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Single-shot thoracic epidural analgesia for neonates undergoing thoracotomy.

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ABSTRACT

Background and Aims: Post-thoracotomy pain in neonates have negative physiological consequences include impaired ventilation and vasoconstriction of both systemic and pulmonary vascular beds leading to compromised organ function.

Methods: A randomized, single center, prospective, controlled study was conducted in El-Shatby university hospital, from august 2017 to September 2019 were 40 neonates, weighing 2.5–4 kg belonging to the ASA physical Grade II to IV, posted for a trachea-oesophagal fistula (TOF) repair via thoracotomy. After general anesthesia, in Group A, intra-operatively received fentanyl 2 μg/kg and paracetamol (10 mg/kg/6 h) intravenously and Group B (thoracic epidural single injection with 0.5 ml/kg of 0.25% of the L-Bupivacaine and 2 μg/kg of fentanyl), post-operatively paracetamol (10 mg/kg/6 h) intravenous (IV) or pain score >4. The primary objective was to compare the effect of the single-shot epidural blockade to intravenous fentanyl on post-thoracotomy pain control, the length of stay (LOS), supplemental analgesic requirements, and the incidence of adverse respiratory events were also measured.

Results: Group A remained hemodynamically stable in the intraoperative period except for occasional bradycardia below 100 which was successfully managed with anticholinergic, and multiple and regular dosage of IV paracetamol was required to maintain adequate analgesia for about 6 h post-operative. While in Group B, good quality of analgesia for 8 h post-operative with a lesser dose of rescue opioids (fentanyl) required to maintain adequate analgesia which shortened length of hospital stay.

Conclusion: Very efficient postoperative analgesia can be achieved via single-shot epidural blockade compared to intravenous fentanyl in neonatal post-thoracotomy pain.

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1. Introduction

The prevention of pain in neonates should be the goal of all caregivers because repeated painful exposures have the potential for deleterious consequences. Neonates at greatest risk of neurodevelopmental impairment as a result of preterm birth are also those most likely to be exposed to the greatest number of painful stimuli in the NICU [1].

Post-thoracotomy pain has negative physiological consequences include impaired ventilation and vasoconstriction of both systemic and pulmonary vascular beds leading to compromised organ function [2].

Opioids provide both sedation and analgesia, have a wide therapeutic window, Fentanyl is the most used analgesic opioid in the neonatal intensive care unit. Fentanyl acts as an agonist binding to μ and κ opioid receptors and has the properties of an analgesic, sedative, and anesthetic. This drug has a rapid onset of action of 2–3 min, a short duration of action of 60 min with bolus doses, and minimal hemodynamic effects [3]. Muscle rigidity and respiratory depression appear after high doses of fentanyl used in anesthetic induction. High doses of fentanyl can cause neuro-excitation and, rarely, seizure-like activity [4].

Opioid-induced respiratory depression (OIRD) caused by the activation of μ-opioid receptors expressed on the surface of neurons in brainstem respiratory centers is considered the most serious side-effect as it is potentially life-threatening. Mild-to-moderate transient respiratory depression from opioids (bradypnoea and/or upper airway obstructions requiring interventions such as supplemental oxygen, chin lift).

Severe OIRD requires naloxone injections and/or tracheal intubation to restore ventilation or cardiac resuscitation in the case of a cardiac arrest secondary to hypoxia [5].

Apart from the unintentional overdose, OIRD could be due to impaired renal elimination of active μ-opioid receptor agonist morphine-6-glucuronide (M6G) or Genetic polymorphism in metabolic enzymes has an important impact on the effect of the parent drug through either excessive creation of active metabolites or inability to produce inactive metabolites which were linked to the *CYP2D6* metabolic gene [6].

Regional anesthesia provides profound analgesia with minimal hemodynamic effects, even in the presence of comorbidities [7]. Neuraxial blockade provides postoperative analgesia but may diminish abdominal

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and intercostal muscle activity, particularly in the compliant chest wall of neonates. On the other hand, it may improve diaphragmatic activity and excursion [8].

The aim of the present study was to compare the effect of the single-shot epidural blockade to intravenous fentanyl on post-thoracotomy pain control, the length of stay (LOS), supplemental analgesic requirements, and the incidence of adverse respiratory events were also measured.

2. Methods

This randomized prospective controlled that was conducted in El-Shatby university hospital from august 2017 to September 2019 after the approval by the Ethics Committee of the Alexandria Main University Hospitals.

A written informed consent was obtained from the parents for the participation of their infants in this study.

Forty neonates of either sex, aged 1 day to 30 days, weighing 2.5–4 kg belonging to the American Society of Anesthesiology physical Grade II to IV, scheduled for trachea-oesophagal fistula (TOF) repair via thoracotomy was included for the study.

Patients suffering from a local infection, neurological disorder, history of an allergic reaction to local anesthetics, sacral/vertebral abnormalities, prematurity, renal anomalies, and coagulation disorders were excluded from the study. During the preoperative visit, all patients were assessed.

No, premedication was done. All patients were fasting according to the American Society of Anesthesiology fasting rules [9].

In the operation theatre, all patients were attached to a multichannel monitor in the form of the continuous electrocardiogram, heart rate, pulse oximeter and noninvasive arterial blood pressure End-tidal capnography was attached after insertion of the endotracheal tube (ETT).

Anesthesia was induced with incremental concentrations of inhalational agent sevoflurane (2%–4%) and oxygen (3 L/min) using a silicone face mask size 0 connected to a Jackson-Rees circuit while maintaining spontaneous ventilation.

Neonates were in the supine position with a small pillow in-between their shoulders. An intravenous line was secured in place bolus fluids 10 ml/kg *Lactated Ringer's* administered.

Tracheal intubation was attempted with a Miller blade size 00–0 without muscle relaxation. ETT advanced to the right main bronchus and gradually pulled back until breath sounds can be heard both left and right. Patients were randomly allocated into two equal groups using a random number generating software (Research Randomizer Version 4.0)

In Group A, after the induction of general anesthesia but before the first incision, patients received a bolus of fentanyl 2 μg/kg intravenously.

While in Group B, neonates had thoracic single injection 0.5 ml/kg of 0.25% of the L-Bupivacaine and 2 μg/kg of fentanyl. Anesthetized neonates were placed into the left lateral position. Under complete aseptic sterile technique with drapes, US cover, and sterile gel identification and mark the T6 spinous process was done. The probe was oriented in a sagittal direction and placed at the level of the marked spinous process of T6 in a parasagittal plane 2 cm from the midline.

The probe then directed medially to identify the dura matter at the T6–T7 intervertebral space. The puncture was performed via the paramedian approach, at the T6–T7 interspace in all patients, with a 22 G needle (B. Braun Melsungen AG). The epidural space is identified by the loss of resistance technique (Figure 1) [10].

Surgery has begun under general anesthesia maintained with sevoflurane. Thoracotomy was done while maintained autonomous respiration. Instead of routine exposure and fistula ligation, the surgeon immediately clamped the lower end of the esophagus just above the stomach with a bulldog clamp.

The whole procedure was accomplished within 5 min. Then, 0.1 mg/kg cisatracurium muscle relaxant and normal PPV was given. All patients received paracetamol (10 mg/kg/6 h) starting immediate postoperatively.

At the end of surgery, they were reversed with 50 μg/kg neostigmine and 20 μg/kg of atropine and were extubated.

Hemodynamic measurements including heart rate mean arterial blood pressure, and oxygen saturation was recorded pre-induction (basal value), immediate post-induction, at starting of surgical manipulation, mean of intraoperative readings with 15 min interval, and at the end of the operation.

Postoperative pain also assessed by blinded observer every 30 min in the first 2 h then every 1 h for the next 10 h using Neonatal Infant Pain Scale (NIPS) Scale [11] (Table 1), and the need for rescue opioid (fentanyl) analgesic use1 μg/Kg/dose (first time of rescue and total opioid consumption). Length of hospital stay (LOS), the incidence of respiratory depression which defined as diminished breathing (rate less than 8–10 bpm, SpO_2 less than 90%) progresses into irregular (or cyclic) breathing and eventually into apnea (the complete cessation of breathing), and other complications as systemic toxicity of local anesthetics, sympathetic blockade, hypotension, and bleeding.

3. Statistical methods

The sample size is approved to be sufficient by the department of Statistics, Medical Research Institute, Alexandria University, Egypt [12].

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution of variables, comparisons between groups for

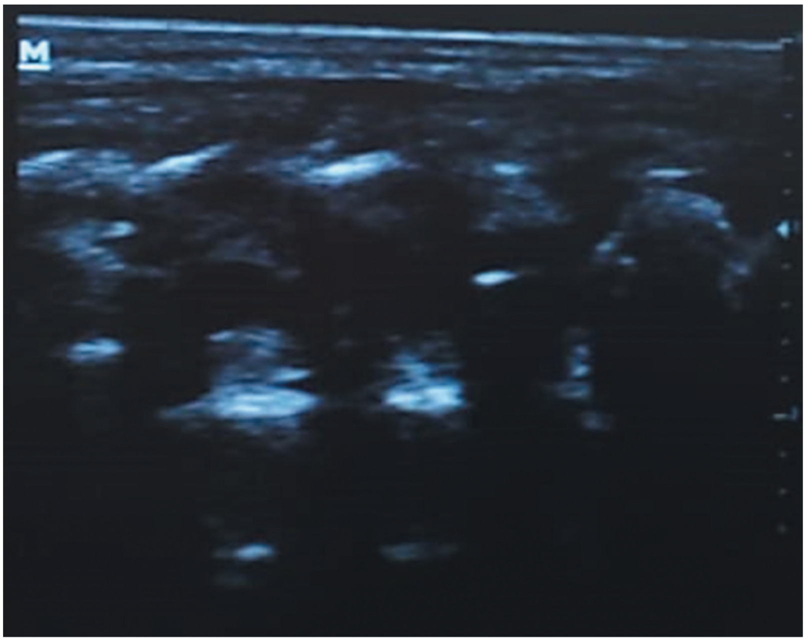


Figure 1. Ultrasound-guided epidural blockade.

Table 1. Neonatal infant pain scale (NIPS) [6].

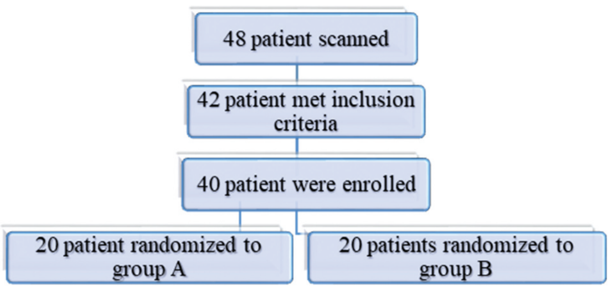
	Score	Finding	Details
Facial expression	0	Relaxed muscle	Restful face, neutral expression
	1	Grimace	Tight facial muscles, furrowed brow,chin,jaw
Cry	0	No cry	Quiet, not crying
	1	Whimper	Mild moaning, intermittent
	2	Vigorous cry	Loud scream, rising, shrill, continous
Breathing patterns	0	Relaxed	Usual pattern for this baby
	1	Changed	Indrawing, irregular, faster, gagging
Arms	0	Relaxed/restrained	No muscular rigididy, occasional movement
	1	Flexed/extended	Tense, straight arms, rigid extension/flexion
Legs	0	Relaxed/restrained	No muscular rigididy, occasional movement
	1	Flexed/extended	tense, straight leg, rigid extension/flexion
State of arousal	0	Sleeping/awake	Quiet, peaceful, sleeping or alert and settled
	1	Fussy	Alert, restless and thrashing

categorical variables were assessed using the Chi-square test (Fisher or Monte Carlo). Student t-test was used to compare two groups for normally distributed quantitative variables while ANOVA with repeated measures and Post Hoc test (Bonferroni) was assessed for comparison between different periods.

Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables, while the Post Hoc Test (Dunn's) for Friedman test was used for comparison between different periods. The significance of the obtained results was judged at the 5% level (*: Statistically significant at $p \leq 0.05$).

4. Results

A total of 48 patients were screened for eligibility; 42 patients met inclusion criteria and were approached to participate, and two parents refused to engage their children in the study [Flowchart 1]. Data were normally distributed within the two groups.



Flow chart 1. Flow diagram.

There was no statistically significant difference between the two groups regarding age, gender, and weight (Table 2).

Regarding hemodynamic measurement, there was a statistically significant decrease of heart rate in Group A compared to Group B post-induction (Group A = 122.2 ± 2.4, Group B = 126.2 ± 6.3, p = 0.012*) and at the starting of surgical manipulation (Group

Table 2. Demographic data of the two groups.

Patients' characteristics	Group A (*n* = 20)	Group B (*n* = 20)
Age (days)	5.8 ± 2.4	7.4 ± 2.1
Weight (kg)	2.7 ± 0.5	2.9 ± 0.6
Gender		
Male	10 (50.0)	12 (60.0)
Female	10 (50.0)	8 (40.0)

Data are presented as mean±SD or *n* (%). SD – Standard deviation.

A = 121.7 ± 2.1, Group B = 126.7 ± 5.6, P = 0.001*) but remained hemodynamically stable in the post-induction period and occasional bradycardia below 100 which was successfully managed with anticholinergic (Table3).

While according to NIPS pain score, both groups had the same analgesic efficacy for 6 h post-operative (Figure 2), the time for first rescue fentanyl dose of Group A was in 5.1 ± 0.4 h, while the analgesic effect of single-shot epidural blockade continued for 8 h postoperatively which was comparable to Group A, and the time of first rescue analgesic requirement was in7.8 ± 0.9 h.

Furthermore, statistically significant increase of incidence of respiratory depression in Group A (35%) was the cause of longer hospital stay (9.5 ± 2.1 days) compared to Group B (6.2 ± 1 day), but there were no statistically significant differences between the two groups regarding the incidence of complications (χ^2 = 0.003, P = 0.990).

5. Discussion

Poor pain relief after surgery can impede recovery and increase the risks of developing complications such as lung collapse, chest infections, and blood clots due to ineffective breathing and clearing of secretions [13].

Effective management of acute pain following thoracotomy may prevent these complications and reduce the likelihood of developing chronic pain [14].

Fentanyl is almost 100 times more potent than morphine and is considered as a selective μ -receptor agonist. Fentanyl has a rapid predictable onset of action with a short duration of action mostly due to its high lipid solubility. It is associated with greater hemodynamic stability [15].

The present study showed that the intravenous bolus dose of fentanyl after induction of anesthesia continued for 5.1 ± 0.4 h, on the other hand, Kearns et al. concluded that the pathology and/or the surgical lesion lengthen $t_{1/2}$ of fentanyl in neonates.

In infants undergoing a surgical operation, the half-life of fentanyl was 463 and 750 min, whereas the population means of fentanyl half-life in healthy neonates is 317 min [16].

Pacifici et al. studied the clinical pharmacology of fentanyl in preterm and found that the opioid-induced respiratory depression (OIRD) was less likely to be severe in the continuous infusion patients than in the bolus patients [17].

Traditionally, opioids have been used for postoperative pain relief in children; however, they are no longer recommended as the first-line analgesics owing to their side effects [18].

Currently, multimodal analgesia is increasingly preferred, where non-opioid analgesics are combined with a small dose of opioids or regional blocks [19].

The introduction of the US has greatly improved the performance of the central neuraxial block. US-guided

Table 3. Comparison between the two studied groups according to Hemodynamic measurements.

	Group A (n = 20)	Group B (n = 20)	t	p
Heart rate				
Pre-induction	146.8 ± 5.6	146.9 ± 6.0	0.055	0.957
Post-induction	122.2# ± 2.4	126.2# ± 6.3	2.648*	0.012*
Start	121.7# ± 2.1	126.7# ± 5.6	3.729*	0.001*
Intra-operative	126.5 ± 7.1	123.9 ± 1.7	1.559	0.127
End	125.5# ± 2.6	118.6# ± 25.0	1.218	0.238
Mean blood pressure				
Pre-induction	52.0 ± 3.1	52.1 ± 3.0	0.051	0.959
Post-induction	39.4 ± 5.9	42.2 ± 2.9	1.897	0.065
Start	40.8# ± 2.4	40.9# ± 6.8	0.062	0.951
Intra-operative	40.2# ± 2.0	38.4# ± 4.6	1.598	0.122
End	39.9# ± 1.8	38.0# ± 4.9	1.621	0.118
Oxygen saturation				
Pre-induction	94.9 ± 1.0	95.1 ± 0.8	0.857	0.397
Post-induction	98.9# ± 0.9	98.8# ± 0.8	0.185	0.854
Start	98.8# ± 0.8	98.9# ± 0.9	0.185	0.854
Intra-operative	92.7# ± 2.0	92.4# ± 1.8	0.419	0.678
End	99.0# ± 0.8	98.9# ± 1.0	0.529	0.600

t: Student t-test, p: p-value for comparison between the two studied.Data expressed by using **mean ± SD**. *: Statistically significant at p ≤ 0.05

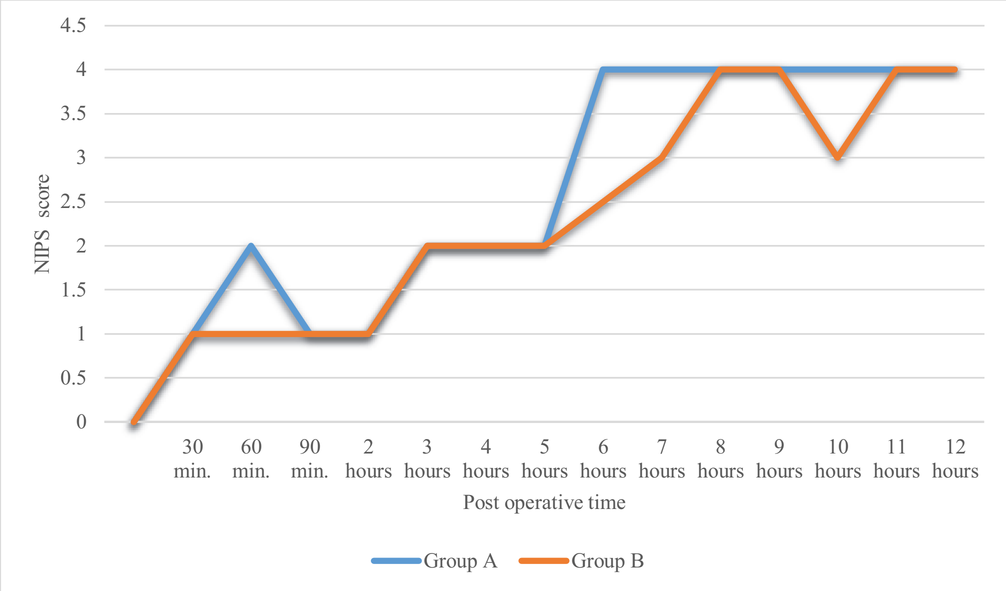


Figure 2. Comparison between the two studied groups according to post-operative pain (NIPS).

neuraxial block in children was first performed by Chawathe et al. [20].

In agreement with the present study Gomez-Chacon et al. reported that intraoperative and postoperative epidural analgesia is associated with a significant reduction in time to extubation and intestinal transit time in major neonatal surgery. There were no complications from epidural analgesia [21].

6. Conclusion

From the present study, we conclude that single-shot thoracic epidural block using bupivacaine with fentanyl provided longer effective postoperative analgesia compared to a bolus dose of intravenous fentanyl; however, resulted in lesser required rescue doses of fentanyl, lesser incidence of respiratory depression, and moreover shorter length of hospital stay. Furthermore, ultrasound-guided technique used in the present study had less complications with more hemodynamic stability.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethics approval and consent to participate

The present study was approved by the ethical committee of the Faculty of Medicine, Alexandria University (IRB no. 00007569, FWA no. 00018699). A consent to participate was obtained as well.

Consent for publication

Written informed consent was obtained from the parents for publication of this article and any accompanying tables/images. The copies of the written consents are available for review by the Editor of this journal upon request.

Data availability statement

All data supporting the study are presented in the manuscript or available upon request.

Disclosure statement

The authors declare that they have no competing interests.

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