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Cryoanalgesia for Pain Management After Pectus Excavatum Repair (COPPER) in Adolescents: A Randomized Controlled Trial

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ABSTRACT

Background: Patients undergoing Pectus Excavatum repair with the minimally invasive approach frequently report severe postoperative pain. The goal of the study is to determine the superiority of cryoanalgesia compared to standard of care for return to normal quality of life.

Methods: A randomized, active controlled, parallel groups trial (category IIb medical device) was designed for patients undergoing pectus excavatum repair. Participants were screened from the elective surgical lists at Istituto Gaslini, Genova, Italy, and they all were part of the academic practice setting. Once enrolled, patients were randomly assigned to one of the two study arms: cryoanalgesia vs. standard of care (epidural-based analgesia). The primary outcome was the Pediatric Quality of Life (PedsQL) and the subcomponents (psychosocial and physical health) 14 days after surgery.

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Results: Protocol was approved by the Ethics Committee (278/2021—DB id 11 421) and conducted between February 2022 and October 2023. Eighty-eight patients were enrolled in the study: forty-five to cryoanalgesia and forty-three in the epidural arm. The PedsQL median (IQR) at the 14th day was 59.8 (48.4, 71.2) vs. 67.9 (58.7, 73.9) (95% CI: 0.46–13; difference 6.5; $p = 0.07$) with ITT analysis, and 59.8 (48.37, 71.20) vs. 69.02 (58.70, 73.91) (95% CI: 0.82, 14; difference 7.4; $p = 0.028$) with PP analysis, in the cryoanalgesia and in the standard of care group, respectively. Irrespective of treatment, a significant decrease in both the PedsQL total score and its subcomponents was found. This effect persisted when stratified by treatment: physical health showed a decrease in both arms, while psychosocial health demonstrated a more marked decrease in the standard of care arm (q-value = 0.028), but not in the cryoanalgesia arm (q-value = 0.056).

Conclusions: Cryoanalgesia did not improve return to baseline quality of life 2 weeks after surgery. However, it showed to be beneficial in the psychosocial component of the PedsQL scale.

Trial Registration: NCT05201820

Cryoanalgesia is a technique based on the temporary nerve blockage by freezing the nerve through the application of a small probe [1]. Cryoanalgesia is well known to be effective in chronic pain management in the context of peripheral neuropathy, but its efficacy for acute postoperative pain is still under debate. While some studies highlight short-term advantages, such as reducing hospital stay and facilitating early discharge, others raise concerns about potential long-term side effects due to the long lasting effect of neurolysis [2, 3].

Pectus excavatum (PE) is the most prevalent chest wall deformity in children. It is typically corrected during adolescence through a minimally invasive surgical procedure (MIRPE), pioneered by Dr. Donald Nuss (Nuss procedure). Surgery involves the thoracoscopic insertion of one, two, or even three bars within the chest cavity [4]. Despite the minimally invasive approach, patients commonly experience severe postoperative pain. The pain often persists from weeks to months, significantly impairing return to normal activities. Multimodal analgesia is a key treatment in this scenario and includes regional anesthesia such as thoracic epidural, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs). Cryoanalgesia has emerged as a promising strategy for managing postoperative pain in patients undergoing MIRPE [5]. The most common technique consists of a cryoprobe insertion during thoracoscopic surgery and its direct application upon each intercostal nerve for a duration of one or 2 min. Operating at −70°C, cryoanalgesia induces a nerve stupor, dampening sensitive transmission and therefore reducing pain.

Recent studies [6–11] showed that cryoanalgesia is associated with a shorter hospital stay compared to thoracic epidural and opioid-based analgesia. They have also reported improved pain control and reduced opioid use. Di Fiore et al. [12] have highlighted the benefits of a multimodal pain management pivoted on cryoanalgesia. Hospital stay is also reduced thanks to the better pain control. Rettig et al. [10] have reported similar favorable outcomes as part of an enhanced recovery after surgery (ERAS) protocol. However, the medium- and long-term risks and benefits of this technique for analgesia in the Nuss procedure are not fully clarified, since most of the published articles focused on the early benefit and the length of hospital stay. Moreover, pain after pectus excavatum is a major problem, but it can be positively or negatively affected by multiple factors. For this reason, a multimodal and personalized approach which might include cryoanalgesia and/or regional anesthesia still remains the way to mitigate pain and improve outcome. Based on these assumptions, a measure like the quality of life scale, which has been used and validated for a wide variety of chronic conditions, and integrates physical and psycho-social health could had been the correct outcome measure for this category of patients. Measures of quality of life have been used also for patients undergoing surgical procedures, like spine surgery. In particular, PedsQL is a multidimensional measure of quality of life which includes subscales for physical and psychosocial health, suitable for adolescents undergoing major surgery like pectus excavatum repair. Moreover, complications after pectus excavatum repair are underreported and the medium- and long-term benefits and complications of cryoablation were not previously reported [11].

The aim of this study was to test the above hypothesis that cryoanalgesia offers superior postoperative return to baseline quality of life and activities compared to the current standard of care with epidural analgesia. As a secondary aim and through a long-term follow-up, pain, need for analgesia, benefits, and side effects of cryoanalgesia versus standard of care are described.

1 | Methods

We conducted a randomized active-controlled, parallel-group, single-centre, superiority trial (category IIb medical device) at IRCCS Istituto Giannina Gaslini in Genova, Italy. The protocol received approval from the Ethics Committee (278/2021—DB id 11 421) and registered on clinicaltrial.gov (NCT05201820).

Participants were screened from the elective surgical lists, and they were all part of the academic practice setting. Once enrolled, patients were allocated to one of the two study arms: standard of care versus cryoanalgesia. Patients and parents were blinded to the arm of allocation, but not clinicians and investigators. Inclusion criteria were patients scheduled for pectus excavatum repair with MIRPE, aged 12 years and over. Patients with any contraindications to anesthesia techniques or medications and logistical challenges in follow-up were excluded. Written consent was obtained from parents or patients themselves if 18-year-old or older.

2 | Interventions

2.1 | Anesthesia and Analgesia Techniques for all Patients

General anesthesia management was standardized as bispectral index (BIS) guided total intravenous anesthesia with propofol and remifentanil, and muscle relaxation with rocuronium. Intraoperative adjustments of propofol and remifentanil were decided by the anesthetist in charge, according to the physiological parameters and the BIS level. Post-operative analgesia included non-steroidal anti-inflammatory drugs (NSAIDs) every 8 h, patient-controlled analgesia (PCA) with morphine (20 mcg/kg boluses repeatable every 10 min, and no background infusion), and rescue analgesia with 15 mg/kg of acetaminophen. Pain management at discharge included 8-h 10 mg/kg of ibuprofen (up to a maximum of 7 days) and oral codeine/paracetamol (30/500 mg) as rescue analgesia.

2.2 | Cryoanalgesia Arm

Specifically designed cryoablation probes (CRYO-S PAINLESS system) were utilized in the procedure. For thoracoscopic purposes, a 12-gauge, 35 cm long blunt-tip atraumatic probe was engineered to optimize performance and ensure the highest level of safety.

Patients were positioned supine, and 2.5 cm transverse skin incisions were made at the sites of bar insertion, between the anterior and middle axillary lines. Cryoanalgesia was performed before the start of the surgical correction of the chest deformity. Lung ventilation on the treated side was temporarily halted using a double-lumen tracheal tube for single-lung ventilation. The cryoprobe was inserted through the same incision or via a separate anterior percutaneous trocar-less access. Five or six intercostal nerves on each side (from T3 to T8) were treated, with the probe in contact with the posterior aspect of the selected intercostal nerve for 2 min at −70°C under direct visual control. The rapid expansion of gas, observed only at the tip of the probe (Joule–Thompson effect), led to the generation of an ice ball at the tip of the cryoprobe, ensuring safe and precise treatment. CO_2 was then vented through the inner cannula, with no gas released into the patient's body. Cryoanalgesia was conducted bilaterally, first on the left side and subsequently on the right side.

2.3 | Standard of Care Arm

Patients enrolled in the standard of care arm received a continuous thoracic epidural analgesia through a catheter positioned between T7 and T10 before surgery. Intraoperatively, a bolus of 0.375% levobupivacaine and a volume ranging from 10 to 20 mL was administered. Then a continuous infusion of 0.125% levobupivacaine plus 1.0 mcg/mL of clonidine running at a rate of 0.2–0.4 mL/kg/h (up to a maximum of 15 mL/h) was started and continued for three postoperative days. The correct position of the epidural catheter was tested daily by the pain team, and a top-up of 8–10 mL of 0.125% levobupivacaine was administered if the level was inadequate.

2.4 | Outcome Measures

The primary outcome of the study was quality of life 14 days after surgery, assessed with PedsQL (Pediatric Quality of life scale core version 4). The generic core scales contain 23 items grouped into two domains: physical health (eight items) and socio-emotional health, which is composed of the three further subdomains: emotional (five items), social (five items), and school (five items). PedsQL is a validated outcome measure for a variety of chronic conditions, including post-surgical quality of life [13]. For the ease of interpretability, items are reverse scored and linearly transformed to a 0–100 scale, so that higher scores indicate better health-related quality of life). Scores ranging between 80 and 90 are considered normal, while lower scores identify minor or moderate reductions in quality of life. However, normal and reduced values should be interpreted in the context of the clinical condition where the scales are applied [14].

In addition, supplementary scales were employed: CALI-9 (Child Activity Limitations Interview), which measures pain related activity limitations, and YAPFAQ (Youth Acute Pain Functional Ability Questionnaire), which assesses functional ability in response to acute or persistent pain. CALI-9 utilizes a 0–100 scale, while YAPFAQ a 0–48 scale. Higher scores indicate greater activity limitations and pain with both scales. These scales were administered in the preoperative period, alongside the collection of demographic data and medical and pharmacological history, and used as baseline measures.

The secondary outcomes included intraoperative and postoperative assessments. Intraoperative measures were: duration of anesthesia (defined from the patient enter the operating room until is transferred to the recovery room), surgery (from knife to skin until last stitch) and the overall duration of the procedure (the sum of anesthesia plus surgery), performance of cryoanalgesia by the surgeon categorized as successful, partially successful, or failed (considered successful when all five nerves on each side were ablated), total amount of remifentanil administered, morphine given at the awakening of anesthesia and in the recovery period, and the immediate post-anesthesia pain score.

Postoperative pain was evaluated by the Pain Research Team daily until patients were discharged from the hospital. Additionally, daily morphine and total morphine consumption, need for rescue pain medications, and time until discharge were documented. Then patients self-reported pain until Day 14 using the numeric rating scale (NRS 0–10), alongside the assessment of pain frequency (no pain; once per day; 2–3 times per day; three or more times per day) and duration (less than 1 h; 1–3 h; half day; entire day) entering pain scores via a dedicated app. Patients were instructed on how to download and use the app, and how to enter scores into the app by the investigators before being discharged from the hospital. Reminders were sent to those patients that did not enter pain scores regularly. PedsQL, CALI, and YAPFAQ scores were also completed by patients using the dedicated app. In case of delayed or missing follow-up, a telephone call was performed to assist patients in completing the follow-up.

Three months post-surgery, patients were evaluated regarding their medication usage for managing surgery-related pain and the presence of neuropathic complications, such as hypoesthesia, allodynia, hyperalgesia, anesthesia, or pruritus. When discharged from the hospital, patients were instructed to on how to assess hypoesthesia with the cold test and how to report the other symptoms. Patients were interviewed via telemedicine to report the above symptoms, and then assessed face-toto-face coupling the surgical with the study follow-up, with the aim of confirming or rejecting the reported symptoms. If symptoms were confirmed, they were recorded in the database for analysis.

2.5 | Randomization

After recruitment, patients were randomly assigned to either the intervention group (cryoanalgesia) or standard of care (epidural) in a 1:1 ratio. A random sequence was generated by a computer random number generator. Group assignment was contained in sequentially numbered, sealed, opaque envelopes that were prepared by an independent statistician.

2.6 | Statistical Analysis

The sample size calculation was based on the assumption that the overall score of the primary outcome measure PedsQL shows a mean improvement of 20 points (SD = 30). The expected difference of 20 points in the PedsQL score was based on the need to assess a clinically relevant difference between treatments, but also on previous studies where the quality of life was used as an outcome measure [15–17]. To test the null hypothesis of equality of treatment at $\alpha = 0.05$ with 80% power and assuming a uniform dropout rate of 10%, it was calculated that 44 patients in each group would be sufficient.

Data were described as mean and standard deviation or median and 95% confidence interval for continuous variables and as absolute and relative frequencies for categorical variables. Non-parametric analysis (Mann–Whitney *U*-test) for continuous variables and Chi square or Fisher's exact test for categorical variables were used to measure differences between the groups. An Intention to treat (ITT) and per protocol (PP) analysis were planned for the primary and secondary outcome measures. P value less than 0.05 was considered statistically significant, and all values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, Illinois USA).

3 | Results

Eighty-eight patients were enrolled in the study from February 2022 to October 2023. Figure 1 illustrates the CONSORT flow chart. Demographic, baseline, and intraoperative characteristics are summarized in Table 1. For the primary analysis (PedsQL 14 days after surgery) and the limitation scales (CALI9 and YAPFAQ) an intention-to-treat (ITT) and per-protocol (PP) analyses were conducted. With the ITT analysis, the median (IQR) PedsQL scores were 59.8 (48.37, 71.20) vs. 67.9 (58.7, 73.9) (95% CI: −0.46, 13; difference 6.5; $p = 0.067$) in the cryoanalgesia and in the standard of care groups, respectively. With the PP analysis, median (IQR) PedsQL scores were 59.8 (48.37, 71.20) vs. 69.02 (58.70, 73.91) (95% CI: 0.82, 14; difference 7.4; $p = 0.028$) in the cryoanalgesia and standard of care group, respectively. Overall, there was a significant decrease in both the PedsQL total score and its subcomponents from baseline until Day 14, irrespective of treatment arm, even after adjustment for multiplicity. This effect persisted when stratified by treatment arm: physical health showed a significant decrease in both arms, while psychosocial health demonstrated a significant decrease in the standard of care arm (q-value = 0.028), but not in the cryoanalgesia arm (q-value = 0.056).

The secondary outcome evaluating activity limitation scores (CALI9 and YAPFAQ) at day 14 post-surgery revealed no discernible difference between the two treatments: CALI median (IQR) scores were 12 (6, 20) vs. 11 (6.7, 15), while YAPFAQ median (IQR) scores were 14 (7, 22) vs. 12.5 (7, 20.2) in the cryoanalgesia and standard of care groups, respectively. Despite a significant rise in activity limitations from baseline, as indicated by both CALI and YAPFAQ scores, both treatment arms exhibited comparable effects 2 weeks post-surgery, with no statistically significant differences observed. Table 2 represents baseline values of PedsQL, PedsQL subscales, CALI9, and YAPFAQ, while Table 3 represents the ITT analysis of PedsQL, PedsQL subscales, CALI9, and YAPFAQ at 14 days between the two arms. The APP analysis of PedsQL, PedsQL subscales, CALI9, and YAPFAQ at 124 days is summarized in the table for Supporting Information.

3.1 | Intraoperative Measures

The duration of surgery was longer in the cryoanalgesia group compared to the standard of care group, as well as the combined duration of surgery and anesthesia in both arms. Additionally, remifentanil consumption during surgery and morphine consumption in the recovery period were significantly higher in the cryoanalgesia arm compared to the standard arm. All cryoanalgesia were reported as being "successful" by the surgeons. The initial pain assessment upon awakening, measured using the NRS scale, was higher in the cryoanalgesia arm than in the epidural arm (2.7 (2.8) vs. 5.2 (3.3); $p = 0.005$) (Table 1).

3.2 | Postoperative Pain Until Discharge

Figure 2 illustrate daily morphine consumption until hospital discharge. Figure 2B illustrates worst NRS pain intensity on movement trends (mean and SD). Similarly, Table 4 reports the mean (SD) worst NRS pain on movement for intensity, frequency, and duration, and the morphine consumption on a day-by-day basis, with asterisks indicating statistical differences. Both treatment groups exhibited overall similar morphine consumption and pain scores. However, patients in the cryoanalgesia group met hospital discharge criteria earlier than those in the

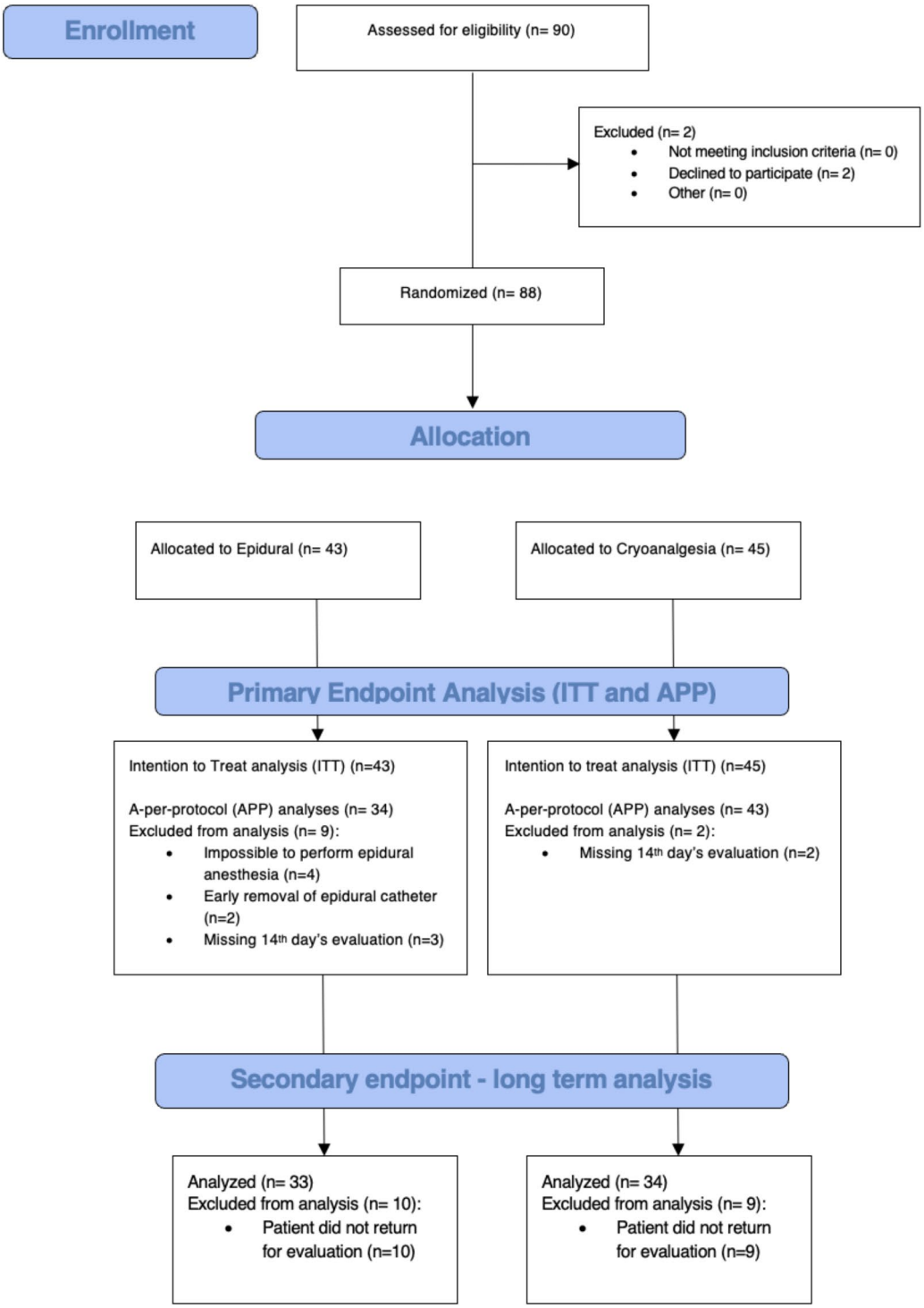

FIGURE 1 | CONSORT flow-chart.

standard of care group, with a shorter hospital stay of 3.4 (1.2) vs. 4.4 (0.9) days ($p < 0.001$), respectively.

3.3 | Follow-Up

Patients were followed daily until the primary endpoint at Day 14 after surgery, with overall pain intensity and frequency (worst NRS) being comparable between the two treatments (Figure 2B). Three months post-discharge, a face-to-face assessment was conducted to evaluate the persistence of symptoms related to the surgical procedure. Out of the 88 enrolled patients, 67 were evaluated. Symptoms such as anesthesia, allodynia, and hyperalgesia were similar between the two treatments. The persistence of hypoesthesia on the chest wall was reported by 18 patients in the cryoanalgesia group versus 8 in the standard group ($p = 0.02$) (Table 5). Complications occurred in 11 out of the 88 included patients, with no intraoperative or postoperative deaths recorded.

TABLE 1 | —Demographic characteristics and baseline measures of patients included.

Characteristics	Overall, $N=88$	Standard of care, $N=43$	Cryoanalgesia, $N=45$
Baseline			
Sex			
Female	15 (17.05%)	8 (18.60%)	7 (15.56%)
Male	73 (82.95%)	35 (81.40%)	38 (84.44%)
Age (years)	15.59 (2.20)	15.51 (2.35)	15.67 (2.06)
Weight (kg)	56 (10)	57 (10)	56 (9)
Height (mt)	1.74 (0.09)	1.74 (0.10)	1.75 (0.09)
BMI	18.47 (2.54)	18.69 (2.79)	18.25 (2.28)
Haller Index	23 (83)	22 (86)	24 (81)
Correction Index	33 (22)	35 (21)	31 (22)
Intraoperative			
Total procedural time (min)	227 (29)	219 (31)	234 (25)
Anesthesia time (min)	152 (27)	136 (25)	167 (19)
Remifentanil consumption (mg)	1.97 (1.09)	1.58 (0.97)	2.34 (1.09)
Morphine consumption (mg)	5.1 (3.1)	4.0 (2.8)	6.2 (3.1)
Pain (NRS) at awake	4.03 (3.36)	2.72 (2.88)	5.22 (3.36)

Abbreviations: BMI, Body Mass Index; Correction Index, calculated by dividing the minimum distance between posterior sternum and anterior spine and the maximum distance between anterior spine and most anterior portion of the chest. NRS: Numeric Rate Scale; Haller Index, calculated by dividing the transverse diameter of the chest by the anterior–posterior distance on CT scan.

TABLE 2 | Preoperative (baseline) median (IQR) values of PedsQL, CALI9, YAPFAQ. Analysis on PedsQL includes subscales on Physical and Psychosocial health.

	Overall, $N=88$	Standard of care, $N=43$	Cryoanalgesia, $N=45$	Difference[a]	95% CI[a,b]
PedsQL	78.2 (67.9, 86.9)	77.2 (70.6, 86.6)	78.3 (66.3, 86.9)	0.56	−4.7, 5.8
PedsQL physical health	81.2 (71.8, 90.6)	81.2 (71.8, 90.6)	79.69 (69.5, 89.8)		
PedsQL psychosocial health	77.5 (66.6, 85.0)	76.6 (70.0, 84.2)	78.3 (65.0, 85.0)		
CALI9	4 (1, 8)	3 (1, 7)	4 (1.7, 9)	−1.2	−3.2, 0.71
YAPFAQ	1 (0, 2)	0.5 (0, 2)	1 (0, 2)	−0.34	−1.3, 0.6

[a]Welch two sample *t*-test.
[b]CI = confidence interval.

4 | Discussion

The main finding from this study is that cryoanalgesia provided similar medium and long-term benefits and no significant improvement in quality of life or activity limitations, when compared with the standard of care. Surprisingly, the PP analysis, which included patients that had not protocol deviations from inclusion to the study termination, showed a trend toward a better quality of life in patients undergoing standard of care treatment. Overall, there was a significant decrease in both the PedsQL total score and its subcomponents, irrespective of treatment arm. However, the physical health domain of PedsQL showed a decrease in both arms, while the psychosocial domain demonstrated a decrease only in the standard of care arm, but not in the cryoanalgesia arm. These findings can be interpreted as a better attitude of patients undergoing cryoanalgesia to restart social activities, despite physical limitations due to the surgical procedure.

Pain intensity, duration, and frequency exhibited distinct post-surgery trends: initial higher pain scores were noted in the cryoanalgesia group, followed by an improvement from the second postoperative day onwards, while patients in the standard of care arm had a better pain control soon after surgery. Pain after PE correction results from multiple factors, which might include the new feeling of the bars pushing the chest from inside and the pre-existing anxiety. For this reason, sometimes, a reported high pain score can be related to similar, if not inferior,

TABLE 3 | Intention to treat (ITT) analysis of the primary and secondary outcome measures 14 days after surgery: PedsQL, Delta PedsQL (difference between baseline and PedQL at 14 days), PedsQL physical health, PedsQL psychosocial health, CALI and YAPFAQ. Data presented as median (IQR), difference and 95% CI.

	ITT—intention to treat analysis						
Characteristic	**Overall, *N* = 88**	**Standard of care, *N* = 43**	**Cryoanalgesia, *N* = 45**	**Difference[a]**	**95% CI[a,b]**	***p*[a]**	***q*[c]**
PedsQL	64.1 (54.9, 73.9)	67.9 (58.7, 73.9)	59.8 (48.4, 71.2)	6.5	−0.46, 13	0.067	
Delta pedsQL	−14.7 (−22.8, −4.3)	−9.8 (−20.1, −1.6)	−16.3 (−25.5, −9.2)	5.4	−0.20, 11	0.059	0.12
PedsQL physical health	50 (34.4, 62.5)	54.7 (38.3, 67.2)	50 (34.4, 59.4)	4.7	−14.4, 23.8		
PedsQL psychosocial health	75 (58.3, 81.7)	75.8 (58.7, 80)	75 (58.3, 81.7)	0.8	−15, 16.6		
CALI9	11.5 (6, 18)	11 (6.7, 15)	12 (6, 20)	−2.2	−5.4, 1.1	0.2	0.3
YAPFAQ	13 (7, 21)	12.5 (7, 20.2)	14 (7, 22)	−1.5	−5.5, 2.5	0.5	0.5

Note: When both *p*-values and *q*-values are presented in the table, consider the latter (*q*-value), which is appropriate in the case of multiple testing. By rejecting the Null Hypothesis for all tests with *q*-value < α (0.05) ensures that the false discovery rate is 0.05. The FDR is the rate at which significant features are truly null [18].
[a]Welch two sample *t*-test.
[b]CI = confidence interval.
[c]False discovery rate correction for multiple testing.

use of analgesics, simply because techniques of respiration and coping might be able to control pain even better than analgesics per se [19].

A reduction in hospital stay and early discharge was seen in the cryoanalgesia group compared to the standard of care. The long-term follow-up revealed a persistent chest wall hypoesthesia in approximately half of the patients who received cryoanalgesia, which could be referred to as the cryotherapy's long-standing effects on the intercostal nerves. On the other hand, some of the patients included in the standard of care arm reported a new onset of symptoms, like hypoesthesia, which could have been related to the surgical insult and the pressure from the bars. This is an important point and deserves attention when a long-term follow-up is performed after pectus excavatum repair. Notably, cryoanalgesia showed a safe profile with no relevant complications at the late follow-up. In fact, the overall complications rate was similar to the one reported in previous studies, and with no differences between the two treatment groups [20, 21].

Results from the COPPER study were partially consistent with other recent studies. In fact, a recent systematic review which included 34 studies summarized that cryoanalgesia is beneficial in reducing the hospital stay and the early opioid consumption similar to the COPPER cohort of patients [22]. Patients that received cryoanalgesia experienced effective analgesia from the second day after surgery, with an early transition to oral medication and prompt mobilization. In addition, persistent chest hypoesthesia at follow-up was suggestive of a lasting effect of cryoablation, but in a limited number of patients.

Cryoanalgesia remains a promising technique, but the enhanced surgical instrumentation for cryoablation, as well as the need to position a double-lumen tracheal tube, remain the main obstacles for a wide application of the technique. The need for a double-lumen tube to facilitate bilateral surgical visualization of cryoablation targets may pose a risk to the patient and entail an additional procedure not required in the standard of care. Moreover, positioning the double-lumen tube can be time-consuming and require specific expertise, particularly in the pediatric population. In addition, cryoablation requires 2 min per intercostal nerve, with an overall longer procedure time compared to the standard treatment. Another drawback is the initial higher pain score and increased consumption of pain medications due to the delayed effects of cryoablation.

4.1 | Strengths and Limitations

The main strength of this study is in its prospective design with a medium- and long-term follow-up, which provided insight into the potential benefits of cryoanalgesia. It is one of the few published RCTs studying cryoanalgesia prospectively and comparing it with a standard multimodal technique, mainly based on epidural. Recent studies on cryoanalgesia focused on pain control and length of stay, and they advocated for studies with a longer follow-up to identify potential long-term benefits or complications [23, 24]. Differently, our study's primary endpoint was the quality of life 2 weeks after surgery, followed by a second follow-up 2 or 3 months after surgery to verify safety and long-term effects of cryoablation. We chose the PedsQL Core V4, which is a modular instrument designed to measure health-related quality of life in adolescents with the aim of exploring physical, socio-emotional, social, and school functions. PedsQL is used for a large variety of conditions to assess quality of life, including post-surgical recovery [25]. Interestingly, the use of PedsQL enabled the possibility to identify a better trend in the psychosocial components of quality of life in those patients undergoing cryoanalgesia. PedsQL is primarily designed to measure overall quality of life (physical, emotional, social, and school functioning) rather than specific pain outcomes. It is definitely a correct outcome measure to detect changes in how pain

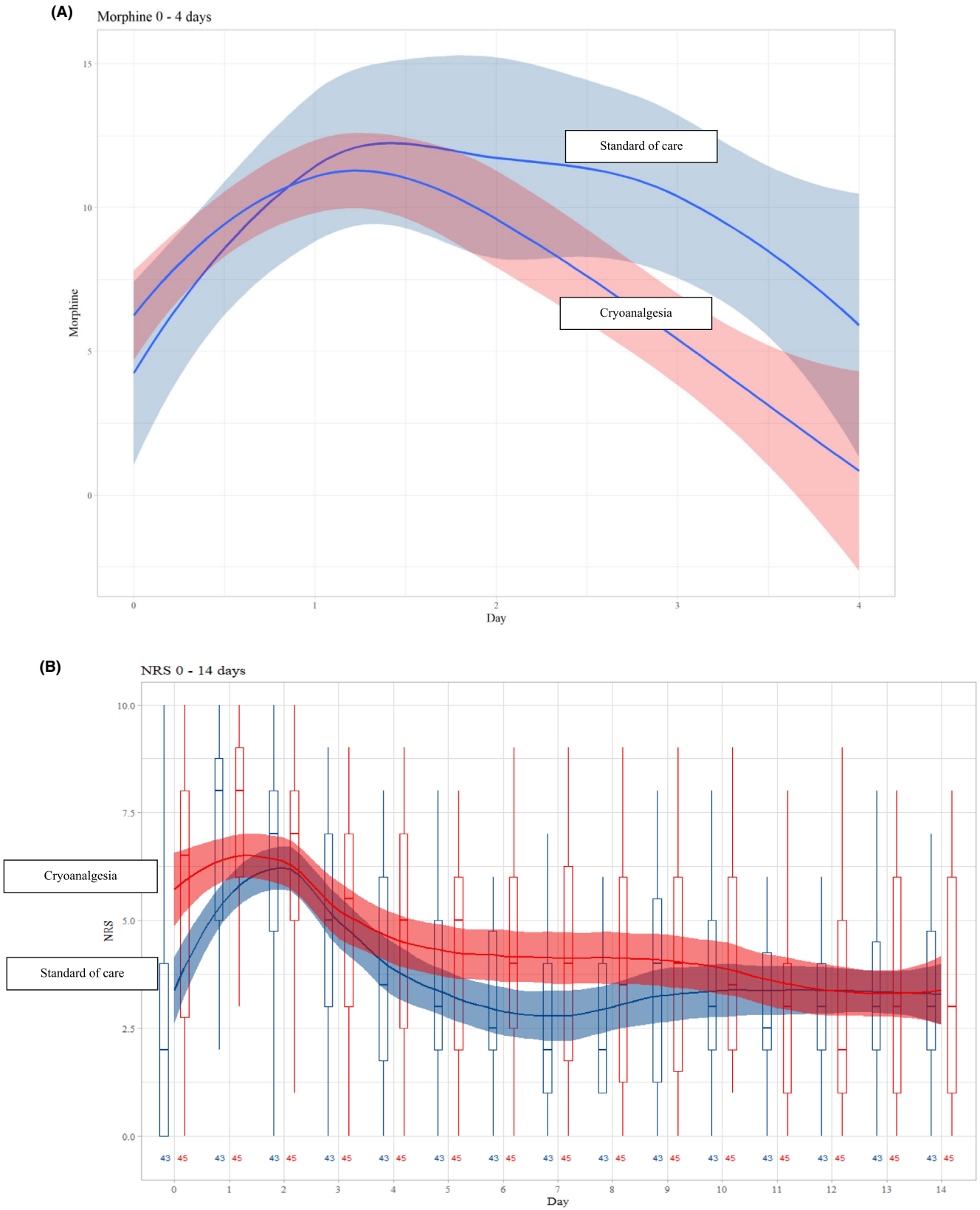

FIGURE 2 | (A) represents morphine consumption (mean and SD) after surgery, until hospital discharge. (B) represents pain intensity (worst NRS on movement) until day 14 after. Gray band represents the standard of care arm, the orange band the cryoanalgesia arm, in the two figures.

impacts daily functioning, which may indirectly reflect differences in pain management strategies like cryoanalgesia. Studies suggest that PedsQL is sensitive enough to detect differences in postoperative recovery and pain management. Therefore, while PedsQL can provide valuable insights into overall quality of life and the broader impacts of a novel treatment like cryoanalgesia,

TABLE 4 | Daily pain intensity (worst NRS on movement), frequency and duration, and morphine consumption day-by-day until hospital discharge.

Characteristics	Overall, $N=88$[a]	Standard of care, $N=43$[a]	Cryoanalgesia, $N=45$[a]	p[b]	q[c]
Day 1					
Pain intensity (worst NRS)					
Mean (SD)	7.09 (2.31)	6.82 (2.39)	7.32 (2.24)	0.363	0.486
Unknown	13	9	4		
Pain frequency (scale = 0:3)					
Not at all	2 (2.7%)	0 (0%)	2 (5.0%)	0.236	0.486
One per day	24 (32%)	14 (40%)	10 (25%)		
2–3 times	32 (43%)	12 (34%)	20 (50%)		
> 3 times	17 (23%)	9 (26%)	8 (20%)		
Unknown	13	8	5		
Pain duration (scale = 0:3)					
< 1 h	53 (70%)	26 (72%)	27 (68%)	0.365	0.486
Few hours	19 (25%)	9 (25%)	10 (25%)		
Half of the day	3 (3.9%)	0 (0%)	3 (7.5%)		
All day	1 (1.3%)	1 (2.8%)	0 (0%)		
Unknown	12	7	5		
Morphine (mg)					
Mean (SD)	12 (10)	13 (13)	12 (7)	0.625	0.625
Unknown	8	5	3		
Day 2					
Pain intensity (worst NRS)					
Mean (SD)	6.23 (2.46)	6.17 (2.44)	6.29 (2.50)	0.824	0.824
Unknown	11	7	4		
Pain frequency (scale = 0:3)					
Not at all	2 (2.6%)	1 (2.8%)	1 (2.5%)	0.106	0.425
One per day	30 (39%)	16 (44%)	14 (35%)		
2–3 times	32 (42%)	17 (47%)	15 (38%)		
> 3 times	12 (16%)	2 (5.6%)	10 (25%)		
Unknown	12	7	5		
Pain duration (scale = 0:3)					
< 1 h	49 (64%)	23 (64%)	26 (63%)	0.405	0.540
Few hours	20 (26%)	11 (31%)	9 (22%)		
Half of the day	5 (6.5%)	2 (5.6%)	3 (7.3%)		
All day	3 (3.9%)	0 (0%)	3 (7.3%)		
Unknown	11	7	4		
Morphine (mg)					
Mean (SD)	11 (8)	12 (10)	10 (6)	0.283	0.540
Unknown	11	6	5		

(Continues)

TABLE 4 | (Continued)

Characteristics	Overall, $N=88$[a]	Standard of care, $N=43$[a]	Cryoanalgesia, $N=45$[a]	p[b]	q[c]
Day 3					
Pain intensity (worst NRS)					
Mean (SD)	4.98 (2.52)	4.93 (2.51)	5.03 (2.58)	0.874	0.927
Unknown	31	16	15		
Pain frequency (scale = 0:3)					
Not at all	2 (3.6%)	1 (3.8%)	1 (3.3%)	0.165	0.331
One per day	25 (45%)	15 (58%)	10 (33%)		
2–3 times	23 (41%)	7 (27%)	16 (53%)		
> 3 times	6 (11%)	3 (12%)	3 (10%)		
Unknown	32	17	15		
Pain duration (scale = 0:3)					
< 1 h	43 (77%)	21 (81%)	22 (73%)	0.927	0.927
Few hours	10 (18%)	4 (15%)	6 (20%)		
Half of the day	1 (1.8%)	0 (0%)	1 (3.3%)		
All day	2 (3.6%)	1 (3.8%)	1 (3.3%)		
Unknown	32	17	15		
Morphine (mg)					
Mean (SD)	8 (13)	11 (15)	4 (5)	0.027	0.110
Unknown	38	14	24		
Day 4					
Pain intensity (worst NRS)					
Mean (SD)	4.29 (2.74)	3.79 (2.65)	4.74 (2.78)	0.219	0.437
Unknown	37	19	18		
Pain frequency (scale = 0:3)					
Not at all	3 (5.9%)	2 (8.3%)	1 (3.7%)	0.799	0.799
One per day	23 (45%)	10 (42%)	13 (48%)		
2–3 times	17 (33%)	9 (38%)	8 (30%)		
> 3 times	8 (16%)	3 (13%)	5 (19%)		
Unknown	37	19	18		
Pain duration (scale = 0:3)					
< 1 h	32 (63%)	16 (67%)	16 (59%)	0.778	0.799
Few hours	14 (27%)	5 (21%)	9 (33%)		
Half of the day	2 (3.9%)	1 (4.2%)	1 (3.7%)		
All day	3 (5.9%)	2 (8.3%)	1 (3.7%)		
Unknown	37	19	18		
Morphine (mg)					
Mean (SD)	4.5 (7.4)	5.6 (8.2)	1.6 (3.9)	0.095	0.380
Unknown	60	23	37		

[a] *n* (%).
[b] Welch Two Sample *t*-test; Fisher's exact test.
[c] False discovery rate correction for multiple testing.

TABLE 5 | The table summarizes incidence of side effects, and the incidence of complications, either medical and surgical complications. Medical complications are mainly related to pain or other symptoms requesting specific pharmacological treatment, while surgical complications are related to conditions that requested a treatment performed by the surgeon (haematoma, bar dislodgment, pneumothorax, haemothorax).

	Standard of care	Cryoanalgesia	*p*
Thoracic allodynia	4 (12.1)	6 (17.6)	0.73
Thoracic hyperalgesia	7 (21.2)	7 (20.6)	1
Thoracic anesthesia	7 (21.2)	8 (23.5)	1
Thoracic hypo-aesthesia	8 (24.2)	18 (52.9)	0.02
Complications (total)	4 (9.3)	7 (15.6)	0.52
Medical	3 (7)	1 (2.2)	0.35
Surgical	1	3 (6.7)	0.24

it should be coupled with pain-specific assessment tools like the YAPFAQ or pain scales for more precise and sensitive measurements. This was how it was done when COPPER was designed. Moreover, cryoanalgesia is widely used for PE pain control, but none of the recent studies considered a long-term assessment [26–28]. Our results are otherwise confirmatory of the safety of the technique with no cryoanalgesia-related side effects.

The study has several limitations. The primary outcome measures are not specific and validated for the study population and may be influenced by numerous confounding factors beyond pain. In fact, pain and quality of life might be affected by multiple factors, including the occurrence of complications. Pectus excavatum repair still remains a surgery with a significant incidence of complications, from mild to severe, usually underestimated and underreported. Even our cohort of patients reported an overall incidence of complications of around 1 in 10 patients. Future studies could benefit from employing measures tailored to patients undergoing pectus excavatum repair. For instance, the utilization of wearable devices could aid in creating a more personalized measure of return to baseline activity levels, sleep patterns, and awake cycles, thus providing a more personalized measure [29–31].

Another limitation pertains to the cryoanalgesia technique used for MIRPE. While this technique is primarily utilized for chronic neuropathic pain, its application to acute postoperative pain is relatively novel. Therefore, it remains unclear whether a 2-min application to 10 intercostal nerves is adequate for pain relief in the acute postoperative setting. Moreover, the technique is not standardized, and its application differs from one institution to another, which makes comparison between studies difficult.

Postoperative pain still remains a significant issue following pectus excavatum repair. It is important to acknowledge that non-pharmacological treatments, like distraction, relaxation techniques, and coping, play a role in helping patients adapt to their new chest shape and compliance. Personalized medicine approaches could be beneficial, given the uncertainty regarding risk factors for outcomes in this patient population.

4.2 | Future Development

In our view, the next step involves utilizing more personalized outcome measures such as wearable devices to measure patients' performances and responses to treatments. Building the so-called "digital twin" could also help identify baseline characteristics, which can be used for postoperative follow-up with the aim to return to early pre-operative conditions, or even superior to baseline. This approach holds promise for tailoring interventions to individual patient needs and optimizing outcomes [31]. Moreover, patients report their physical and mental status using subjective descriptions that might significantly change every day after surgery. Personalized medicine should take subjective reporting into consideration, converting it into a more objective and comparable measure and applying tailored treatments.

Another consideration should be made on the onset of cryoanalgesia. It typically takes 24–48 h until it works. Then, incorporating a single short regional anesthesia block should be considered to provide a bridge between surgery and the effect of cryoanalgesia, as already shown by other trials [32, 33].

Finally, long-term follow-up is essential for gaining a deeper understanding of the evolution of cryoablation and its potential long-standing effects. Continuous monitoring and assessment of patients over an extended period are crucial for evaluating the durability and sustainability of pain relief provided by cryoablation, as well as any associated complications or sequelae that may arise over time.

5 | Conclusions

The application of cryoanalgesia for postoperative pain control after pectus excavatum repair is a promising technique. If included in a multimodal pain management strategy, cryoanalgesia has the potential to reduce hospital stay and facilitate early return to normal life. However, early postoperative pain control should be considered while cryoanalgesia shows its effects. The long-term effects of cryoanalgesia have been explored, with no side effects recorded in our population. This is an important finding to promote the safety of cryoanalgesia.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.