

Epidural Analgesia and Abnormal Coagulation in Patients Undergoing Minimal Invasive Repair of Pectus Excavatum

Ara S. Media¹, Frank V. de Paoli^{1,4}, Hans K. Pilegaard⁵, Anne-Mette Hvas^{2,5}, Peter Juhl-Olsen³, Thomas D. Christensen^{1,5}

¹Department of Cardiothoracic and Vascular Surgery, ²Clinical Biochemistry, ³Cardiothoracic Anesthesia, Aarhus University Hospital, Aarhus, ⁴Department of Physiology, Aarhus University, Aarhus, ⁵Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

ABSTRACT

Background: Epidural analgesia (EA) is effective in patients undergoing minimal invasive repair of pectus excavatum (MIRPE) but is associated with major complications such as epidural hematomas. It is recommended to assess coagulation status in patients receiving anticoagulant therapy prior to EA, although no consensus exists in patients without a history of bleeding tendency or anticoagulant therapy. Thus, the aim of this paper was to assess 1) the prevalence of abnormal routine coagulation parameters, i.e., international normalized ratio (INR) and platelet count, and 2) the safety of EA in patients undergoing MIRPE.

Methods: In this retrospective study, we identified 1,973 patients undergoing MIRPE at our center between 2001 and 2019. Complications related to EA were registered for all patients. Information on coagulation parameters was present in 929 patients. Patients with spontaneously elevated INR ≥ 1.5 were referred for assessment of coagulation factor VII in order to assess the cause of the elevated INR.

Results: Of 929 patients with coagulation information available, 18 patients had spontaneously elevated INR ≥ 1.5 (1.9%). In patients with INR ≥ 1.5 , 12 patients underwent further assessment of factor VII, with all patients having a slightly reduced factor VII close to the lower reference range. The majority of the 1,973 patients undergoing MIRPE received EA (99.6%) with very low complication rates (0.2%) and no incidence of epidural hematomas.

Conclusion: In patients undergoing MIRPE, coagulation screening prior to EA should not be mandatory as it revealed no clinically relevant consequences. EA is safe with very low complication rates.

Keywords: Epidural analgesia, INR, pectus excavatum

Address for correspondence: Dr. Ara S. Media, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200, Aarhus N, Denmark.

E-mail: aramed@rm.dk

Submitted: 31-Aug-2021 **Accepted:** 01-Mar-2022 **Published:** 11-Apr-2022

INTRODUCTION

Pectus excavatum (PE) is the most common chest wall abnormality affecting 1:3-400 of male newborns.^[1] Minimal invasive repair of pectus excavatum (MIRPE) is the treatment of choice for patients with moderate to severe pectus excavatum.^[2] The instantaneous remodeling and correction of the chest wall during the procedure are

associated with substantial postoperative pain.^[3] Although the optimal postoperative pain management regiment is disputed, some studies favor epidural analgesia (EA) over alternatives such as patient-controlled analgesia (PCA), nerve blocks, or cryoablation.^[3-6] However, EA is associated with severe complications, including epidural hematomas and infection.^[7]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Media AS, de Paoli FV, Pilegaard HK, Hvas AM, Juhl-Olsen P, Christensen TD. Epidural analgesia and abnormal coagulation in patients undergoing minimal invasive repair of pectus excavatum. Ann Card Anaesth 2022;25:153-7.

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.aca_115_21

The occurrence of epidural hematomas is a major concern with EA despite very low reported incidence,^[8] and risk factors include abnormal coagulation status.^[9] Therefore, the American Society of Regional Anesthesia and Pain Medicine guidelines recommend predefined intervals between anticoagulation therapy and insertion as well as the removal of epidural catheters. Furthermore, assessment of coagulation status is recommended in patients receiving anticoagulant medication.^[10] There is no consensus in patients requiring EA where abnormal coagulation is not expected. PE is associated with connective tissue diseases such as Marfan syndrome and Ehlers Danlos, both of which have a higher prevalence of bleedings as compared to healthy controls.^[11,12] However, the prevalence of abnormal coagulation parameters in PE patients undergoing MIRPE is unknown.

Thus, the aims of this study were to 1) estimate the prevalence of abnormal routine coagulation parameters and 2) assess the safety of EA in patients undergoing MIRPE.

METHODS

Study population and data collection

From 2001 to 2019, 1,973 patients underwent correction of moderate to severe PE with the modified Nuss procedure ad modum Pilegaard at Aarhus University Hospital, Denmark.^[13] Permission to perform data collection was granted by the head of the Department of Cardiothoracic and Vascular Surgery. According to Danish law, quality improvement studies do not require approval from an ethics committee, and anonymized data can be published. Patients were included if registered under the procedure code for correction of PE (KGAF10). Exclusion criteria were missing medical records or misclassification [Figure 1]. Medical records were retrospectively assessed between 2018 to 2019. Information was registered on gender, age, length of hospital stay (including the day of surgery), operating time, number of bars inserted, and two routine coagulation parameters; International Normalized Ratio (INR) and platelet count. Furthermore, surgical bleeding complications (i.e., significant perioperative bleedings or postoperative hematomas mentioned in medical charts), analgesic strategy, and severe complications related to analgesia were registered.

Biochemical analysis

Blood samples were obtained routinely prior to operation with measurements of INR and platelet count. In patients with increased INR, an additional blood sample was obtained to determine coagulation

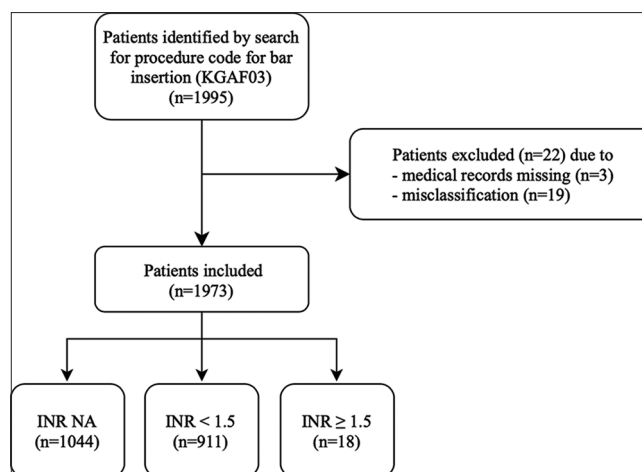


Figure 1: Consort diagram showing the inclusion of the 1,973 patients undergoing MIRPE in this study. Abbreviations: MIRPE = Minimal Invasive Repair of Pectus Excavatum; INR = International Normalized Ratio; NA = Not Available

factor VII. For INR and factor VII measurements, venous blood specimens were collected into 2 ml Vacuette 9NC tubes (Venosafe Terumo Europe N.V. Belgium) containing coagulation sodium citrate 3.2%. Plasma was prepared by centrifugation for 10 min at 2800 g (centrifugal force). INR was determined instantly with Sysmex CS5100 (Sysmex, Denmark) in the tubes with thromboplastin with an ISI value of 0.98 – 1.00, and the calibration was performed according to international guidelines.^[14] Factor VII was determined with ACL TOP 550 (ILS, Denmark). Samples for platelet count measurements were collected in 2 mL Vacuette EDTA tubes (Venosafe Terumo Europe N.V. Belgium) and determined on Sysmex XN9000 (Sysmex, Denmark).

Perioperative analgesic strategy

Patients with normal or close to normal coagulation parameters (INR <1.5 or platelet count $\geq 100 \times 10^9 \text{ L}^{-1}$) proceeded to surgery within one week with the standard analgesic strategy at our center. In patients with abnormal coagulation parameters (INR ≥ 1.5 and/or platelet count $< 100 \times 10^9 \text{ L}^{-1}$), the analgesic strategy was planned together with the anesthesiologist. Based on the anesthesiologist's evaluation of the patients' individual risk, patients either proceeded to surgery with EA, surgery with PCA or were referred for further coagulation assessment at the local department with expertise in coagulation defects. Here, measurement of coagulation factor VII was conducted, and based on the findings, the analgesic strategy was chosen accordingly. Patients with abnormal coagulation parameters and who were not referred for further coagulation assessment prior to surgery were contacted, and evaluation of coagulation status was performed after retrospective data collection.

Epidural catheters were inserted immediately prior to general anesthesia by anesthesia specialist physicians at the Department of Cardiothoracic and Vascular Anesthesia or by anesthesia fellows under supervision. Catheters were inserted through 18G Touhy cannulas at the high-thoracic level. Hanging-drop- or loss-of resistance techniques were used in a median or paramedian approach at the discretion of the individual anesthetist. During general anesthesia, EA was maintained with bupivacaine 0.5% and, upon extubation, epidural infusions typically consisted of bupivacaine 0.1–0.125% with or without fentanyl (2 ug/mL) and epinephrine (2 ug/mL).

Patients were anesthetized with propofol, fentanyl, and rocuronium and subsequently intubated. Postoperative analgesics routinely included intravenous ketorolac, oral non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol. Routinely, the EA was discontinued, and the epidural catheter was removed on the second postoperative day. Patients were discharged on the same day with oral paracetamol, NSAIDs, and opioids for 4–6 weeks.

Statistical analysis

All data were registered in REDCap^[15] (Research Electronic Data Capture, REDCap Consortium, Vanderbilt University Medical Center, Tennessee, USA), and statistical analyses were performed in Stata (StataCORP, version 15.1, Texas, USA). Normal distribution was assessed with quantile-quantile plots. Continuous variables were reported as means with standard deviation or medians with interquartile ranges. Differences between continuous variables were assessed with the Mann-Whitney U test or unpaired student's t-test, and differences between categorical variables were assessed with Chi² or Fisher's exact test, where appropriate. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Of the 1,992 patients identified, 1,973 patients were included [Figure 1]. Table 1 shows the baseline and perioperative characteristics of the study population. The median age was 17 years, and the male to female ratio was 5:1. All except seven patients were treated with EA (99.6%). In four patients, complications potentially related to EA were observed (0.2%). One patient experienced a spinal headache. Consequently, EA was discontinued, and the patient was subsequently treated with a blood patch and PCA. The second patient had symptoms equivalent to cauda equina syndrome but quickly regained full neurologic function spontaneously. The third patient experienced upper extremity motor impairment, but the subsequent

spinal cord magnetic resonance scan was normal. In the fourth patient, the epidural catheter was placed subdural, causing loss of conscience upon administration of the test dose (4 mL lidocaine (2%) with epinephrine (5 %)), immediate intubation, and postponement of surgery. Uneventful surgery was carried out two weeks later. Seven patients were treated with PCA (0.4%); four patients, due to technical inability to insert an epidural catheter; one patient due to spontaneously elevated INR ≥ 1.5 ; and two patients diagnosed with Ehlers-Danlos syndrome with a potentially increased bleeding tendency. No patients received anticoagulant therapy prior to surgery.

Due to a change of the hospitals' electronic medical chart systems in 2012, biochemical data was only accessible after this time point, leaving biochemical data from 929 patients eligible for analysis. Of these, 18 patients had a spontaneously elevated INR ≥ 1.5 (1.9%), while no patient had a platelet count $< 100 \times 10^9 \text{ L}^{-1}$. The group with INR ≥ 1.5 was slightly younger than the group with INR < 1.5 ($P = 0.03$). No other factors differed significantly across INR groups [Table 1]. The surgical procedure was postponed in nine patients (50%) in the group with elevated INR, while surgery was performed without delay in the remaining nine patients. None of the patients with INR ≥ 1.5 had surgical bleeding complications, while this occurred in 12 patients with INR < 1.5 (1.3%). All patients with INR ≥ 1.5 except one were treated with EA without complications.

Of the 18 patients with spontaneously elevated INR ≥ 1.5 , 12 patients underwent further coagulation assessment with measurement of factor VII [Table 2]. Factor VII was low within the normal reference range or just below the reference range ($[0.5\text{-}2.0] \times 10^3 \text{ IU} \times \text{L}^{-1}$) in these patients. Only one patient had significantly depleted levels of factor VII ($0.17 \times 10^3 \text{ IU} \times \text{L}^{-1}$) and underwent further genetic assessment without any positive findings.

DISCUSSION

This study found a prevalence of abnormal coagulations parameters based on an assessment of INR and platelet count of merely 1.9% in patients undergoing MIRPE. The causes of spontaneously elevated INR ≥ 1.5 were attributed to reduced levels of factor VII being close to the lower reference limit, and this group underwent surgery with no complications related to EA or surgical bleedings. Furthermore, we found a low incidence of complications with routine use of EA in patients undergoing MIRPE.

The slightly reduced levels of factor VII in patients with spontaneously elevated INR ≥ 1.5 were expected, as INR is

Table 1: Baseline and perioperative characteristics of the 1,973 patients undergoing minimal invasive repair of pectus excavatum

	All Patients		No INR available		INR<1.5		INR≥1.5		P
Gender									
Male, n (%)	1678	(85%)	909	(87%)	753	(83%)	16	(89%)	0.49
Female, n (%)	295	(15%)	135	(13%)	158	(17%)	2	(11%)	
Age (years)	17	(5)	17	(6)	16	(5)	15	(2)	0.03
Operation time (mins)	31	(18)	33	(18)	34	(17)	30	(22)	0.86
Length of hospital stay (days)	3	(2)	3	(2)	3	(2)	3	(2)	...
No. of Bars, n (%)									
1	1441	(73%)	782	(75%)	645	(71%)	14	(78%)	0.77
2	514	(26%)	252	(24%)	258	(28%)	4	(22%)	
3	18	(1%)	10	(1%)	8	(1%)	0	(0%)	
Laboratory tests									
INR	1.1	(0.1)	NA		1.1	(0.1)	1.5	[1.5-1.7]	...
Platelet Count (x 10 ⁹ /L)	240	(± 52)	NA		240	(± 52)	260	(± 74)	0.11
Analgesia type									
Epidural analgesia, n (%)	1966	(99.6%)	1038	(99.4%)	911	(100%)	17	(94%)	...
PCA, n (%)	7 (1)	(0.4%)	6 (1)	(0.6%)	0	(0.0%)	1	(6%)	
Analgesia complications, n (%)	4	(0.2%)	2	(0.2%)	2	(0.2%)	0	(0%)	...
Bleeding complication, n (%)	31	(1.6%)	19	(1.8%)	12	(1.3%)	0	(0%)	1.00

Data are indicated by n (%), median (IQR) or [min-max], or mean (± SD). Abbreviations: INR=International Normalized Ratio; IQR=InterQuartile Range; mins=minutes; PCA=Patient Controlled Analgesia; NA=Not Available

Table 2: Patients (n=18) with spontaneously elevated preoperative INR ≥1.5

Case no.	Gender	Age	INR	Platelet Count	Analgesia type	Analgesia complication	Surgery Postponed	Coagulation Assessment
1	M	16	1.5	170	EA	No	No	NA
2	M	16	1.5	424	EA	No	No	NA
3	M	15	1.5	271	EA	No	No	VII 0.62
4	F	13	1.6	176	EA	No	Yes	VII 0.54
5	M	43	1.6	259	PCA	No	Yes	VII 0.54
6	M	15	1.5	281	EA	No	Yes	VII 0.66
7	M	13	1.5	311	EA	No	No	NA
8	M	15	1.5	224	EA	No	Yes	VII 0.61
9	M	13	1.5	251	EA	No	No	NA
10	M	23	1.5	163	EA	No	No	NA
11	M	16	1.5	202	EA	No	No	VII 0.47
12	F	15	1.7	334	EA	No	No	VII 0.17
13	M	14	1.6	267	EA	No	Yes	VII 0.41
14	M	13	1.5	322	EA	No	Yes	VII 0.61
15	M	16	1.5	285	EA	No	Yes	VII 0.41
16	M	15	1.5	356	EA	No	Yes	VII 0.66
17	M	18	1.5	239	EA	No	Yes	VII 0.38
18	M	16	1.5	142	EA	No	No	NA

Abbreviations: INR=International Normalized Ratio; M=Male; F=Female; EA=Epidural Analgesia; PCA=Patient Controlled Analgesia; NA=Not Available. Factor VII reference range [0.5;2.0] × 10³ IU × L⁻¹

an indicator of the extrinsic pathway and is largely affected by levels of factor VII. Levels of factor VII are lower in children and adolescents than in adults, and levels of factor VII as low as 0.10 have not been shown to be associated with surgical bleedings.^[16,17] Routine measurements of INR and platelet count are often used as a screening for abnormal coagulation in clinical practice despite the fact that several studies indicate that these parameters are of limited value in predicting perioperative bleeding.^[18] Furthermore, a meta-analysis including 25 studies showed a poor association between elevated INR and bleeding complications in various invasive clinical procedures ranging from internal organ biopsies to bronchoscopy and angiography.^[19] As INR was developed and documented merely to monitor the effect

of vitamin-K antagonists, it has been advocated only to use INR in patients taking vitamin K-antagonists.^[20]

Our findings support the general notion that EA is a safe analgesic strategy in healthy patients undergoing MIRPE. The previously reported incidences of epidural hematomas should be interpreted with caution as these numbers are based on either retrospective register studies or case series and are therefore prone to bias.^[10] In spite of this fact, the risk of serious adverse effects including epidural hematomas varies across different study populations, and the risk is dependent on several factors such as patient age, sex, type of surgery, presence of abnormal coagulation, or anticoagulant therapy.^[7,8,21] Risk estimates of incidences

of epidural hematomas range from 1/200,000 in females undergoing childbirth to 1/3,600 in older females undergoing knee arthroplasty.^[8] Moreover, in patients with abnormal coagulation parameters, 2/630 patients developed epidural hematomas.^[9] Both cases occurred in patients with both epidural catheters and spinal drains undergoing abdominal aortic aneurism repair. The mean age of the study population was 67 years, and the majority of the patients received anticoagulant therapy.

No cases of spinal hematomas have been reported in patients treated with EA undergoing MIRPE. Patients undergoing MIRPE are characterized by (1) the large majority of patients being healthy males,^[22] (2) the prevalences of abnormal INR and PC being very low, (3) no patient receiving anticoagulant medication, 4) as MIRPE is elective surgery, all patients being without concurrent systemic infection, and (5) the MIRPE procedure being associated with a low risk of bleeding. All these factors reduce the risk of serious adverse effects when applying EA to highly theoretical and very low estimates.

Strengths and limitations

This is the first large-scale study to investigate the prevalence of abnormal coagulation parameters and safety of EA in patients undergoing MIRPE. Furthermore, data completeness was very high, with EA complication data available for all of the included patients. However, the frequency of serious adverse events following EA in healthy patients is very low, and this study is insufficiently powered to address the question of EA safety.

CONCLUSION

In patients undergoing MIRPE, the routine coagulation screening prior to epidural analgesia should be restricted to patients with a bleeding history or patients receiving anticoagulants. The use of epidural analgesia is safe with very low rates of serious complications.

Financial support and sponsorship

Department funding only.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Kelly RE, Lawson ML, Paidas CN, Hruban RH. Pectus excavatum in a 112-year autopsy series: Anatomic findings and the effect on survival. *J Pediatr Surg* 2005;40:1275-8.
- Nuss D, Obermeyer RJ, Kelly RE. Nuss bar procedure: Past, present and future. *Ann Cardiothorac Surg* 2016;5:422-33.
- Frawley G, Frawley J, Cramer J. A review of anesthetic techniques and outcomes following minimally invasive repair of pectus excavatum (Nuss procedure). *Paediatr Anaesth* 2016;26:1082-90.
- Stroud AM, Tulanont DD, Coates TE, Goodney PP, Croitoru DP. Epidural analgesia versus intravenous patient-controlled analgesia following minimally invasive pectus excavatum repair: A systematic review and meta-analysis. *J Pediatr Surg* 2014;49:798-806.
- Archer V, Robinson T, Kattail D, Fitzgerald P, Walton JM. Postoperative pain control following minimally invasive correction of pectus excavatum in pediatric patients: A systematic review. *J Pediatr Surg* 2020;55:805-10.
- Harbaugh CM, Johnson KN, Kein CE, Jarboe MD, Hirschl RB, Geiger JD, et al. Comparing outcomes with thoracic epidural and intercostal nerve cryoablation after Nuss procedure. *J Surg Res* 2018;231:217-23.
- Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR, Horlocker TT, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: Executive summary 2015. *Reg Anesth Pain Med* 2015;40:401-30.
- Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology* 2004;101:950-9.
- Gulur P, Tsui B, Pathak R, Koury KM, Lee H. Retrospective analysis of the incidence of epidural haematoma in patients with epidural catheters and abnormal coagulation parameters. *Br J Anaesth* 2015;114:808-11.
- Horlocker TT, Vandermeulen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American society of regional anesthesia and pain medicine evidence-based guidelines (fourth edition). *Reg Anesth Pain Med* 2018;43:263-309.
- Behr CA, Denning NL, Kallis MP, Maloney C, Soffer SZ, Romano-Adesman A, et al. The incidence of Marfan syndrome and cardiac anomalies in patients presenting with pectus deformities. *J Pediatr Surg* 2019;54:1926-8.
- Kornhuber KTI, Seidel H, Pujol C, Meierhofer C, Rösenthaller F, Pressler A, et al. Hemostatic abnormalities in adult patients with Marfan syndrome. *Cardiovasc Diagn Ther* 2019;9:S209-20.
- Hoffmann T, Vad H, de Paoli F. Correction of pectus excavatum using the modified nuss procedure, ad modum pilegaard. *Multimed Man Cardiothorac Surg MMCTS* 2018;2018. doi: 10.1510/mmcts.2018.028.
- Egberg N, Fagerberg I, Hillarp A, Lindahl TL, Stigendal L. Guidelines on preparation, certification, and use of certified plasmas for ISI calibration and INR determination - A rebuttal. *J Thromb Haemost* 2005;3:2370-1.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
- Benlakkhal F, Mura T, Schved JF, Giansily-Blaizot M; French Study Group of Factor VII Deficiency. A retrospective analysis of 157 surgical procedures performed without replacement therapy in 83 unrelated factor VII-deficient patients. *J Thromb Haemost* 2011;9:1149-56.
- Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood* 1992;80:1998-2005.
- Larsen JB, Hvas AM. Predictive value of whole blood and plasma coagulation tests for intra- and postoperative bleeding risk: A systematic review. *Semin Thromb Hemost* 2017;43:772-805.
- Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: An evidence-based review. *Transfusion* 2005;45:1413-25.
- Keeling D. International normalized ratio in patients not on vitamin K antagonists. *J Thromb Haemost* 2007;5:188-9.
- Thomas O, Lybeck E, Flisberg P, Schött U. Pre- to postoperative coagulation profile of 307 patients undergoing oesophageal resection with epidural blockade over a 10-year period in a single hospital: Implications for the risk of spinal haematoma. *Perioper Med* 2017;6:1-10. doi: 10.1186/s13741-017-0070-7.
- Media AS, Christensen TD, Katballe N, Pilegaard HK, de Paoli FV. Prevalence of comorbidities in a surgical pectus excavatum population. *J Thorac Dis* 2021;13:1652-7.