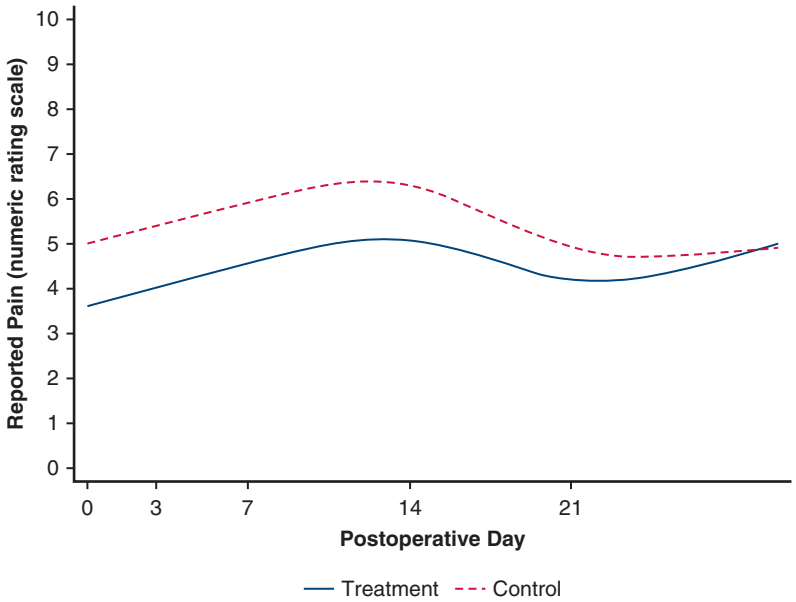


FIGURE 2. Maximum pain scores. Maximum pain per postoperative day for intervention versus control groups. Maximum pain level defined as the greatest patient-reported pain score per postoperative day. Greater values reflect greater pain.

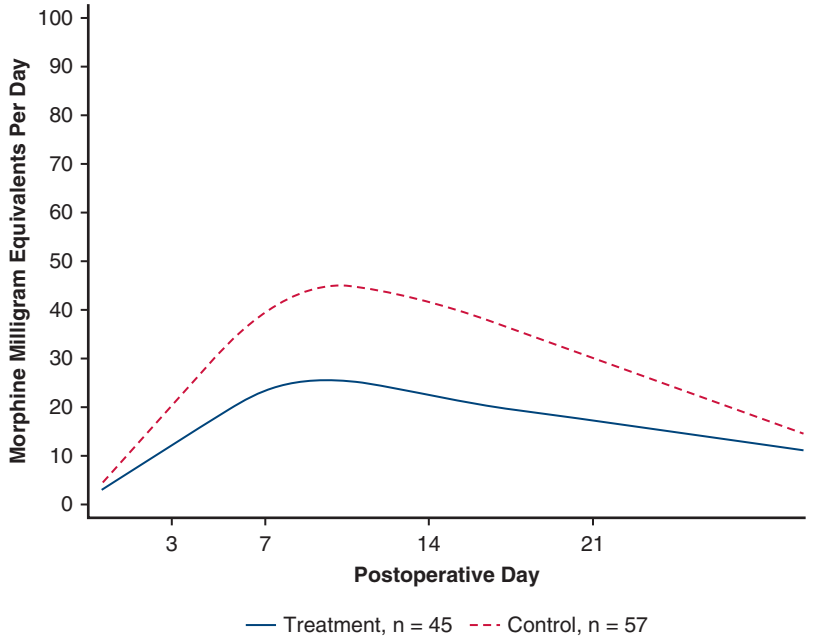


FIGURE 3. Oral opioid use. Oral opioid use in morphine milligram equivalents per postoperative day for intervention versus control groups.

Patients in both groups achieved similar perioperative outcomes, including median length of mechanical ventilation and hospital stay (Table 2). Survival at 30 days was significantly greater in the intervention compared with the control group. Survival at 1 year was also greater in the intervention group, but this difference was not significant (Table 2).

Chronic opioid use at 3 and 6 months' posttransplant was lower in the intervention compared to the control group; however, observed differences were not statistically significant. At 12 months' posttransplant, the control group had a sharper decline in opioid use compared with the intervention group, but group differences were not statistically

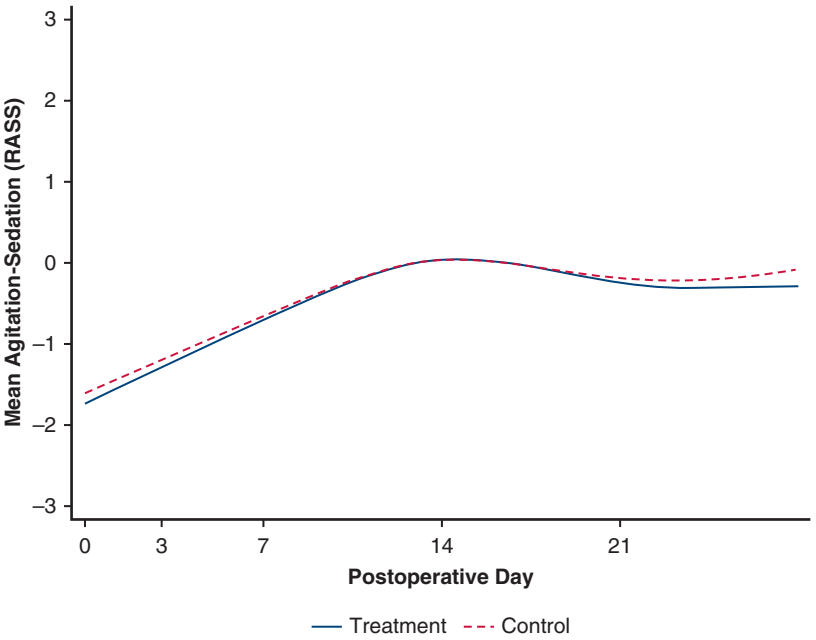


FIGURE 4. Postoperative Richmond Agitation-Sedation Scores (*RASS*) comparisons for intervention versus control groups. RASS 10-point scale includes 4 levels of anxiety or agitation (+1 "restless" to +4 "combative"), 1 level to denote a calm and alert state (0), and 5 levels of sedation (−1 "drowsy" to −5 "unarousable").

TABLE 2. Secondary outcomes

Outcome	Intervention N = 45	Control N = 57	Difference % points (95% CI)
Length of ventilation, median (IQR)			
Single, N = 24	2 (1, 5)	1 (1, 2)	0 (–2, 1)
Bilateral, N = 76	3 (2, 6)	3 (1, 7.5)	0 (–1, 1)
Length of stay, d, median (IQR)			
Single, N = 24	10 (14, 22)	14 (13, 18)	1 (–4, 6)
Bilateral, N = 78	22.5 (17, 28)	21 (14.5, 29)	–2 (–7, 2)
Outpatient opioid use			
3-mo use, n (%), N = 97	13/45 (29%)	20/52 (38%)	–9.6 (–28.3, +9.1)
6-mo use, n (%), N = 96	8/44 (18%)	14/52 (27%)	–10.0 (–28.3, +9.1)
12-mo use, n (%), N = 92	6/42 (14%)	4/50 (8%)	–9.6 (–28.3, +9.1)
Outpatient opioid use among patients without preoperative chronic pain syndrome			
3-mo opioid use, n (%), N = 72	6/533 (18%)	12/39 (31%)	–12.6 (–32.1, +7.0)
6-mo opioid use, n (%), N = 72	4/33 (12%)	7/39 (18%)	–5.8 (–22.2, +10.6)
12-mo opioid use, n (%), N = 69	2/32 (6%)	1/37 (3%)	3.5 (–6.3, +13.4)
Survival (cumulative incidence)			
30-d	1.0	0.93	7.0 (0.6, 13.4)*
1-y	0.93	0.88	5.6 (−6.1, +17.3)

CI, Confidence interval; *IQR*, interquartile range. *Confidence bounds do not cross 0 and reflect differences that are statistically significant at conventional levels.

significant (Table 2). We performed a sensitivity analysis that excluded all patients with preoperative chronic pain syndromes. Findings were consistent in this analysis; the intervention group demonstrated a nominal reduction in opioid use at 3 and 6 months compared with the control group, but findings did not reach statistical significance (Table 2).

A summary of the changes in FEV1 over time is depicted in Figure 5. At 1 and 3 months' posttransplant, FEV1 values in the intervention and control groups were similar (1 month: 66% interquartile range [IQR] [59, 74] vs 67.5% IQR [58, 83]; 3 months: 68% IQR [58, 77] vs 71.5% IQR [60.5, 89]). At 6 and 12 months' posttransplant, we observed improvements in FEV1 over time in the intervention group (6 months: 73% IQR [54, 87]; 12 months: 83.5% IQR [73, 88]) but declines over time in the control group (6 months: 67% IQR [57, 79]; 12 months: 63.5% IQR [57, 84]) (Table E5).

DISCUSSION

Findings from this study suggest that intraoperative cryoablation is an effective pain-management strategy for lung transplantation. Our intervention group reported lower pain scores and had substantial reductions in oral opioid requirements. We also observed lower chronic opioid use at 3 and 6 months' posttransplant in the intervention group. The use of cryoablation did not result in any clinically meaningful differences in perioperative outcomes. We did observe superior 30-day and 1-year survival among the intervention compared with the control group, although differences were small. Finally, patients in the intervention group achieved sustained improvements in FEV1 over time (Video Abstract).

Few studies have focused on postoperative pain and opioid-sparing pain-management approaches in lung transplantation. Overall, we found that pain levels initially increased over the first 2 weeks following surgery and then decreased. This postoperative pain trajectory has been previously identified in the literature[1] and corresponds to important clinical milestones that patients may perceive as painful. Although both groups followed a similar postoperative pain trajectory, we found that the intervention group reported lower pain scores at each time point. Median pain scores were approximately 1 point less and maximum pain scores up to 1.5 points less than the control group over time, differences that are clinically relevant.[10] We also observed an opioid-sparing benefit with the use of cryoablation. The intervention group had lower daily opioid use immediately; this was sustained for the duration of hospitalization. The benefit of cryoablation seemed to increase over time as the difference in opioid use became increasingly more pronounced in the first 2 postoperative weeks, as patients were weaned from IV medications and engaged in more physical activity. Our finding that the intervention group was able to

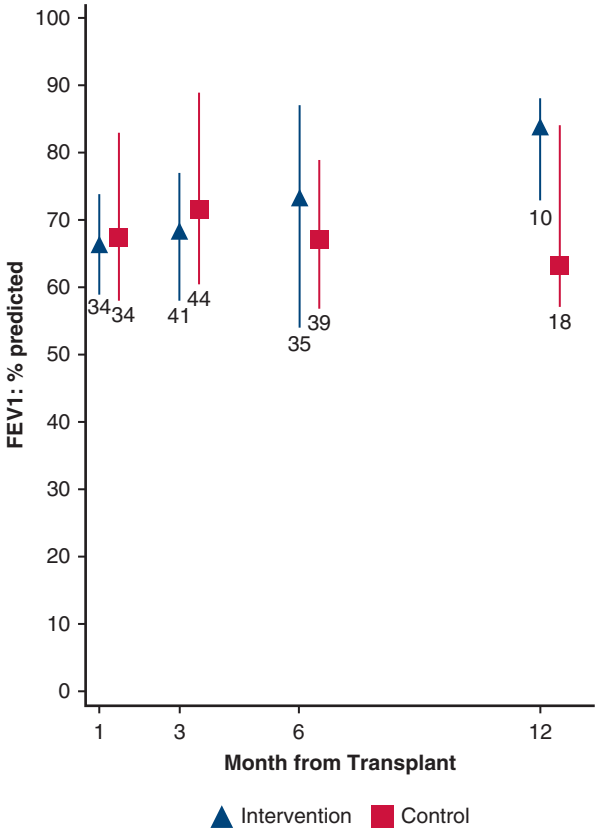


FIGURE 5. Percent predicted FEV1. Comparisons for percent predicted FEV1 over time for the intervention and control group. The triangles (intervention group) and squares (control group) depict the median percent predicted FEV1 for the specified month after transplant. Bars demonstrate interquartile ranges. *FEVI*, Expiratory volume at 1 second.

achieve clinically relevant reductions in pain with reduced opioid use is critically important because severity of postoperative pain and introduction of opioids are important predictors of chronic pain and opioid use,[25,26] both of which are prevalent issues in this population.

Although cryoablation seems to be effective at reducing pain and opioid use, not all patients in the intervention group experienced pain relief; 9% required a postoperative epidural. It is not clear why epidural rescue was required in a subset of patients. We speculate that this could be due to technical error in failing to ablate the intercostal nerve, particularly in patients with obesity when this nerve is not visible. It is also possible that epidural rescues were needed in patients with a preexisting chronic pain syndrome in which pain was not alleviated by cryoablation. Mechanisms to explain this observation need to be further explored.

We observed a nominal reduction in opioid use at 3 and 6 months' posttransplant among the intervention compared with the control group. Findings were similar in our sensitivity analysis that excluded patients with preoperative pain syndromes. Findings suggest that cryoablation may have positive effects on reducing pain and subsequent opioid use after discharge. This raises an important question about whether interventions, such as cryoablation, that reduce exposure to prescribed opioids may reduce chronic opioid use. This is a critical issue in lung transplantation that has not been adequately addressed.

There is some concern in the literature that the use of cryoablation may cause changes in chest wall mechanics due to intercostal muscle paralysis that may affect respiratory function.[27] However, we did not observe negative effects with the use of cryoablation on respiratory function over time. We observed a steady increase in FEV1 over time in the intervention group that became markedly better than the control group by 6 months' posttransplant, whereas the control group had similar improvements in FEV1 within the first 3 months, but then subsequent declines. These findings are important, but the mechanisms linking the use of cryoablation to improved respiratory function are unknown and an important area for future research.

We acknowledge that our study has several limitations. This was a single-center study, which could potentially limit the generalizability of our findings. However, the sociodemographic and clinical characteristics of our cohort are comparable with the national lung transplant population.[28] Our sample was relatively small, with few patients with infectious lung disease, all of whom were randomly allocated to the control group. Although we were able to achieve a larger sample than previous studies,[20,29] future research should ensure an adequate case mix among the intervention and control groups. The intervention was initiated by 1 of 2 surgeons at our center, and intervention effects were retrospectively examined. Although treatment allocation was effectively random, there may have been differences in patient or clinical factors between the 2 surgical groups that introduced bias. Recognizing this, we examined group differences and implemented a statistical approach to limit bias from confounding. It is possible that observed differences in pain and subsequent opioid use may be due to differences in surgical technique, postoperative management, complications, or unmeasured confounders. However, pain control is protocolized at our center, and both cohorts were managed by the same ICU team. Furthermore, preintervention historical comparison between the 2 surgical cohorts showed no difference in pain or opioid use, suggesting that our center's effort to standardize practice to achieve similar outcomes has been relatively effective. Because of the retrospective nature of this study, we were limited to the Numeric Rating Scale as our pain measure. However, this pain measure is commonly used in clinical practice across specialties, providing an opportunity for comparisons across studies.

In conclusion, the use of intraoperative cryoablation appears to be a novel and effective approach for treating pain and reducing opioid use in lung transplantation.

A future randomized clinical trial with randomization across institutions and within surgeons is needed to confirm these findings and overcome our study's limitations. A more detailed pain assessment may be useful to better understand multidimensional information about pain. Mediators and moderators such as wounds that could explain or impact postoperative pain and opioid use need to be examined. Better pain management and reduced opioid use may lead to improved clinical outcomes, facilitate functional recovery, and improve HRQOL; this is a critically important area for future research.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: pain, lung transplantation, patient-reported outcomes

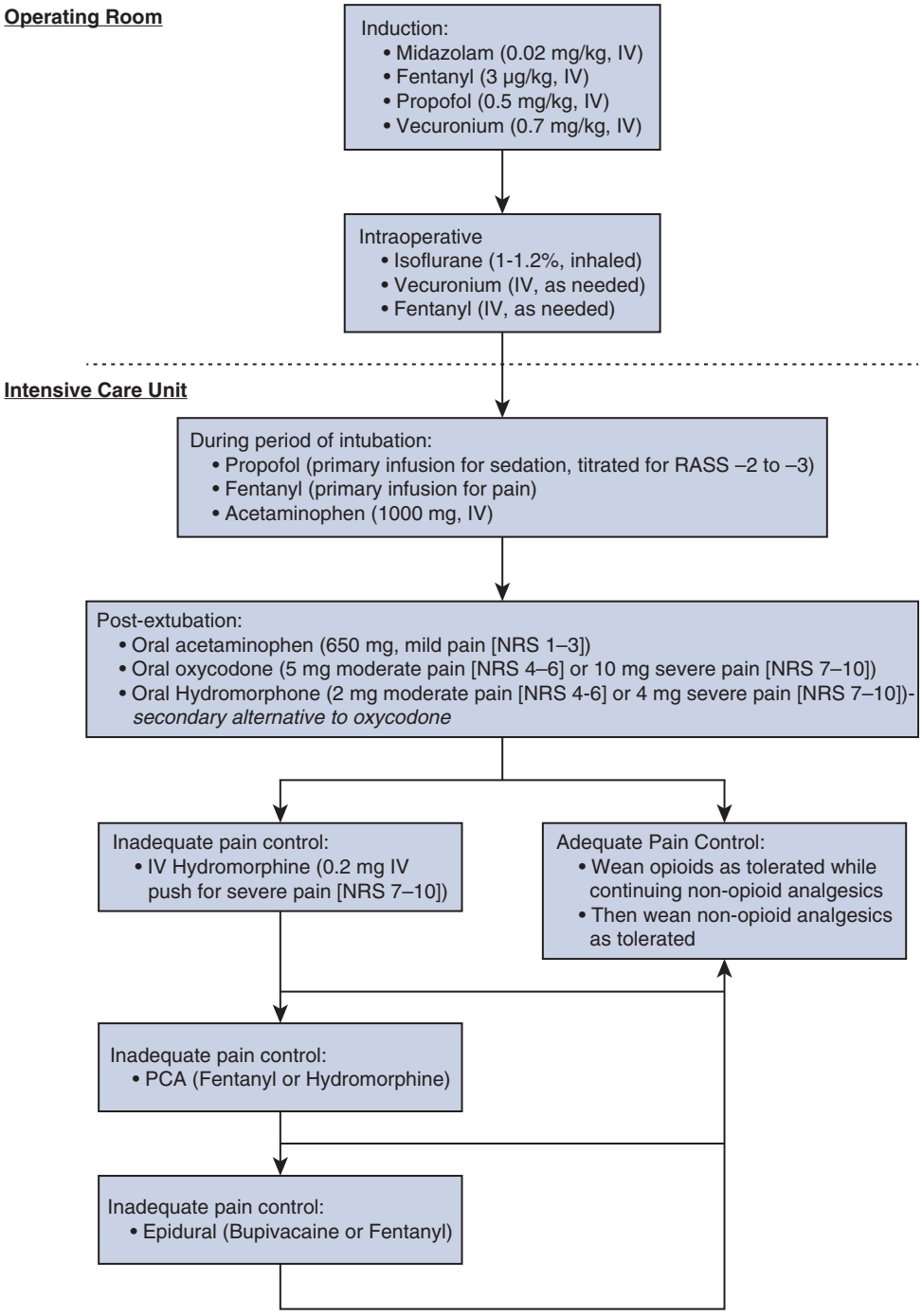

FIGURE E1. Standard intraoperative anesthesia and postoperative pain management protocol. This chart presents our standardized intraoperative anesthesia and postoperative pain management protocol for lung transplantation. *IV*, Intravenous; *RASS*, Richmond Agitation-Sedation Scores; *NRS*, Numeric Rating Scale; *PCA*, patient-controlled analgesia.

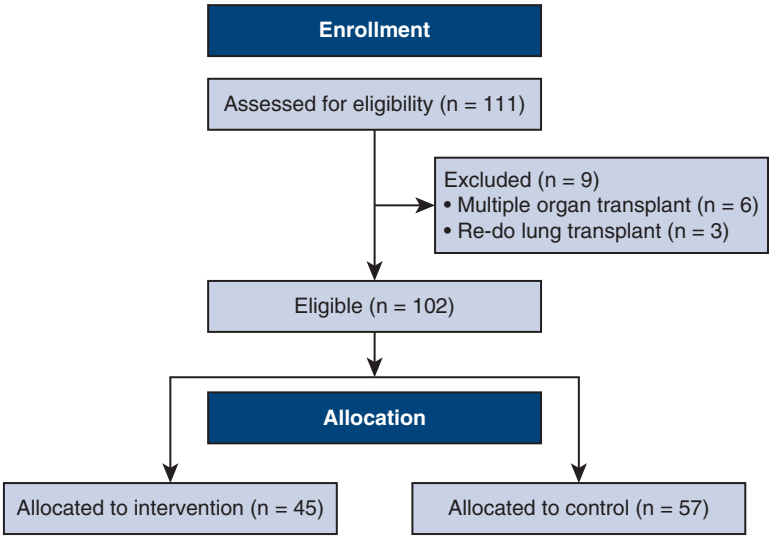

FIGURE E2. Study flow diagram. Presented are data on the number of patients assessed for eligibility, excluded and exclusion criteria, patients eligible, and allocation to intervention and control.

TABLE E1. Differences in median pain scores by group

Day	Intervention	Control	Difference	95% CI
3	2.7	3.7	1.0	0.4-1.8*
7	3.1	4.1	1.0	0.1-1.9*
14	3.5	4.4	0.9	−0.3 to +2.1
21	2.8	3.4	0.6	−0.8 to +1.9

Median pain expected values as of days 3, 7, 14, and 21 posttransplant for intervention versus control groups based on a mixed effects model weighted to standardize for patient characteristics. Greater values reflect greater pain. (See main text for details on statistical modeling). *CI*, Confidence interval. *Confidence bounds do not cross 0 and reflect differences that are statistically significant at conventional levels.

TABLE E2. Differences in maximum pain scores by group

Day	Intervention	Control	Difference	95% CI
3	4.0	5.4	1.5	0.2-2.5*
7	4.6	5.9	1.3	0.2-2.5*
14	5.1	6.3	1.2	−0.3 to +2.6
21	4.2	4.9	0.7	−1.0 to +2.5

Maximum pain expected values as of days 3, 7, 14, and 21 posttransplant for intervention versus control groups based on a mixed effects model weighted to standardize for patient characteristics. Maximum pain level defined as the greatest patient-reported pain score per postoperative day. Greater values reflect greater pain. (See main text for details on statistical modeling). *CI*, Confidence interval. *Confidence bounds do not cross 0 and reflect differences that are statistically significant at conventional levels.

TABLE E3. Differences in postoperative oral opioid use by group

Day	Intervention	Control	Difference	95% CI
3	12.3	20.5	−8.3	−14.6 to −1.9*
7	23.4	39.9	−16.5	−28.6 to −4.3*
14	22.6	41.6	−19.1	−34.3 to −4.0*
21	15.9	28.2	−12.9	−30.4 to +4.5

Expected values for oral opioid use in morphine milligram equivalents as of days 3, 7, 14, and 21 posttransplant for intervention versus control groups based on a mixed effects model weighted to standardize for patient characteristics. (See main text for details on statistical modeling). *CI*, Confidence interval. *Confidence bounds do not cross 0 and reflect differences that are statistically significant at conventional levels.

TABLE E4. Differences in RASS by group

Day	Intervention	Control	Difference	95% CI
3	−1.3	−1.2	0.10	−0.30 to + 0.51
7	−0.7	−0.6	0.06	−0.25 to +0.37
14	0.03	0.03	0.00	−0.26 to +0.26
21	−0.3	−0.3	0.00	−0.17 to 0.18

RASS expected values as of postoperative days 3, 7, 14, and 21 for intervention versus control groups based on a mixed effects model weighted to standardize for patient characteristics. (See main text for details on statistical modeling.) RASS 10-point scale includes 4 levels of anxiety or agitation (+1 "restless" to +4 "combative"), 1 level to denote a calm and alert state (0), and 5 levels of sedation (−1 "drowsy" to −5 "unarousable"). *CI*, Confidence interval.

TABLE E5. Percent Predicted FEV1

	Intervention				Control			
Month	n	Median	25th*	75th*	n	Median	25th*	75th*
1	34	66	59	74	34	67.5	58	83
3	41	68	58	77	44	71.5	60.5	89
6	35	73	54	87	39	67	57	79
12	10	83.5	73	88	18	63.5	57	84

Predicted FEV1 values (median and 25th and 75th percentiles) over time by intervention and control group. *FEVI*, Expiratory volume at 1 second; n = number of patients available for measurement at the follow up time. *Percentile.