Journal of Pediatric Surgery 55 (2020) 1444–1447

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Pectus Excavatum

Postoperative pain control modalities for pectus excavatum repair: A prospective observational study of cryoablation compared to results of a randomized trial of epidural vs patient-controlled analgesia

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ARTICLE INFO

Article history:
Received 14 May 2019
Received in revised form 30 August 2019
Accepted 5 September 2019

Key words:
Cryoablation
Cryoanalgesia
Minimally invasive pectus excavatum repair

ABSTRACT

Background: Pain following bar placement for pectus excavatum is the dominant factor post-operatively and determines length of stay (LOS). We recently adopted intercostal cryoablation as our preferred method of pain control following minimally invasive pectus excavatum repair. We compared the outcomes of cryoablation to results of a recently concluded trial of epidural (EPI) and patient-controlled analgesia (PCA) protocols.
Methods: We conducted a prospective observational study of patients undergoing bar placement for pectus excavatum using intercostal cryoablation. Results are reported and compared with those of a randomized trial comparing EPI with PCA. Comparisons of medians were performed using Kruskal-Wallis H tests with alpha 0.05.
Results: Thirty-five patients were treated with cryoablation compared to 32 epidural and 33 PCA patients from the trial. Cryoablation was associated with longer operating time (101 min, versus 58 and 57 min for epidural and PCA groups, $p < 0.01$), resulted in less time to pain control with oral medication (21 h, versus 72 and 67 h, $p < 0.01$), and decreased LOS (1 day, versus 4.3 and 4.2 days, $p < 0.01$).
Conclusion: Intercostal cryoablation during minimally invasive pectus excavatum repair reduces LOS and perioperative opioid consumption compared with both EPI and PCA.
Level of Evidence: II.

Pectus excavatum, a posterior displacement of the sternum, is the most common chest wall deformity with an incidence of ~1 in 1000 live births [1]. Repair is currently done by placing a bar posterior to the sternum to elevate it while the chest remodels over the course of a few years [2]. Although this minimally invasive approach is simple and less morbid than open resection of costal cartilages, it is associated with severe post-operative pain which is the dominant factor determining the post-operative course [2].

Common methods of pain control include thoracic epidural (EPI) and patient-controlled analgesia (PCA). Complications of EPI include misplacement, malfunction, ineffective distribution, and inadequate pain control which lead to the addition of a PCA as a bridge to oral pain medication [3]. There are conflicting data on whether stand-alone PCA adequately controls early post-operative pain [4,5]. Thus, efforts to reduce pain after minimally invasive pectus excavatum repair continue and a newer method, intercostal cryoablation, is gaining popularity [6–13]. Current studies of cryoablation in pectus excavatum repair have been limited by their retrospective nature, rapidly evolving pain control protocols, and small sample sizes [7,9,11–14]. Despite these limitations, preliminary studies on cryoablation are promising, suggesting improved patient outcomes compared to other pain control modalities. In this study, we compared the outcomes of cryoablation to results of a recently completed 2-center randomized trial of EPI versus PCA protocols at our institution.

1. Materials and methods

Following IRB approval (#17080489), we reviewed prospectively collected data on patients who underwent minimally invasive pectus excavatum repair with intercostal cryoablation by six surgeons at our institution from November 2017 to September 2018. These same six surgeons also operated on patients in the randomized trial of EPI versus PCA and all have performed a minimum of 50 minimally invasive pectus repairs.

1.1. Intercostal cryoablation protocol

Our cryoablation protocol has been previously described [13]. Cryoablation is performed using the CryoICE probe (©AtriCure, Inc.,

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https://doi.org/10.1016/j.jpedsurg.2019.09.021
0022-3468/

Table 1
Patient characteristics reported as proportions or medians with interquartile ranges [IQR].

	Epidural (n = 32)	PCA (n = 33)	Cryoablation (n = 35)	p-Value
Male (%)	90.6	93.9	82.4	0.30
Age (y)	15 [14,16]	14 [13,16]	16 [14,17]	0.02*
Height (m)	1.8 [1.7,1.8]	1.7 [1.7,1.8]	1.7 [1.7,1.8]	0.42
Weight (kg)	56.6 [52,61.6]	56.1 [48,58.4]	57.1 [50,64]	0.23
BMI (kg/m^2)	18.8 [17.6,19.8]	18.6 [17.2,19.1]	18.2 [17,20]	0.78
Haller Index	3.4 [3.3,4.2]	3.5 [3.3,4.7]	4.6 [3.6,5.4]	<0.01*
Correction Index (%)	30 [27,30]	30 [30,40]	35 [30,47]	<0.01*

Mason, OH). This is accomplished thoracoscopically by placing the probe directly on the target intercostal nerve using the same side incision used for bar placement. A 5 mm port is placed at the posterior aspect of this incision and the probe is directly inserted through the chest wall at the anterior aspect of the incision. The probe can be bent slightly to facilitate the appropriate angle to reach the intercostal nerve. Starting with the fourth intercostal nerve, we freeze for 120 s, after which, the machine triggers a thaw cycle that lasts approximately 3–5 s. We sequentially freeze each intercostal nerve to the 7th intercostal nerve bilaterally. Post-operatively, the patients were placed on an oral pain regimen once they were tolerating a regular diet. The oral pain regimen consisted of gabapentin (300 mg, max 900 mg, every 8 h), acetaminophen (15 mg/kg, max 1 g, every 6 h), ibuprofen (10 mg/kg, max 600 mg, every 6 h), extended-release oxycodone (10 mg, max 10 mg, every 12 h), and as needed oxycodone (5 mg, max 7.5 mg, every 4 h).

1.2. Epidural vs PCA multi-institutional prospective randomized trial

Results from a recently concluded two-center, prospective, randomized trial comparing EPI versus PCA for pain control following repair of pectus excavatum are used for comparison (article in press). This trial took place from May 2013 to August 2016 following IRB approval (#12120535) and was registered with clinicaltrials.gov (NCT01863498). Patients were excluded if they underwent open repair, a re-do operation, had a known allergy to pain medication in the protocol, existing contraindications to epidural catheter placement, and a requirement for two bars to be placed. The consent process was continually audited by the IRB. A computer-generated individual unit of randomization was utilized in a non-stratified sequence in blocks of four. All data were analyzed on an intention-to-treat basis, and patients remained in their assigned group. Post-operatively, the patients in both arms were placed on an oral pain regimen when they were tolerating a regular diet and upon discontinuation of the EPI or PCA. This oral regimen consisted of acetaminophen (15 mg/kg, max 1 g, every 6 h), ibuprofen (10 mg/kg, max 600 mg, every 6 h), extended release oxycodone (10 mg, max 40 mg, every 12 h), and oxycodone as needed for breakthrough pain (0.05–0.15 mg, max 10 mg/dose, every 3 h).

1.3. Outcome measures

Our primary outcome of interest was length of stay (LOS). Secondary outcome measures included total operating room time, time to incision, operative time (time from incision to closure), time to regular diet, time to start oral pain medications, time to use of only oral pain medications, time to removal of supplemental oxygen, and post-operative maximum pain scores. Patients were asked to rate their pain level on the Numeric Rating Scale (NRS), which assigns pain a number value of 0–10, with 10 representing the highest level of pain at the time of assessment. Patients' pain levels were recorded by nursing staff with every vital sign check (typically every 4 hours) once on the inpatient ward. Additionally, pain levels were recorded throughout their stay in the post-anesthesia care unit immediately following surgery (a minimum of two times). Daily and total inpatient stay opioid usage for EPI and PCA groups were abstracted from medical records of trial patients from our institution, and converted to morphine milligram equivalents (MME) for comparison to the MME in the cryoablation group.

1.4. Statistical analysis

Analysis was performed for EPI, PCA, and cryoablation groups. Descriptive statistics were calculated with categorical variables reported in percentages and continuous variables reported as medians with interquartile ratios (IQR). Kruskal-Wallis H test for comparisons between the three groups were performed using STATA (StataCorp 2017. Stata Statistical Software: Release 15. College, Station, TX: StataCorp LLC) in which alpha at 0.05 was considered statistically significant.

2. Results

2.1. Patient characteristics

There were 32, 33, and 35 patients in the EPI, PCA, and cryoablation groups, respectively. Patient demographics and clinical characteristics of each group are shown in Table 1. We found that the cryoablation group was older ($p = 0.02$) and had higher Haller and correction indices ($p < 0.01$ and $p < 0.01$, respectively).

2.2. Hospital course outcomes

Outcomes of the hospital course for each group are shown in Table 2 with significant differences in all outcomes including operative times, time to oral pain medications, time to oral pain medications alone, time to removal of supplemental oxygen, and LOS. The maximum post-operative pain score on the day of surgery was lower in the cryoablation group compared to the EPI and PCA groups (6 [IQR 5, 8] vs 7 [IQR 4, 7] and 8 [IQR 6, 10], respectively, $p < 0.01$). There were no

Table 2
Hospital course outcomes reported as medians with interquartile ranges [IQR].

	Epidural (n = 32)	PCA (n = 33)	Cryoablation (n = 35)	p-Value
Total Operating Room Time (min)	124 [106,144]	103 [87,115]	142 [115,163]	<0.01*
Time to Incision (min)	52 [44,59]	30 [25,34]	27 [24,30]	<0.01*
Operative Time (min)	58 [51,79]	57 [47,68]	101 [78,124]	<0.01*
Time to Diet (h)	19.9 [8.4,31.1]	20 [11.4,28]	1.1 [0.8,1.9]	<0.01*
Time to Oral Pain Meds (h)	68 [65,71.2]	52.8 [44.3,70.5]	3.75 [2.9,5.8]	<0.01*
Time to Oral Pain Meds Alone (h)	71.7 [50.4,82.7]	66.6 [50,70]	20.9 [11.6,28.4]	<0.01*
Time to Removal of Supplemental O_2 (h)	0.82 [0.3,15]	9 [2,23.5]	1 [2.2,2.6]	0.01*
Length of Stay (d)	4.3 [4.1, 5.1]	4.2 [3.4,5.2]	1 [1,1.3]	<0.01*

Table 3
Daily Maximum Pain Scores reported as medians with interquartile ranges [IQR].

	Epidural (n = 32)	PCA (n = 33)	Cryoablation (n = 35)	p-value
POD 0	7 [4,7]	8 [6,10]	6 [5,8]	0.01*
POD 1	6 [5,8]	5 [4,7]	5 [4,7]	0.12
POD 2	6 [4,7]	5 [4,8]	6.5 [5,7]	0.80
POD 3	6 [6,8]	5 [4,7]	4.5 [2,7]	0.16
POD 4	5 [3,7]	5 [3,6]	4.5 [3,6]	0.39

statistically significant differences in maximum pain scores on post-operative days (POD) 1–4 between groups (Table 3). All patients in the cryoablation group were discharged prior to POD 5, therefore we have no comparison of maximum pain scores for all three groups beyond POD 4. There were no statistically significant differences in maximum pain scores on POD 5 and POD 6 between the EPI and PCA group. The daily and total inpatient stay MME for each group from our institution is shown in Fig. 1, with the cryoablation group (n = 35) requiring significantly less MME each post-operative day and for the total length of their hospital stay compared to the EPI (n = 20) and PCA groups (n = 20). One patient in the cryoablation group developed a right-sided pneumothorax requiring chest tube placement and no complications occurred in the EPI or PCA groups.

3. Discussion

Pain control following minimally invasive pectus excavatum repair is the sole driver of LOS. Not only does inadequate pain control prolong LOS, but it can limit mobility, increase opioid consumption, and increase healthcare visits and re-admissions once discharged. Therefore, optimization of post-operative pain control is an integral part of caring for patients undergoing repair. In this study, we compared the hospital course of patients undergoing minimally invasive pectus excavatum repair using a thoracic EPI with those who received PCA or intercostal cryoablation. We have demonstrated that patients undergoing cryoablation had a significantly shorter post-operative LOS and a decreased time to oral pain medication alone compared to both the EPI and PCA groups. Direct comparison of these three pain control modalities is important, as existing studies on optimal pain management strategies for minimally invasive pectus excavatum repair have been limited to comparison of two methods alone, either EPI versus PCA, EPI versus cryoablation, or non-cryoablation versus cryoablation. Furthermore, most comparisons of cryoablation to the other modalities did not have protocols in place for the other modalities.

Studies comparing EPI with PCA show no clear superiority between the two [3–5,15]. Three randomized trials comparing these pain control modalities in pectus excavatum repair have conflicting results. One study with 28 patients found no improvement in pain scores or complications with EPI compared to PCA, but did not examine LOS [15]. Conversely, another study of 40 patients reported lower pain scores and less additional pain medication in the epidural group compared to the PCA group, but no difference in LOS at 8–9 days [16]. We previously conducted our own prospective randomized trial comparing EPI to PCA in 110 patients which showed better pain scores in the early post-operative period for the EPI group, but better pain scores in the late post-operative period prior to discharge for the PCA group, with no difference in LOS at about 4.5 days [4]. A systematic review of EPI versus PCA after minimally invasive pectus excavatum repair concluded that there was no difference between the two as they had comparable safety and efficacy, differences in pain control in the early post-operative period were not clinically relevant, and there were no statistically significant differences in LOS [5]. Thus, the body of published evidence suggests EPI and PCA are roughly equivalent, and improvements in clinical outcomes using either of these methods are modest at best. This has led to the emergence of studies examining cryoablation as a potentially superior pain control modality in the repair of pectus excavatum.

Studies comparing cryoablation to other pain control methods are limited in the literature, with the majority of them being retrospective reviews with small numbers and only one randomized trial published just this year [7,12–14]. Furthermore, many of these studies used variations of multi-modal therapies in their groups including combinations of EPI, PCA, local anesthetic infusion catheters, and/or intercostal nerve blocks, which make direct comparisons difficult to interpret. Regardless, certain findings in cryoablation studies such as reduced LOS and increased operative times, remain consistent and are supported by our findings in this larger study comparing all three modalities as stand-alone methods.

Length of stay in the aforementioned cryoablation studies ranged from 1.2 days to 3.47 days [7,9,12–14]. In this study, LOS in the cryoablation group was significantly shorter at 1 day compared to both the EPI and PCA groups at 4 days. This dramatic decrease in LOS is primarily the result of adequate post-operative pain control as evidenced by a reduction in not only daily MME required, but also a reduction in the total MME required for the entire length of hospital stay. Further evidence of the efficacy of cryoablation for post-operative pain control is shown by the improvements seen in other hospital course outcomes such as the time to starting oral pain medication, the time to oral pain medications alone, and time to removal of supplemental oxygen all observed in this group. We also observed a lower maximum

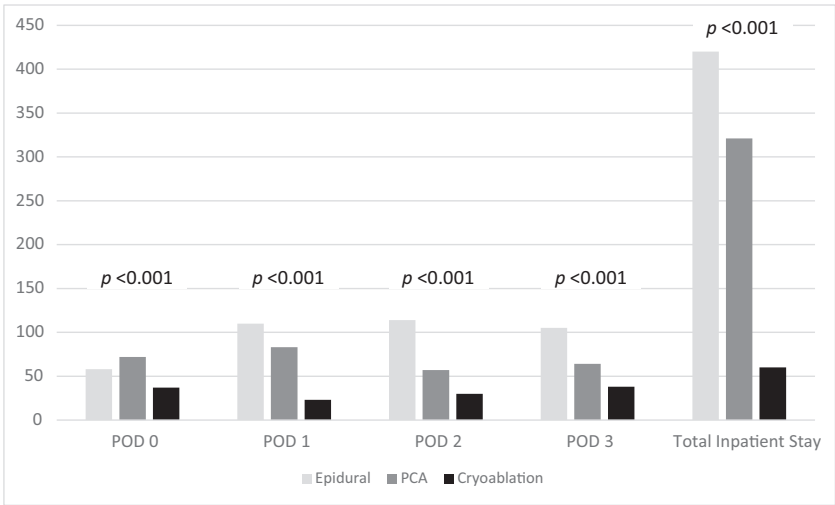

Fig. 1. Median morphine milligram equivalents (MME).

pain score on POD 0 in the cryoablation group that then equilibrated with the EPI and PCA groups further out from the day of surgery. Though pain scores are clinically useful in determining need for medication administration at a single point in time, they are subjective measures that are difficult to compare as equivalent scores between patients may not mean equivalent pain. However, the fact that cryoablation patients do not require supplemental oxygen for an extended amount of time implies adequate respiratory function in the setting of a newly reconstructed chest wall. Additionally, the reduced time to pain medication alone means they are no longer requiring intravenous breakthrough medication for uncontrolled pain. Not only do these findings confirm adequate pain control in the post-operative period, but they also reflect the elimination of additional pain control methods to transition to an oral regimen as in the case of using a PCA to transition off an epidural or prolonged use of intermittent intravenous breakthrough medications. This is why we were able to reduce our total LOS to 1 day in our cryoablation patients.

Also consistent in the literature and confirmed by our study, is the increased operative time with cryoablation. Here we show that cryoablation increases the operative time by approximately 40 min compared to EPI and PCA groups. While retrospective studies have shown increases in operative times by 20–30 min [7,13], a recently published randomized trial comparing epidural to cryoablation in 20 patients demonstrated an increase in operative time by 68.5 min [14]. This wide range of operative times is likely due to variations in technique and experience that may improve with time. In addition, we found that the increased operative time for cryoablation is somewhat negated by the increased time to incision in the EPI group, on the order of 20 min. This reduces the increase in total operating room time by approximately 20 min in the cryoablation group compared to the EPI group. Nonetheless, use of cryoablation necessitates an increased operative time by at least 20 min, as the freeze time is 2 min for each of the 10 nerves [6]. Furthermore, the shortest LOS reported in previous studies is 3 days while ours is only 1 day, so incurred costs from increased operating room time is offset by inpatient costs avoided by the reduced LOS.

One of the limitations of our study is the small sample size for each group. Sixty-five patients were in the EPI versus PCA randomized trial used in this study and the trial was stopped when we adopted cryoablation at our institution. At the time of data analysis, 35 patients were in our prospective observational study of cryoablation and used as a comparison group. Despite this limitation, this remains the largest study of stand-alone cryoablation for pectus excavatum repair in children to date. Prior to this, the largest study is a retrospective review of 26 cryoablation patients, however they used local anesthetic infusion catheters in combination with cryoablation, which complicate the interpretation of their results [7,10].

An additional limitation is the lack up follow-up data in this study. One of the side effects of cryoablation is decreased sensation postoperatively, although this appears to be temporary. Existing studies evaluating cryoablation used during thoracotomy report recovery of the nerve within 1–3 months for the majority of patients, but can be up to 6 months in some patients [17]. We did not specifically examine this outcome for this study due to the focus on hospital course differences between EPI, PCA, and cryoablation in order to determine the optimal method of pain control in the peri-operative period. However, our ongoing prospective observational study of cryoablation includes short and long-term follow-up until the bar is removed, in order to assess opioid usage and any late post-operative complications.

4. Conclusions

Intercostal cryoablation during minimally invasive pectus excavatum repair decreases LOS and perioperative opioid consumption compared with both EPI and PCA. Cryoablation is now our preferred pain control modality in pectus excavatum repair and follow-up results from our prospective observational study will help to further elucidate any long-term additional benefits or late complications.

Acknowledgements

We would like to thank Jessica Wise and Pete Muenks for their assistance with this study.

Disclosures

Declarations of interest: none.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Fokin AA, Steurwald NM, et al. Anatomical, histologic, and genetic characteristics of congenital chest wall deformities. Semin Thorac Cardiovasc Surg 2009;21(1):44–57.
[2] Nuss D, Obermeyer RJ, et al. Nuss bar procedure: past present and future. Ann Cardiothorac Surg 2016;5(5):422–33.
[3] St Peter SD, Weesner KA, et al. Is epidural anesthesia truly the best pain management strategy after minimally invasive pectus excavatum repair? J Pediatr Surg 2008;43(1):79–82.
[4] St Peter SD, Weesner KA, et al. Epidural vs patient-controlled anesthesia for postoperative pain after pectus excavatum repair: a prospective. randomized trial J Pediatr Surg 2012;47(1):148–53.
[5] Stroud AM, Tulanont DD, et al. Epidural analgesia versus intravenous patient-controlled analgesia following minimally invasive pectus excavatum repair: a systematic review and meta-analysis. J Pediatr Surg 2014;49(5):798–806.
[6] Kim S, Idowu O, et al. Use of transthoracic cryoanalgesia during the Nuss procedure. J Thorac Cardiovasc Surg 2016;151(3):887–8.
[7] Keller BA, Kabagambe SK, et al. Intercostal nerve cryoablation versus thoracic epidural catheters for postoperative analgesia following pectus excavatum repair: preliminary outcomes in twenty-six cryoablation patients. J Pediatr Surg 2016;51(12):2033–8.
[8] Sancheti M. Freeze the pain away: the role of cryoanalgesia during a Nuss procedure. J Thorac Cardiovasc Surg 2016;151(3):889–90.
[9] Graves C, Idowu O, et al. Intraoperative cryoanalgesia for managing pain after the Nuss procedure. J Pediatr Surg 2017;52(6):920–4.
[10] Das B, Sadhasivam S. Response to intercostal nerve cryoablation versus thoracic epidural catheters for postoperative analgesia following pectus excavatum repair. J Pediatr Surg 2017;52(6):1076.
[11] Morikawa N, Laferriere N, et al. Cryoanalgesia in patients undergoing Nuss repair of pectus excavatum: technique modification and early results. J Laparoendosc Adv Surg Tech A 2018;28(9):1148–51.
[12] Harbaugh CM, Johnson KN, et al. Comparing outcomes with thoracic epidural and intercostal nerve cryoablation after Nuss procedure. J Surg Res 2018;231:217–23.
[13] Sujka J, Benedict LA, et al. Outcomes using cryoablation for postoperative pain control in children following minimally invasive pectus excavatum repair. J Laparoendosc Adv Surg Tech A 2018;28(11):1383–6.
[14] Graves CE, Moyer J, et al. Intraoperative intercostal nerve cryoablation during the Nuss procedure reduces length of stay and opiod requirement: A randomized clinical trial. J Pediatr Surg 2019;S0022–3468(19)30204–0.
[15] Butkovic D, Kralik S, et al. Postoperative analgesia with intravenous fentanyl PCA vs epidural block after thoracoscopic pectus excavatum repair in children. Br J Anaesth 2007;98(5):677–81.
[16] Weber T, Matzl J, et al. Superior postoperative pain relief with thoracic epidural analgesia versus intravenous patient-controlled analgesia after minimally invasive pectus excavatum repair. J Thorac Cardiovasc Surg 2007;134(4):865–70.
[17] Moorjani N, Zhao F, et al. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: a human prospective randomized trial and a histological study. Eur J Cardiothoracic Surg 2001;20(3):502–7.