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Intercostal nerve cryoablation versus thoracic epidural for postoperative analgesia following pectus excavatum repair: a systematic review and meta-analysis

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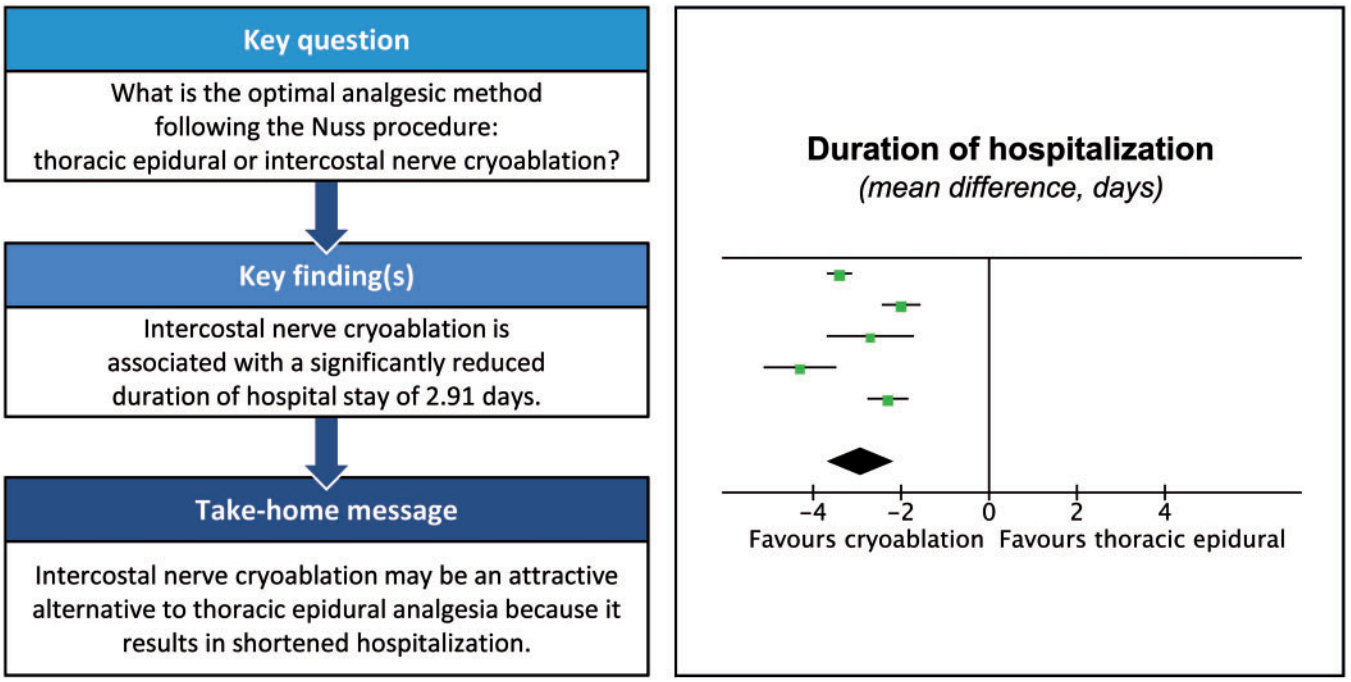

Abstract

OBJECTIVES: Minimally invasive pectus excavatum repair via the Nuss procedure is associated with significant postoperative pain that is considered as the dominant factor affecting the duration of hospitalization. Postoperative pain after the Nuss procedures is commonly controlled by thoracic epidural analgesia. Recently, intercostal nerve cryoablation has been proposed as an alternative method with long-acting pain control and shortened hospitalization. The subsequent objective was to systematically review the outcomes of intercostal nerve cryoablation in comparison to thoracic epidural after the Nuss procedure.

†These two authors contributed equally to this study.

METHODS: Six scientific databases were searched. Data concerning the length of hospital stay, operative time and postoperative opioid usage were extracted. If possible, data were submitted to meta-analysis using the mean of differences, random-effects model with inverse variance method and I^2 test for heterogeneity.

RESULTS: Four observational and 1 randomized study were included, enrolling a total of 196 patients. Meta-analyses demonstrated a significantly shortened length of hospital stay [mean difference -2.91 days; 95% confidence interval (CI) -3.68 to -2.15; $P < 0.001$] and increased operative time (mean difference 40.91 min; 95% CI 14.42–67.40; $P < 0.001$) for cryoablation. Both analyses demonstrated significant heterogeneity (both $I^2 = 91\%$; $P < 0.001$). Qualitative analysis demonstrated the amount of postoperative opioid usage to be significantly lower for cryoablation in 3 out of 4 reporting studies.

CONCLUSIONS: Intercostal nerve cryoablation during the Nuss procedure may be an attractive alternative to thoracic epidural analgesia, resulting in shortened hospitalization. However, given the low quality and heterogeneity of studies, more randomized controlled trials are needed.

Keywords: Thoracic epidural analgesia • Intercostal nerve cryoablation • Pectus excavatum • Nuss procedure • Hospitalization

ABBREVIATIONS

CI	Confidence interval
MD	Difference in mean
MME	Morphine milligram equivalents
PCA	Patient-controlled analgesia
SD	Standard deviation

INTRODUCTION

Pectus excavatum is the most common congenital anterior chest wall deformity with an estimated incidence of 1 in 300–400 live births [1–3]. Surgical correction of the deformity by the Nuss procedure is currently considered as the gold standard treatment because of its minimally invasive character, minimal blood loss, short operative time and no need for resection of cartilage [4]. However, the instantaneous reshaping of the chest wall by the Nuss bar is also associated with significant and lengthy postoperative pain. Controlling this postoperative pain is the primary factor that affects the duration of hospitalization [5]. Possible pain therapies include thoracic epidural analgesia, intravenous patient-controlled analgesia (PCA), regional blocks and multimodal anaesthesia [6]. A web-based survey among primarily paediatric hospitals found thoracic epidural to be the primary analgesic modality in 91% of institutions while PCA was predominantly used upon epidural failure [7]. Despite the routine use of epidural analgesia, 35% of patients receiving the Nuss procedure experience a failed catheterization attempt or dysfunctional catheter that is removed within 24 h [8]. The assumption that routine epidural catheter placement offers the optimal pain treatment strategy may therefore be questioned [8]. An alternative method of pain relief is cryoablation or freezing of the intercostal nerves. This technique was first introduced in 1974 to prevent post-thoracotomy pain [9] while its use during the Nuss procedure was not described until 2016 [10]. Cryoablation is performed by application of a long-shafted probe that is cooled to approximately -60°, causing Wallerian degeneration of the nerve axons and thereby preventing pain transmission [11]. The advantage of cryoablation is that its analgesic effect lasts until complete axonal regeneration after 4 weeks [12]. Furthermore, this technique lacks the effects of epidural anaesthesia on sensory and motor functions of the lower limbs and the risk of complications such as urinary retention and infection and also lacks common side effects of morphinomimetics such as nausea and dizziness. Cryoablation may accordingly be superior to conventional analgesic methods to control the significant and lengthy pain after the Nuss procedure. Up until now, several small sample size series have compared cryoablation and thoracic epidural analgesia to control pain after the Nuss procedure. To support clinical decision-making, evidence should ideally arise from well-designed and comprehensive literature reviews. To date no such review has been published. The subsequent aim of this review is to systematically assess all randomized and non-randomized studies that compare cryoablation of the intercostal nerves and thoracic epidural as primary analgesic method after the Nuss procedure with length of hospital stay as the primary outcome. Secondary outcomes include the operative time, use of adjunct analgesic medication or methods, total opioid usage, postoperative pain scores and complications.

METHODS

Protocol and registration

Prior to start, a review protocol was drawn. This systematic review was written in compliance with the PRISMA statement [13].

Eligibility criteria

Types of participants. Participants of any race, gender, age and body mass index who underwent minimally invasive repair of pectus excavatum by the Nuss procedure were eligible for inclusion.

Types of interventions. Studies that compared thoracic epidural analgesia with intercostal nerve cryoablation during the Nuss procedure for minimally invasive repair of pectus excavatum were considered. Studies involving co-interventions or adjunct pain medication were not excluded, provided that they were well documented.

Outcome measures. The primary outcome was postoperative length of hospital stay. Secondary outcomes and their corresponding definitions are mentioned below.

Types of studies. Both observational and randomized studies were examined for eligibility.

Search and study selection

Potentially eligible studies were identified by searching electronic scientific databases and trial registries. Only studies reported in English were considered. No publication date restrictions were imposed. The search terms were only applied to the title and abstract fields. The search strategy was first constructed for the PubMed database (searched through the National Library of Medicine) and subsequently adapted for the EMBASE (OvidSP), Web of Science (ISI Web of Knowledge), CINAHL (EBSCOhost) and Cochrane Library (Cochrane Library) databases (see the search queries in Supplementary Material, Data S1–S5). Identical queries were used to search the PROSPERO, WHO-ICTRP and Clinicaltrials.gov registries. An additional manual-related articles and cross-reference search was conducted to identify reports that were not found through the aforementioned searches. This additional search also served as an indicator of the quality and completeness of the database search strategy. All searches were performed by a trained researcher (J.H.T.D.). The last search was performed on January 9th, 2020. Duplicates were discarded using the Mendeley find duplicates function (Mendeley Desktop v1.19.4 for MacOS, Mendeley Ltd, Elsevier, Amsterdam, the Netherlands). The remaining non-duplicate articles were judged for eligibility based on their title and abstract. Thereafter, full text of potentially eligible articles was read and assessed according to the predefined eligibility criteria. Studies meeting these criteria were included for systematic review, and if possible, meta-analysis. Study selection was performed in a standardized, unblinded manner by 2 independent reviewers (J.H.T.D. and M.J.A.M.B.). Inter-reviewer disagreements were, if not solvable between reviewers, resolved by the consultation of E.R.d.L.

Data collection and data items

Data were extracted by 1 reviewer (J.H.T.D.) and validated by a second reviewer (M.J.A.M.B.). Inter-reviewer disagreements were, if not solvable between reviewers, resolved by the consultation of E.R.d.L. Studies reporting continuous variables as mean and standard deviation (SD) were extracted as such. Variables reported as median and interquartile range or standard error of the mean were converted prior to extraction. Methods of conversion were reported elsewhere [14, 15]. If needed, values were derived from the available graphs. Information was extracted from each included paper on: (i) general study characteristics: study design, country, enrolment period and length of follow-up; (ii) study population characteristics: age, gender, body mass index, preoperative pectus excavatum severity index (e.g. Haller index or Correction index); (iii) characteristics of the intervention: brand of the cryoablation device used, cryoablation temperature and duration, the number of levels of intercostal nerves that were ablated, medication used for epidural analgesia, number of Nuss bars placed and use of sternal elevation techniques (e.g. the Crane method [16]); (iv) primary outcome measure: postoperative length of hospital stay; and (v) secondary outcome measures: operative time (i.e. from incision to closure), blood loss, postoperative pain scores, time to removal of epidural catheter, use of additional pain medication, time to oral pain medications alone, total opioid usage [in morphine milligram equivalents (MME)], discharge opioid prescription, time to return of normal chest wall sensation (only for the cryoablation group) and complications. Adverse events that occurred during initial surgery or within 30 days after the procedure were considered to be complications.

Risk of bias in individual studies

The presence of bias within randomized controlled trials was evaluated by the updated Cochrane risk-of-bias tool for randomized trials (RoB 2) [17]. The RoB 2 tool produces a risk-of-bias judgement based on a 5-point scale that includes: low risk of bias, moderate risk, serious risk, critical risk or no information. Non-randomized studies were evaluated by the Cochrane risk-of-bias tool for non-randomized studies of interventions (ROBINS-I), which judges studies on a 3-point scale, namely low risk of bias, some concerns or high risk [18].

Summary measures and synthesis of results

Quantitative synthesis of primary and secondary outcome measures was solely performed if studies were deemed sufficiently homogeneous. If not, data were reported as such. For the quantitative synthesis of continuous data, the difference in means (MD) was used to assess variables measured on the same scale among all studies. The standardized mean difference was chosen if studies reported their outcomes using different scales. An MD or standardized mean difference <0 favours intercostal nerve cryoablation over thoracic epidural analgesia. Meta-analyses were performed by Review Manager (RevMan v5.3 for Macintosh, Cochrane Collaboration, Oxford, UK) using a random-effects model with inverse variance method and I^2 test for heterogeneity. $P < 0.05$ was considered as statistically significant. An I^2 value of >50% in conjunction with a P-value of ≤ 0.10 indicated the presence of statistically significant heterogeneity among included studies. Outcomes were reported in forest plots. Subgroup analyses were not prespecified but performed if needed.

Risk of bias across studies

The probability of publication bias was explored both visually by a funnel plot [standard error by (standardized) mean difference] and statistically by Egger's linear regression test and Begg's and Mazumdar's rank correlation test. $P \leq 0.10$ was considered as statistically significant. Publication bias analyses were performed by Jamovi (Jamovi v0.9 for Macintosh, MAJOR software package add-on; https://www.jamovi.org, Sydney, Australia) since Cochrane's Review Manager does not provide the above-mentioned statistical tests.

RESULTS

Study selection

See the PRISMA flow diagram in Fig. 1. The PubMed ($n = 64$), EMBASE ($n = 342$), Web of Science ($n = 1536$), Cochrane Library ($n = 21$) and CINAHL ($n = 20$) database searches provided a cumulative 1983 studies. The PROSPERO ($n = 140$), WHO-ICTRP ($n = 62$) and Clinicaltrials.gov ($n = 44$) registries provided an additional 246 studies. No records were identified through the cross-reference and related articles searches. No unpublished data

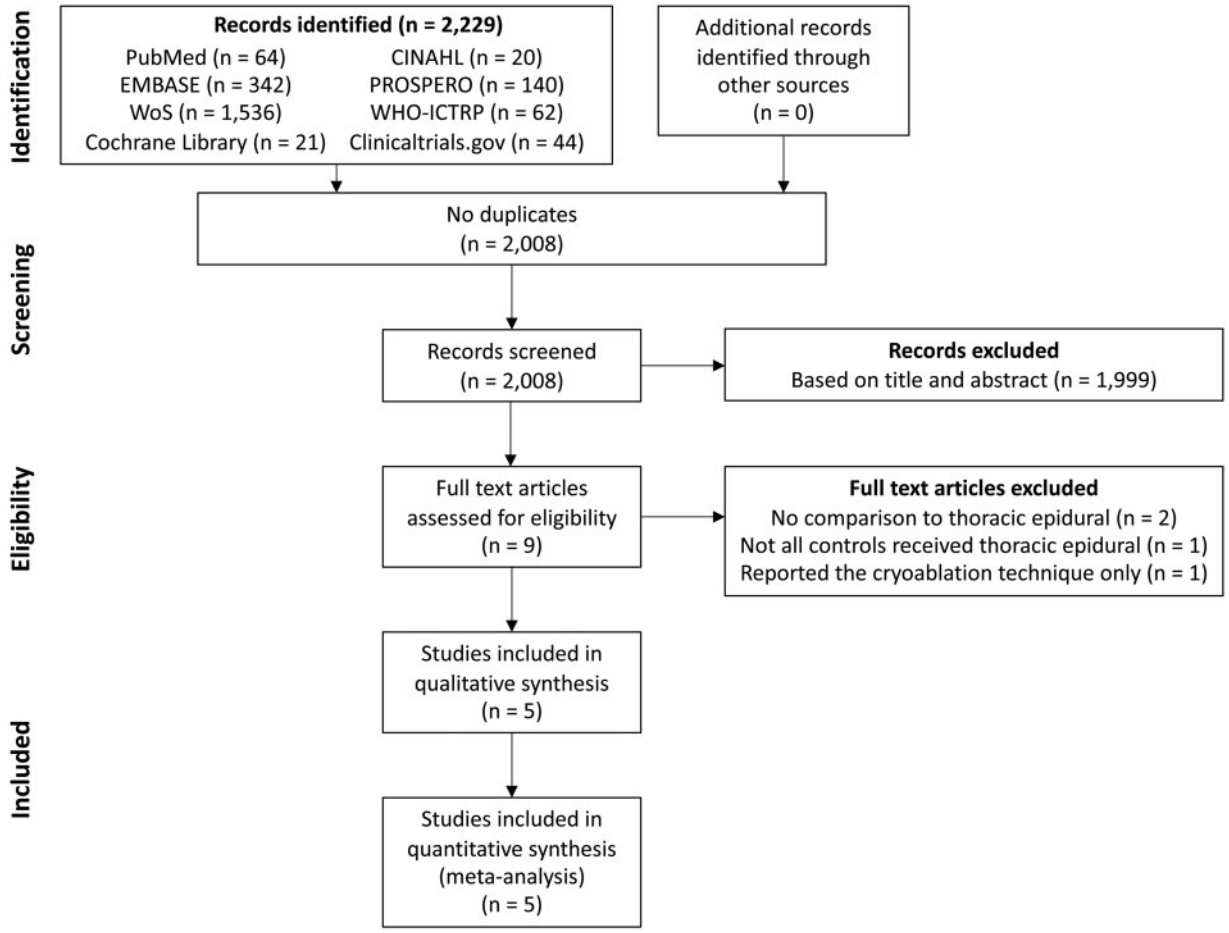

Figure 1: PRISMA flow diagram of the study selection procedure.

were obtained. Of the 2229 citations, 221 duplicates were discarded. Title and abstract of the remaining 2008 studies were screened for eligibility, whereupon another 1999 records were discarded. The full text of the 9 remaining articles was read and thoroughly assessed for eligibility. Of these, 4 did clearly not meet the above-mentioned eligibility criteria and were excluded. Reasons for exclusion were as follows: no comparison to thoracic epidural analgesia ($n = 2$); not all controls received thoracic epidural analgesia ($n = 1$); the intercostal nerve cryoablation surgical technique was only reported ($n = 1$). The remaining 5 studies were considered eligible for systematic review, qualitative syntheses and pooling by quantitative synthesis (i.e. meta-analysis).

Study characteristics

Methods. Of the included papers, 1 was a single-centre randomized controlled trial, 3 were retrospective observational (2 single centre and 1 multicentre), and 1 study performed a single-centre, single-arm prospective observational study and compared its results to a retrospective cohort (see Table 1). Studies were all conducted in the USA and enrolled patients between March 2013 and September 2018. The mean length of follow-up ranged from no follow-up after hospital discharge to 19.6 and 12 months for the thoracic epidural and cryoablation group, respectively.

Participants. In total, 196 participants were included, of which 100 (51%) in the thoracic epidural and 96 (49%) in the cryoablation group (see Table 1). Individuals were predominantly male (gender was reported for 147 of the 181 participants). The mean age of participants in the cryoablation group ranged from 15.6 to 20.9 years. The mean age of the thoracic epidural group was not reported by Graves *et al.* [22] and ranged from 15.0 to 17.0 years for the remaining studies. The mean body mass index ranged from 18.7 to 19.8 kg/m^2 and 18.4 to 20.3 kg/m^2 for the epidural and cryoablation group, respectively. All participants underwent minimally invasive repair of their pectus excavatum by the Nuss procedure. The study of Harbaugh *et al.* [21] was the only one to include 2 participants with previous pectus repair in the thoracic epidural group. The preoperative mean Haller index in the epidural group was not reported by Graves *et al.* [22] and ranged from 3.3 to 3.8 for the other studies. In comparison, the mean Haller index in the cryoablation group ranged from 4.2 to 4.8. This difference was only found to be statistically significant for the study of Harbaugh *et al.* [21] and Dekonenko *et al.* [19]. In addition, Dekonenko *et al.* [19] also reported a statistically significant difference regarding preoperative Correction index [epidural: 29.0% (SD 2.3) vs cryoablation: 37.3% (SD 13.1)].

Interventions. For cryoablation, all studies utilized an Atricure (Atricure Inc., OH, USA) cryosurgical system. Cryoablation temperature was set to -60° [20–23], and each nerve was ablated for 120 s [19–23], followed by a thaw cycle of several to 5 s [19, 22]

Table 1: Study and baseline characteristics

Author	Country	Study design	Treatment arm	Enrolment period	Number of participants, *n*	Male, *n* (%)	Age, mean (years)	BMI, mean (kg/m^2)	Preoperative Haller index	Preoperative correction index	Length of FU (months)
Dekonenko *et al.* [19]	USA	Data from a previous randomized controlled trial	EPI	May 2013–August 2016	32	29 (90.6)	15.0 (SD 1.6)	18.7 (SD 1.7)	3.6 (SD 0.7)	29.0 (SD 2.3)	0
		Single-arm, single-centre prospective observational study	CRYO	November 2017–September 2018	35	29 (82.4)	15.7 (SD 2.3)	18.4 (SD 2.3)	4.5 (SD 1.4)	37.3 (SD 13.1)	0
Graves *et al.* [20]	USA	Single-centre randomized controlled trial	EPI	May 2016–March 2018	10	8 (80)	16.1 (SD 2.0)	19.8 (no SD)	3.7 (SD 0.6)	NR	12 (no SD)
			CRYO	May 2016–March 2018	10	9 (90)	20.9 (SD 4.3)	20.3 (no SD)	4.2 (SD 0.5)	NR	12 (no SD)
Harbaugh *et al.* [21]		Single-centre retrospective observational study	EPI	April 2015–July 2016	13	11 (85)	17.0 (SD 1.7)	NR	3.3 (SD 1.0)	NR	NR
			CRYO	July 2016–August 2017	19	19 (100)	15.7 (SD 1.6)	NR	4.3 (SD 1.0)	NR	NR
Graves *et al.* [22]	USA	Single-centre retrospective observational study	EPI	NR	15	NR	NR	NR	NR	NR	NR
			CRYO	June 2015–April 2016	10	8 (80)	16.8 (SD 6.2)	NR	4.8 (SD 1.4)	NR	7.6 (SD 2.2)
Keller *et al.* [23]	USA	Multicentre retrospective observational study	EPI	March 2013–January 2016	26	23 (88)	15.3 (SD 1.6)	NR	3.8 (SD 1.0)	NR	19.6 (SD 8.0)
			CRYO	March 2013–January 2016	26	20 (77)	15.6 (SD 1.5)	NR	4.2 (SD 1.4)	NR	5.3 (SD 2.8)

BMI: body mass index; CRYO: cryoablation; EPI: thoracic epdiural; FU: follow-up; NR: not reported; SD: standard deviation.

Table 2: Interventional characteristics

Author	Treatment arm	Type of cryoablation device	Temperature cryoablation (°C)	Duration of cryoablation (s)	Duration of thaw cycle (s)	Number of ablated nerves	Level of thoracic epidural	Medication used for epidural analgesia	Number of Nuss bars implanted
Dekonenko *et al.* [19]	EPI						NR	NR	1 bar in every case
	CRYO	CryoICE probe (Atricure Inc., OH, USA)	NR	120	3–5	T4-T7, bilaterally			1 bar in every case
Graves *et al.* [20]	EPI						T5-6 or T6-7	0.1% ropivacaine and 2 µg/ml fentanyl	NR
	CRYO	Atricure cryosurgical system (Atricure Inc., OH, USA)	-60	120	NR	5 intercostal nerves, bilaterally depending on the level of incision			NR
Harbaugh *et al.* [21]	EPI						NR	0.0625 or 0.125% bupivacaine and hydromorphone 5 mcg/ml	3 cases with more than 1 bar
	CRYO	Atricure cryoICE (Atricure Inc., OH, USA)	-60	120	NR	4–5 intercostal nerves bilaterally, depending on the level of incision			1 bar in every case
Graves *et al.* [22]	EPI						NR	NR	NR
	CRYO	CryoICE probe (Atricure Inc., OH, USA)	-60	120	Few seconds	4–5 intercostal nerves bilaterally, depending on the level of incision			NR
Keller *et al.* [23]	EPI						NR	Hydromorphone with or without bupivacaine	1 bar in every case
	CRYO	CryoICE probe (Atricure Inc., OH, USA)	-60	120		T3-T7, bilaterally			2 cases with 2 bars

CRYO: cryoablation; EPI: thoracic epidural; NR: not reported.

Table 3: Primary and secondary outcome measures

Author	Treatment arm	Postoperative LOHS (days)	Operative time (min)	Blood loss (ml)	Time to removal of epidural catheter	Time to oral pain medications (h)	Time to oral pain medications alone (h)	Postoperative total opioid usage (oral morphine milligram equivalents)	Complications	Time to return of normal sensation
Dekonenko *et al.* [19]	EPI	4.5 (SD 0.8)	62.7 (SD 21.7)	NR	NR	68.1 (SD 4.8)	68.1 (SD 25.1)	420 (no SD)	0	
	CRYO	1.1 (SD 0.2)	101.0 (SD 35.6)	NR	NR	4.2 (SD 2.2)	20.3 (SD 13.0	60 (no SD)	1 pneumothorax	NR
Graves *et al.* [20]	EPI	5.0 (SD 0.5)	76.8 (SD 12.2)	NR	NR	NR	NR	684.0 (SD 191.8)	1 pneumothorax	
	CRYO	3.0 (SD 0.5)	145.3 (SD 10.0)	NR	NR	NR	NR	268.0 (SD 165.2)	0	At 3 months: 6/10; at 1 year: all
Harbaugh *et al.* [21]	EPI	6.0 (SD 1.7)	109.0 (SD 70.6)	NR	NR	NR	NR	2.1 (SD 1.9)[a]	1 reoperation, secondary to hematothorax. 1 pneumothorax	
	CRYO	3.3 (SD 0.8)	141.0 (SD 54.5)	NR	NR	NR	NR	2.3 (SD 2.0)[a]	2 reoperations due to bar displacement, 2 hematothorax or pneumothorax, 1 slipped bar and 1 superficial site infection	Gradual return at 2–4 months. Two patients with numbness up to 9 months postoperatively
Graves *et al.* [22]	EPI	6.3 (SD 1.3)	NR	NR	NR	NR	NR	NR	NR	
	CRYO	2.0 (SD 0.8)	NR	NR	NR	NR	NR	NR	1 bilateral pleural effusion	At 2 months: 5/10. At 3 months: 6/10. At 4 months: 8/10. In 2 cases: persistent numbness at 8 and 9 months
Keller *et al.* [23]	EPI	5.8 (SD 0.9)	94.3 (SD 23.6)	12.4 (SD 10.3)	Between 2 and 3 days	NR	95.0 (SD 23.0)	119.8 (SD 95.1)[b]	0	
	CRYO	3.5 (SD 0.8)	114.2 (SD 27.9)	16.9 (SD 8.7)		NR	45.1 (SD 17.0)	49.0 (SD 32.7)[b]	3 displaced bars	

[a]In oral morphine equivalents per kilogram.
[b]Total intravenous opioid usage only.
CRYO: cryoablation; EPI: thoracic epidural; LOHS: length of hospital stay; NR: not reported; SD: standard deviation.

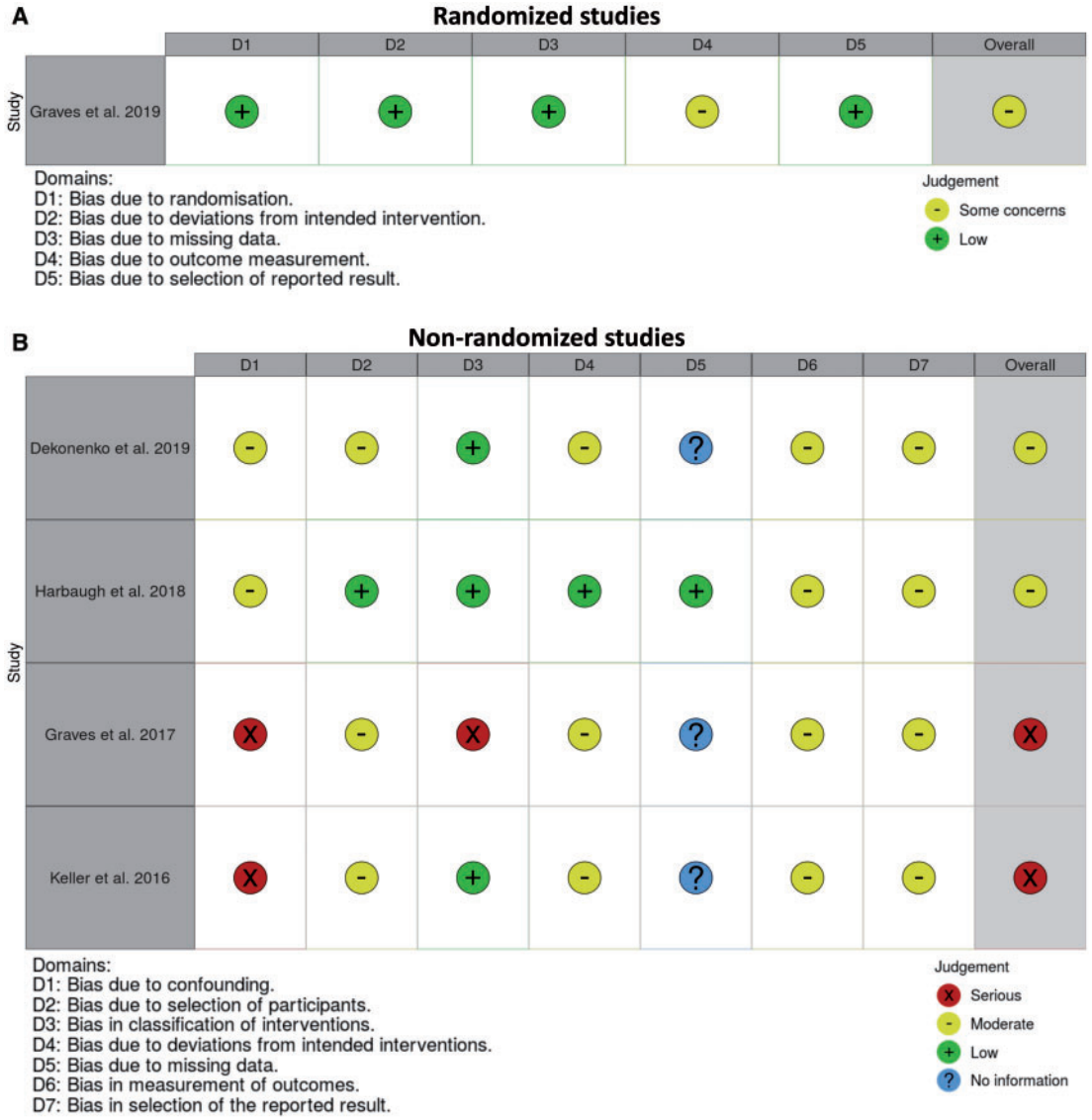

Figure 2: Risk-of-bias assessment within (**A**) randomized studies and (**B**) non-randomized studies.

(see Table 2). Dekonenko *et al.* [19] and Keller *et al.* [23] always applied cryoablation to levels T4-7 and T3-7, respectively. Harbaugh *et al.* [21] and Graves *et al.* [22] always ablated 4–5 intercostal nerves depending on the level of incision, whereas the more recent study of Graves *et al.* [20] ablated 5 intercostal nerves (i.e. 1 at the level of incision and 2 above and below).

Only Graves *et al.* [20] reported the location of thoracic epidural catheter placement, namely between T5-6 or T6-7. Among all reporting studies, epidural infusion consisted of bupi- or ropivacaine in combination with an opioid (hydromorphone or fentanyl) [20, 21, 23]. In the epidural group, 3 participants received multiple bars, whereas in the cryoablation group, 2 participants received 2 bars and the Crane method was used in 4 patients [19, 21, 23].

Outcomes. All included studies reported the length of postoperative hospital stay on the same scale among both groups. Secondary outcomes were at least reported by 1 study each (see Table 3).

Risk of bias within studies

Of the non-randomized studies, 2 were judged to possess a serious risk of bias [22, 23], whereas the remaining 2 were judged as moderate risk [19, 21]. The largest share in bias arose due to potential confounding (see Fig. 2). For the randomized study of Graves *et al.* [20], some concerns of bias were present in the measurement of outcomes.

Synthesis of results

Qualitative synthesis. Blood loss during surgery was only reported by Keller *et al.* [23]. Estimated blood loss was slightly lower for the thoracic epidural group [12.4 ml (SD 10.3) vs 16.9 ml (SD 8.7) for the cryoablation group], however, the method by which these values were estimated was not reported. Postoperative pain scores appraised on the numeric rating scale did not significantly differ between groups [19–21]. Keller *et al.* [23] only reported pain scores for the cryoablation group (see Fig. 3). Epidural catheters were removed between 2 and 3 days

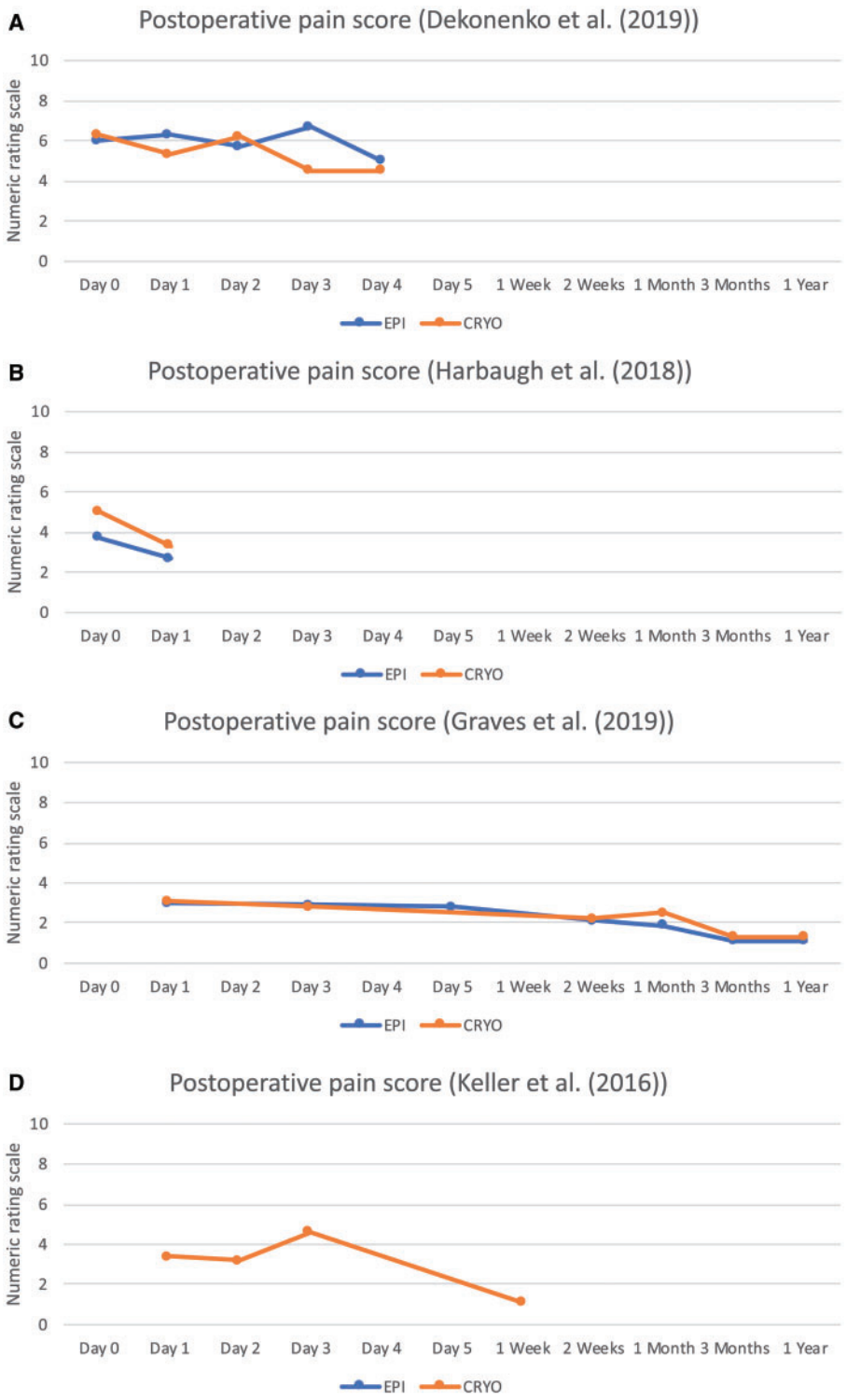

Figure 3: Mean postoperative pain scores (reported on the numeric rating scale) of the thoracic epidural and cryoablation group over time. EPI: thoracic epidural; CRYO: cryoablation.

after surgery by Keller *et al.* [23], while removal times were not reported by any other study. Supplementary pain medication provided directly after surgery demonstrated substantial heterogeneity among included studies (Supplementary Material, Data S6). Additional PCA pumps with hydromorphone were given to all participants of both groups by Graves *et al.* [20], whereas Harbaugh *et al.* [21] used PCA in 4 (30.8%) patients in the epidural, and 13 (68.4%) patients in the cryoablation group due to inadequate pain control. Moreover, an additional intercostal nerve block was given to 2 patients in the cryoablation group [21]. In the study of Keller *et al.* [23], 7 (26.9%) participants received additional local subcutaneous infusion catheters in the epidural

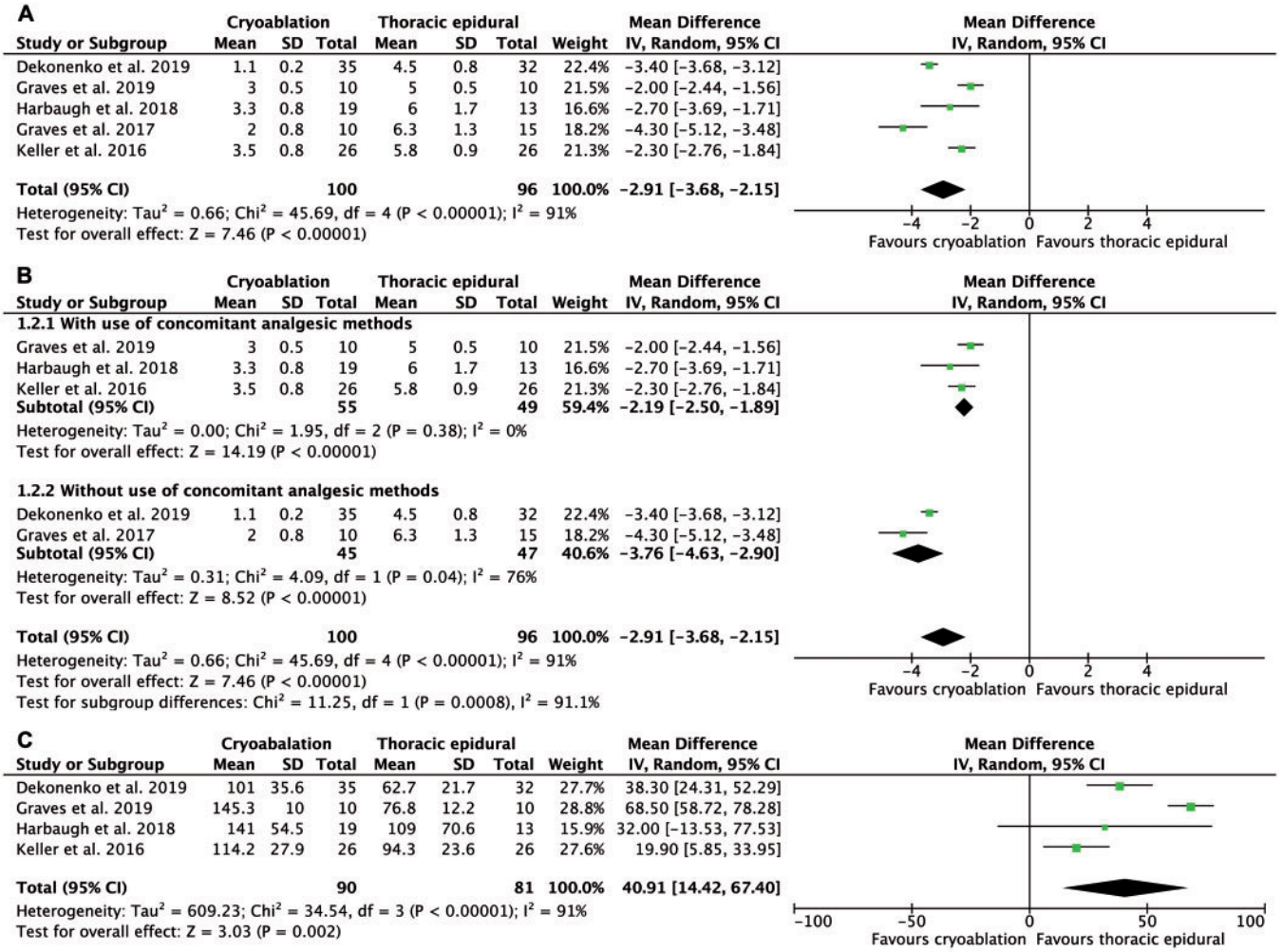

Figure 4: Meta-analyses (random-effects model with inverse variance method) demonstrating the effect of cryoablation and thoracic epidural on (**A**) the length of hospital stay, (**B**) the length of hospital stay among subgroups that did and did not use additional methods of analgesia and (**C**) the operative time. CI: confidence interval; IV: inverse variance; SD: standard deviation.

group, in contrast to 24 (92.3%) participants in the cryoablation group. No exact rationale was provided for this abundant usage of local infusion catheters by Keller *et al.* [23]. Two studies reported the time to oral pain medications alone to be 2- to 3-fold lower for cryoablation ($P < 0.01$ and $P < 0.001$) [19, 23]. Total postoperative opioid usage was reported by 4 out of 5 studies [19–21, 23]. Despite diverging definitions, 3 studies demonstrated a statistically significant difference in opioid usage that favoured cryoablation [19, 20, 23]. For the study of Dekonenko *et al.* [19], total opioid usage during inpatient stay was obtained from the available graph and was 420.0 MME for the thoracic epidural and 60.0 MME for the cryoablation group. This difference was statistically significant ($P < 0.001$). The most recent study of Graves *et al.* [20] also found statistically significant reduced mean opioid usage in the cryoablation group [268.0 MME (SD 165.2) vs 684.0 MME (SD 191.8) for the epidural group; $P < 0.001$]. Keller *et al.* [23] only reported the mean total intravenous opioid usage and revealed similar results [49.0 (SD 32.7) vs 119.8 MME (SD 95.1) for the cryoablation and epidural group; $P = 0.001$]. Harbaugh *et al.* [21] was the only one to find no statistically significant mean difference in postoperative opioid usage. Graves *et al.* [20] reported the recovery of chest sensation in all patients, 1 year after cryoablation. Gradual return typically occurred between 2 and 4 months [20–22]. However, some degree of numbness at 8 and 9 months was also reported in 1 and 3 patients, respectively [21, 22]. None of the included studies reported on the motor function and sensibility following epidural analgesia. Eleven (11.0%) complications occurred in the cryoablation group, in comparison to 3 (3.1%) complications in the thoracic epidural group. None of these complications could be directly related to the technical performance of the analgesic therapies. The majority of complications in the cryoablation group were bar displacements ($n = 6$; 6.0%) (see Table 3).

Quantitative synthesis. Data regarding the length of postoperative hospital stay and duration of surgery were recorded by 5 and 4 studies, respectively. For both variables, identical definitions were used among studies. The mean length of hospital stay ranged from 4.5 to 6.3 days following thoracic epidural and 1.1 to 3.5 days following cryoablation. All individual study results demonstrated statistically significant shorter hospitalization in favour of cryoablation [19–23]. This trend was reproduced by meta-analysis that demonstrated cryoablation to be associated with a significantly shorter mean length of hospitalization

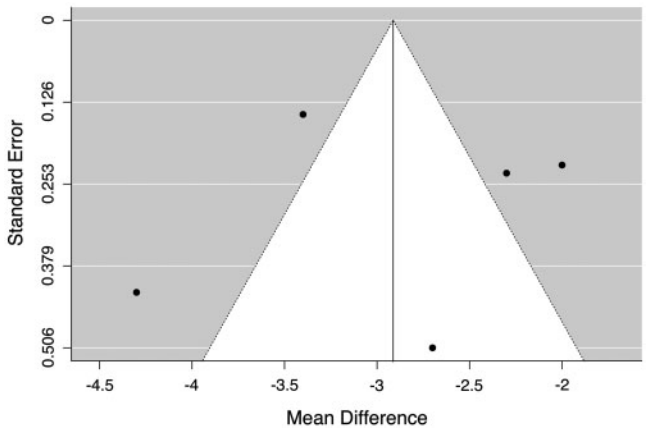

Figure 5: A standard error by mean difference plot of the primary outcome to detect the presence of publication bias.

[Fig. 4A; MD -2.91, 95% confidence interval (CI) -3.68 to -2.15; $P < 0.001$]. However, meta-analysis also detected a significant level of heterogeneity ($I^2 = 91\%$; $P < 0.001$). *Post hoc* subgroup analysis was performed to assess the effect of the use of concomitant analgesic methods on the length of hospital stay and heterogeneity. Subgroup analysis revealed a statistically significant difference among studies that did ($n = 3$) and did not ($n = 2$) use additional modalities of analgesia (PCA, intercostal nerve block or local infusion catheters) ($I^2 = 91.1\%$; $P < 0.001$). The subgroup using additional analgesic techniques demonstrated a lower decrease in hospitalization for the cryoablation group (Fig 4B; MD -2.19, 95% CI -2.50 to -1.89; $P < 0.001$), compared to the subgroup without additional analgesic methods (MD -3.76, 95% CI -4.63 to -2.90; $P < 0.001$). In addition, no heterogeneity was detected among studies in the subgroup that used concomitant analgesic methods ($I^2 = 0.0\%$; $P = 0.38$).

The mean operative time ranged from 62.7 to 109.0 min for the epidural group and 101.0 to 145.3 min for the cryoablation group. The difference in operative time reached statistical significance in 3 [19, 20, 23] out of 4 [19–21, 23] studies, favouring thoracic epidural analgesia. Pooled analysis demonstrated a statistically significant increased operative time among participants who received cryoablation during surgery (Fig. 4C; MD 40.91, 95% CI 14.42 to 67.40; $P = 0.002$). However, again meta-analysis detected a significant level of heterogeneity ($I^2 = 91\%$; $P < 0.001$).

Risk of bias across studies

A contour-enhanced funnel plot of the primary outcome was constructed (see Fig. 5). On inspection potential asymmetry was seen in the bottom left side of the plot, indicating the potential presence of publication bias. However, as this is a region of high significance, publication bias is less likely [24]. This was statistically confirmed by the Begg's and Mazumdar's rank correlation test ($P = 1.00$) and Egger's linear regression test ($P = 0.61$).

DISCUSSION

This systematic review and meta-analysis compared cryoablation of the intercostal nerves and thoracic epidural analgesia as primary analgesic method after the Nuss procedure with length of hospital stay as primary outcome. Four non-randomized and 1 randomized study were included, enrolling a total of 196 patients. Characteristics of included patients corresponded with previously reported series on the Nuss procedure [25, 26]. Quantitative analyses showed cryoablation of the intercostal nerves to be associated with a significantly reduced length of hospital stay of 2.91 days compared to thoracic epidural analgesia. However, a significant level of heterogeneity was detected ($I^2 = 91.0\%$; $P < 0.001$). This heterogeneity potentially arose from differences in the use of additional pain therapies, given that the majority of cryoablation patients in 3 out of 5 studies received additional PCA pumps, local infusion catheters or intercostal nerve blocks [20, 21, 23]; resulting in a relatively longer length of hospitalization. This was confirmed by subgroup analysis, which demonstrated a statistically significant longer length of hospital stay among studies that used additional pain therapies compared to those that did not ($I^2 = 91.1\%$; $P < 0.001$). However, it has to be remarked that the number of studies included per subgroup was rather low (3 and 2, respectively). Although the use of additional pain therapies may explain the observed heterogeneity, it is unknown whether additional pain therapies are necessary given the diversity of their use. Nevertheless, it should be noted that all patients have their individual pain perception and susceptibility. A tailor-made approach for additional pain relief could therefore be warranted. Future research should critically evaluate whether adjunct pain therapies are indicated since these may have a direct effect on the duration of hospitalization.

Despite shorter hospitalization in favour of cryoablation, no significant differences in pain scores were found among both groups (Fig. 3) [19–21]. However, given that the general postoperative aim is to reduce the patients' pain experience to an acceptable level, pain scores are unlikely to differ. The length of hospitalization and use of opiates were subsequently considered to be the most important determinants in the comparison of pain management techniques. Besides a reduction in hospitalization, postoperative opioid requirement was found to be significantly lower among cryoablation patients in 3 out of 4 individual studies [20, 21, 23]. Dekonenko *et al.* [19] and Graves *et al.* [20], moreover, reported the differences in postoperative opioid usage to become larger following adjustment for the length of hospital stay.

The shortened hospitalization associated with cryoablation may not only improve patient recovery but could also cut healthcare costs; however, to compare the cost-effectiveness of both techniques, all expenses including ancillary costs should be evaluated in future research. The overall increased operation time associated with cryoablation was 40.91 min and ranged from 19.90 to 68.50 min per study [19–21, 23]. This increase partially resulted from the freeze–thaw cycles lasting around 2 min per nerve (4–5 nerves were ablated bilaterally). The remaining part may be attributed to anatomic preparation and cryoprobe positioning, whereby the wide range of times was most likely due to variations in techniques and experience that is likely to improve over time. On the contrary, the time needed for epidural catheterization has previously been reported to be 11 min [27], while the total time needed to obtain adequate pain relief may be lengthened due to epidural catheter(ization) failure that is known to occur in 35% of patients receiving the Nuss procedure [8]. Another disadvantage of epidural is the frequent need for urinary catheterization, subsequently impairing patient mobility and lengthening recovery.

Complications occurred in 11.0% and 3.1% of cases in the cryoablation and thoracic epidural group, respectively. None of these complications could be directly related to the analgesic therapy procedures. The most common complication in the cryoablation group was displacement of the Nuss bar (6.0%). This was comparable to the upper limit of previously reported series (after the introduction of stabilizers) that found displacement rates of 1.8–5.8% [26, 28–30]. Keller *et al.* [23] suggested that bar displacement following cryoablation might result from enhanced pain control resulting in increased physical activity. Pain thus may be protective of bar displacement due to reduced activity. However, this hypothesis was not supported by the fact that no difference in pain scores was found in this review. Nevertheless, a technically well-performed procedure and patient education and selection remain key to prevent bar displacement, while bar instability, early excessive exercise, operation at a young age and Grand Canyon type pectus excavatum [28] are known risk factors for displacement, regardless of the analgesic method used.

Zobel *et al.* [31] investigated the resolution of chest numbness and incidence of neuropathic pain following cryoablation and found numbness of patients aged 21 or below to resolve within 3.4 months without neuropathic pain. In our series, normal chest sensation returned between 2 and 4 months after surgery while numbness persisted in 4 patients up to 8 to 9 months after cryoablation. No patients experienced chronic neuralgia. Nevertheless, 1 patient experienced transitory neuropathic pain [22] while another patient returned to the emergency department because of neuropathic pain [23]. In the latter, Keller *et al.* [23] had not prescribed a neuropathic analgesic on discharge like the other patients had. Keller *et al.* [23] was the only one to prescribe gabapentin after discharge whereas it was standardly provided by 2 studies during hospital stay [19, 23]. Recapitulating, we can assume that the incidence of neuropathic pain in young patients, as included in this study, is low.

Limitations

The main limitations of this review include the low number of included studies and participants, the fact that only one randomized trial was included, the overall methodological quality that ranged from some concerns to serious risk of bias, the use of data conversion methods and the heterogeneity among included studies. In addition, despite the funnel plot asymmetry and statistical analyses were not indicative for publication bias, its presence cannot be completely excluded while the tests used are known to be underpowered if less than10 studies are included.

CONCLUSION

Cryoablation of the intercostal nerves during the Nuss procedure may be an attractive alternative to thoracic epidural analgesia with reduced length of hospital stay of 2.91 days. However, given the overall low methodological quality and heterogeneity of studies, well-designed randomized controlled trials are necessary to corroborate the current evidence.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

Author contributions

Jean H.T. Daemen: Conceptualization; Formal analysis; Methodology; Visualization; Writing—original draft. **Erik R. de Loos:** Methodology; Resources; Supervision; Writing—original draft. **Yvonne L.J. Vissers:** Conceptualization; Methodology; Supervision; Writing—review & editing. **Maikel J.A.M. Bakens:** Formal analysis; Methodology; Writing—original draft. **Jos G. Maessen:** Supervision; Writing—review & editing. **Karel W.E. Hulsewé:** Conceptualization; Supervision; Writing—original draft.

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