Original Article

JHSMR Journal of Health Science and Medical Research

The Effectiveness of Intraoperative Thoracic Epidural Analgesia in Major Abdominal and Thoracic Surgery and Its Prediction of Severe Pain at Discharge from the Post-Anesthetic Care Unit: A Prospective Cohort Study

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Received 12 April 2023 ● Revised 18 May 2023 ● Accepted 19 May 2023 ● Published online 25 July 2023

Abstract:

Objective: To assess the factors associated with ineffective thoracic epidural analgesia (iTEA) in the post-anesthesia care unit (PACU) among patients requiring TEA.

Material and Methods: This prospective cohort was conducted on 146 patients requiring post-operative TEA. The verbal numeric rating scale (VNRS) was employed to assess TEA effectiveness on PACU arrival at 10, 20, and 30 minutes after surgery; iTEA was determined if the VNRS score was more than 3 and 4 at rest and during activity, respectively. The patient characteristics, and intra- and post-operative epidural management were collected. The risk factors of iTEA were evaluated using mixed-effects models. Moreover, factors associated with severe pain at PACU discharge were evaluated using logistic regression analyses.

Results: The incidence of iTEA on PACU arrival, and at 10, 20, and 30 minutes after PACU arrival were 53.4%, 51.4%, 50.7%, and 36.3%, respectively. Intra-operative intravenous morphine supplementation and the cumulative fentanyl equivalent dose (every 10 mcg) were significantly associated with preventing the risk of iTEA on PACU arrival (OR 0.27; 95% CI=0.07-0.92) and during PACU stay (OR 0.87; 95% CI=0.77-0.97) compared to those who did not receive opioids. Moreover, iTEA on PACU arrival was a significant risk for severe pain at 30 minutes (adjusted OR 4.77; 95% CI=1.57-18.10).

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J Health Sci Med Res .....
doi: 10.31584/jhsmr.2023970
www.jhsmr.org

Conclusion: This study demonstrates a high incidence of iTEA immediately after surgery, and that intravenous opioid supplementation during and after surgery reduces the risk of iTEA. Lastly, iTEA on PACU arrival is a strong predictor of severe pain at discharge from PACU.

Keywords: abdominal surgery, ineffective thoracic epidural analgesia, intraoperative epidural management, pain management, post-operative pain, recovery room, thoracic epidural analgesia, thoracic surgery

Introduction

Thoracic epidural analgesia (TEA) is widely used to manage post-operative pain after major abdominal and thoracic surgery[1-4] and is considered superior to other methods in managing and reducing post-surgical pain[1-5]. In addition, it facilitates the recovery of bowel function[3-5] and reduces the length of hospital stay in open abdominal surgery[3,6]. It has been well-documented to improve the patient's quality of life after surgery[7]. However, previous studies have reported a high incidence of epidural analgesia failure, after major surgery, with rates up to 40%. Its identified causes are primary and secondary catheter failure and inadequate epidural management[8].

Inadequate pain control after major abdominal and thoracic surgery can have numerous consequences[9] chronic post-thoracotomy pain[10] and pulmonary complications after thoracic surgery[11-12] requiring a longer duration of ventilator support or hospitalization[12]. These complications can result in delayed recovery and ultimately prolong hospital admission[3]. A previous study reported that 50% of patients undergoing combined general and epidural anesthesia for abdominal and thoracic surgery had inadequate post-operative epidural analgesia, which led to significant suffering reported by the patients[13].

According to our literature review, the factors determining the ineffectiveness of TEA (iTEA) during the immediate post-operative period in patients undergoing major abdominal and thoracic surgery have not yet to be evaluated. Hence, this study aimed to evaluate the factors associated with iTEA in the immediate post-operative period in patients undergoing major abdominal and thoracic surgery that require post-operative TEA.

Material and Methods

Study design and population

This prospective cohort study was approved (REC. 62-374-8-6) by the Human Research Ethics Committee of Prince of Songkla University and registered on the Thai Clinical Trial Registration (TCTR20200116003) website (https://www.thaiclinicaltrials.org/). The study was conducted between March 2020 and December 2020 at Songklanagarind Hospital, a university tertiary care hospital, in full compliance with the ethical principles for medical research in human subjects. All patients aged ≥18 years old that were scheduled for elective major abdominal and thoracic surgery and required post-operative TEA were approached and screened for the study. Written informed consent was obtained from all eligible patients. Patients who were unable to communicate or had a contraindication to neuraxial block were excluded. Moreover, patients that experienced primary or secondary catheter failure received combined spinal-epidural anesthesia, or were transferred directly from the operating theater to the intensive care unit were excluded from the analysis.

Intra-operative thoracic epidural catheter placement and pain management

The anesthetic technique was selected by the

attending anesthesiologist, and sedative drugs were not prescribed before the surgery. On the day of the surgery, the thoracic epidural catheter placement (TEP) was performed in the procedure room inside the operating theater within an hour before the operation. First, the epidural needle insertion was done using the landmark anatomical-based or real-time ultrasound-guided techniques, based on the preference of the attending anesthesiologist. Once the epidural space was identified, a 3-5 cm epidural catheter was inserted and traced into the space through the epidural needle, and it was secured using the subcutaneous tunneling technique to prevent the spontaneous migration of the catheter. The correct placement of the catheter was tested by the administration of 3 ml of 2% lidocaine with adrenaline (5 mcg/ml). The intra-operative use of TEA, anesthetic agent of choice (lidocaine with adrenaline or bupivacaine combined with an opioid), continuous infusion or intermittent bolus, and intravenous analgesia and opioids depended on the preference of the attending anesthesiologist. Immediate post-operative care, including pain management, was given in the post-anesthesia care unit (PACU). Pain scores were recorded on at 0 (arrival), 10, 20, and 30 minutes after the patient arrived at PACU.

Data collection

Independent variables

The recorded patient data included age, body weight, height, comorbidities, current diagnosis, American Society of Anesthesiologists (ASA) classification, and baseline pain score before surgery. Moreover, information concerning TEP-related factors such as patient position, TEP technique (conventional vs. real-time ultrasound-guided), intervertebral level, number of attempts, and successfulness of the TEP procedure was collected. Data concerning intra-operative factors like anesthesia technique, technique of epidural administration, type and concentration of epidural drugs, intravenous (IV) opioid administration, type of co-analgesic medications, incision size, and duration of surgery were also collected. In addition, patient treatment details during the PACU stay were recorded at 10-minute intervals, and they consisted of the (high vs. low) concentration of bupivacaine, infusion rate, and the type of co-analgesic medications. The secondary epidural failure, defined as the inability to administer epidural drugs or a premature catheter removal (before 3 days), was also recorded.

Dependent variables

The severity of pain was evaluated using the Verbal Numeric Rating Scale (VNRS with a score range of 0–10; 0=no pain, 10=worst pain). The patients were asked to rate their pain score at rest and during activity at 0, 10, 20, and 30 minutes after arrival at PACU.

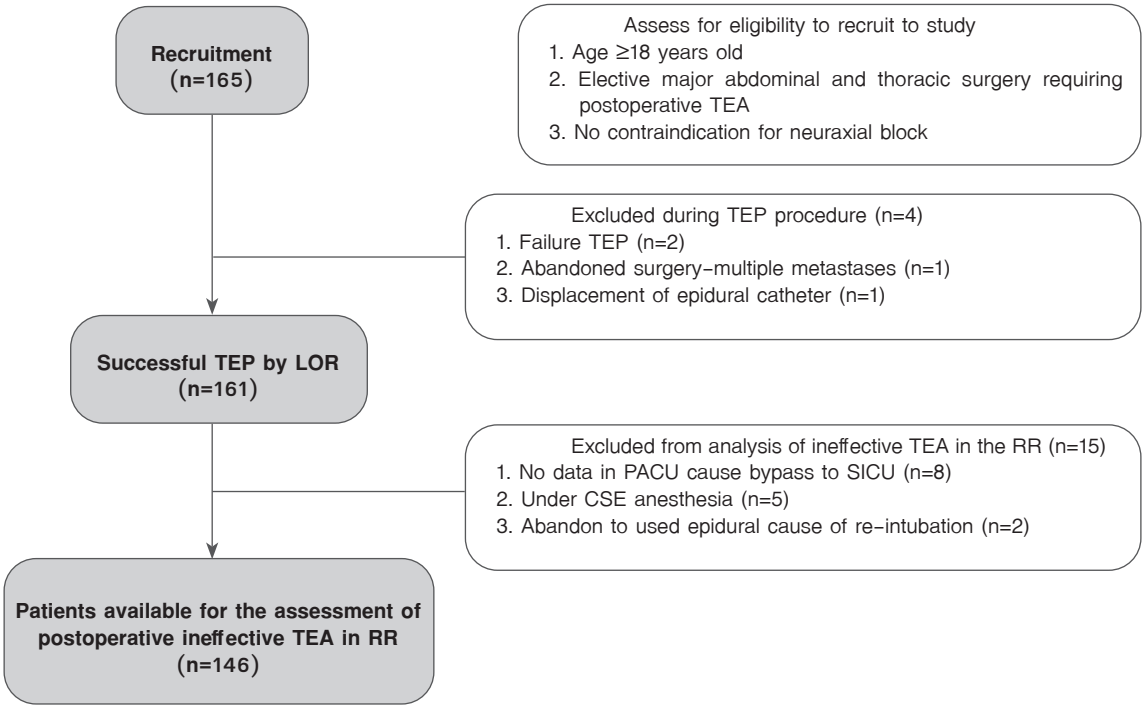
Statistical analysis

The sample size was calculated using the N4study application[15] based on a previous study analyzing epidural failure, which showed that the proportions of epidural analgesia failure (outcome) in patients who had asymmetrical sensory blockade (exposure group) and symmetrical sensory blockades (non-exposure group) were 0.16 and 0.4, respectively[16]. These proportions were used to estimate the required sample size to evaluate the factors associated with iTEA with a ratio of 4:1 between the groups. In order to have a power of 0.8 and a confidence of 0.95, 165 participants needed to be recruited in the study.

In regards to the opioid consumption at PACU, we calculated the fentanyl-equivalent dose because both morphine and fentanyl were used. Since the patients received multiple types of co-analgesic medications, the cumulative types of co-analgesic adjuvant therapy were calculated for both the intra- and post-operative periods.

For descriptive results, the categorical variables were reported using number and percentage, whereas the

continuous variables were reported as mean and standard deviation (S.D.) or median and interquartile range (IQR) as appropriate. Student's t-test or the Wilcoxon test were used wherever appropriate to evaluate associations between dependent and continuous independent variables, while the chi-square test or Fisher's exact test were used to explore associations between outcomes and categorical independent variables. We used the chi-square test for trends to compare the rate of iTEA over time. A random-intercept mixed-effects model was used because it allows for time-varying independent variables and repeated measurements of the outcome[17]. In relation to the cumulative types of co-analgesia, the lag periods of 0, 10, and 20 minutes were evaluated owing to the potential delayed onset effects of the administered drugs. A univariate analysis employing a mixed-effects model was performed. Potential independent variables for the multivariate analysis were considered according to both the clinical significance and the statistical significance of <0.2. Then the multivariate mixed-effects model analysis was performed to select a subset of variables that were considered the most relevant to the iTEA. Additionally, we evaluated the intra-operative factors that associated with iTEA at PACU arrival as well as the intra- and post-operative factors that associated with severe pain (VNRS score of >6 at rest or during activity) at 30 minutes after PACU arrival; both of them were evaluated using logistic regression modeling. The Akaike Information Criterion (AIC) was used as the indicator for selecting the variables. A p-value of ≤0.05 was considered to be statistically significant.



CSE=combined spinal epidural, LOR=loss of resistance, PACU=post-anesthetic care unit, TEA=thoracic epidural analgesia, TEP=thoracic epidural placement, SICU=surgical intensive care unit

Figure 1 Flow chart representing the study selection process

Results

One hundred and sixty-five (165) patients were assessed for eligibility and four patients were excluded at the TEP step. Hence, 161 cases underwent a successful TEP. However, 15 of these cases were excluded from the analysis because of incomplete PACU data (n=8), combined spinal-epidural technique (n=5), and inability to assess outcomes (n=2). Finally, 146 patients were included in the analysis as shown in the patient recruitment flow chart (Figure 1).

Table 1 reports the demographic characteristics of the patients as well as their intra- and post-operative parameters. The median age of our patients was 60 years, and the majority of the procedures were thoracic surgery (43.2%) and upper abdominal surgery (28.1%). The TEP procedure was performed using the anatomical landmark and the real-time ultrasound-guided techniques at proportions of 72.6% and 27.4%, respectively. The thoracic epidural catheter was placed above the T8 (57.5%) followed by the T8-T9 (39%) intervertebral spaces, and in most of the cases (77.4%) TEP success was achieved in less than 3 attempts. Three cases (1.8%) experienced a primary failure of TEP, whereas secondary failure occurred in 20 participants (12.1%).

As for the intra-operative use of epidural analgesia, the majority of participants received 2% lidocaine (44.5%) via the continuous infusion method (77.3%). Twelve percent of the patients did not receive any intra-operative epidural drugs. The average infusion rate of the intra-operative epidural analgesics was 3.05 ml/hr; the average doses of lidocaine and bupivacaine were 27 mg/hr and 3.1 mg/hr, respectively. Sixteen participants (11.0%) received IV morphine during surgery.

In PACU, low- and high-concentration bupivacaine was used in 66.4% and 33.6% of participants, respectively. The average infusion rate and bupivacaine dose were 5.0 ml/hr and 0.065 mg/kg/hr, respectively. At PACU arrival, iTEA was reported by 78 participants (53.4%). The effective group had a higher use of the ultrasound-guided technique for the TEP (35.3% vs. 20.5%; p-value=0.046), a lower number of TEP attempts (83.8% vs. 71.8%; p-value=0.08), and a higher use of intra-operative IV morphine supplement (17.7% vs. 5.1%; p-value=0.016) than the ineffective group.

Table 1 Demographic characteristics, and intra- and post-operative information according to effectiveness of thoracic epidural analgesia at PACU arrival

Variables	Total (n=146)	Effective group (n=68)	Ineffective group (n=78)	p-value
Age (years)	60.0 (51.0, 70.0)	62.0 (50.8, 71.0)	58.5 (52.0, 68.8)	0.49
Gender (male); n (%)	75 (51.4)	34 (50.0)	41 (52.6)	0.89
BMI (kg/m^2)	23.1 (20.4, 26.4)	23.6 (20.6, 26.5)	22.6 (20.4, 26.0)	0.52
ASA classification; n (%)				
I	2 (1.4)	1 (1.5)	1 (1.3)	0.99
II	108 (73.9)	50 (73.5)	58 (74.4)	
III	36 (24.7)	17 (25.0)	19 (24.4)	
Underlying conditions; n (%)				
Cardiovascular disease	68 (46.6)	33 (48.5)	35 (44.9)	0.78
Respiratory disease	21 (14.4)	8 (11.8)	13 (16.7)	0.55
Endocrine disease	30 (20.6)	16 (23.5)	14 (17.9)	0.53
Liver disease	30 (20.6)	14 (20.6)	16 (20.5)	1.00
Renal disease	31 (21.2)	13 (19.1)	18 (23.1)	0.70
Type of surgery; n (%)				
Thoracic	63 (43.2)	30 (44.1)	33 (42.3)	0.61
Upper abdomen	41 (28.1)	16 (23.5)	25 (32.1)	
Lower abdomen	18 (12.3)	11 (16.2)	7 (8.9)	
Whole abdomen	21 (14.4)	10 (14.7)	11 (14.1)	
Other	3 (2.1)	1 (1.5)	2 (2.6)	

Table 1 (continue)

Variables	Total (n=146)	Effective group (n=68)	Ineffective group (n=78)	p-value
Intra-operative TEP and thoracic epidural management				
Intervertebral level; n (%)				
Above T8	84 (57.5)	39 (57.4)	45 (57.7)	0.83
T8-T10	57 (39.0)	26 (38.2)	31 (39.7)	
Below T10	5 (3.4)	3 (4.4)	2 (2.6)	
TEP technique; n (%)				
Landmark	106 (72.6)	44 (64.7)	62 (79.5)	0.046
Real-time USG	40 (27.4)	24 (35.3)	16 (20.5)	
Epidural approach; n (%)				
Midline	90 (61.6)	47 (69.1)	43 (55.1)	0.083
Paramedian	56 (38.4)	21 (30.9)	35 (44.9)	
Successful TEP performed by; n (%)				
Resident doctor	21 (14.4)	7 (10.3)	14 (17.9)	0.28
Staff doctor	125 (85.6)	61 (89.7)	64 (82.1)	
Number of TEP attempts; n (%)				
<3 attempts	113 (77.4)	57 (83.8)	56 (71.8)	0.08
≥3 attempts	33 (22.6)	11 (16.2)	22 (28.2)	
Intra-operative epidural analgesia; n (%)				
Not used	18 (12.3)	7 (10.3)	11 (14.1)	0.52
1% lidocaine	14 (9.6)	6 (8.8)	8 (10.3)	
2% lidocaine	65 (44.5)	28 (41.2)	37 (47.4)	
0.1-0.2% bupivacaine	49 (33.6)	27 (39.7)	22 (28.2)	
Type of epidural administration				
Bolus	29 (22.6)	14 (22.9)	15 (22.4)	0.94
Continuous infusion	99 (77.3)	47 (77.1)	52 (77.6)	
Epidural dose (excluding test dose)				
Dose (ml)	8 (4.0, 14.0)	8 (3.0, 14.0)	10 (5.0, 14.0)	0.50
Infusion rate (ml/hr)	3.1±2.4	3.2±2.5	2.9±2.2	0.57
Average dose of lidocaine (mg/hr)	27.0±33.0	22.0±29.0	31.0±35.0	0.12
Dose of bupivacaine (mg/hr)	3.1±5.2	4.0±5.8	2.3±4.3	0.06
Intra-operative fentanyl dosage (mcg)	150.0 (100.0, 200.0)	150.0 (100.0, 200.0)	150.0 (100.0, 200.0)	0.80
IV morphine supplementation; n (%)	16 (11.0)	12 (17.7)	4 (5.1)	0.02
Average IV morphine dosage (mg)	0.9±3.9	1.7±5.4	0.2±1.1	0.01
Duration of surgery (mean, min)	150 (100.0, 276.2)	157.5 (100.0, 280.0)	145 (97.5, 265.0)	0.74
Adjuvant analgesia; n (%)				
None	79 (54.1)	35 (51.5)	44 (56.4)	0.62
1 type	50 (34.3)	26 (38.2)	24 (30.8)	
>1 type	17 (11.6)	7 (10.3)	10 (12.8)	
Skin incision size				
<10 cm	18 (12.3)	8 (11.8)	10 (12.8)	0.97
10-20 cm	91 (62.3)	43 (63.2)	48 (61.5)	
>20 cm	37 (25.3)	17 (25.0)	20 (25.6)	
PACU information and outcome measurements				
Type of LA for post-operative epidural infusion				
0.0625% bupivacaine	97 (66.4)	41 (60.3)	56 (73.7)	0.08
0.1% bupivacaine	49 (33.6)	27 (39.7)	20 (26.3)	
Post-operative epidural infusion				
Rate (ml/hr)	5.0±0.8	5.0±0.9	4.9±0.75	0.62
Rate (mg/kg/hr)	0.07±0.02	0.07±0.02	0.06±0.02	0.11
Secondary catheter failure	17 (11.6)	4 (5.9)	13 (16.7)	0.08

ASA=American Society of Anesthesiologists classification, BMI=body mass index, IV=intravenous, LA=local anesthetic drug, PACU=post-anesthetic care unit, TEP=thoracic epidural placement, USG=ultrasound-guided

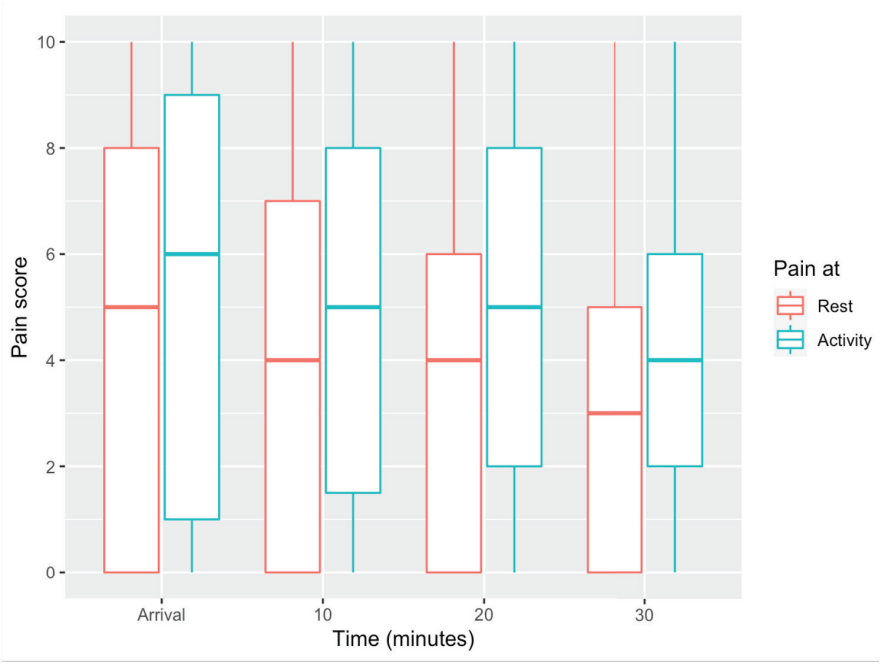


Figure 2 Box plot of pain score distributions at rest (red) and during physical activity (green) in patients with indwelling thoracic epidural analgesia in the recovery room, collected at 10–minute intervals

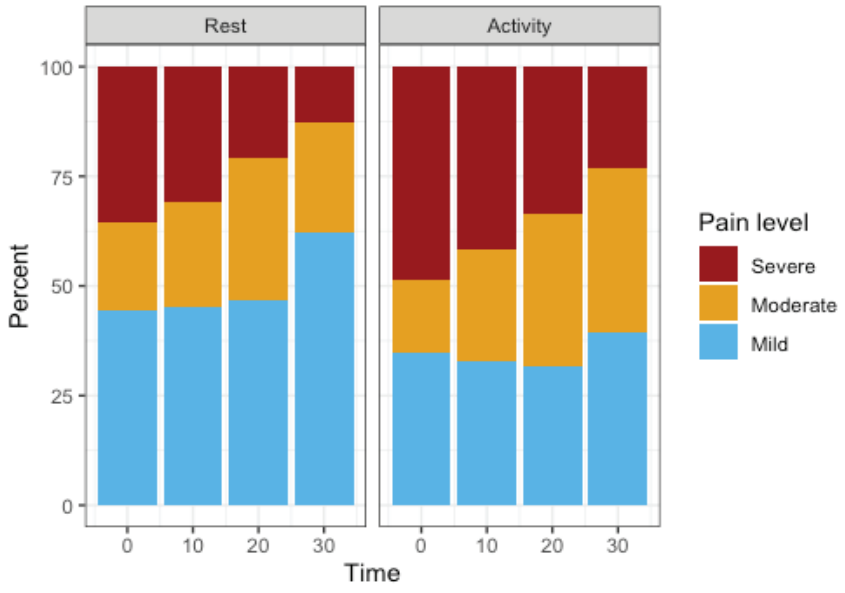


Figure 3 Stacked bar plot of the number of patients stratified by severity of pain (severe=red, moderate=yellow, and mild=blue) at rest and during physical activity, assessed every 10 minutes up to the maximum duration of 30 minutes in the post–anesthetic care unit

Table 2 Univariate and multivariate logistic models of factors associated with ineffective TEA at PACU arrival (T0)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Number of TEP attempts: ≥3 attempts vs. <3 attempts	2.04	0.92, 4.73	0.08	1.85	0.77, 4.64	0.17
Technique of TEP: Real-time ultrasound-guided vs. landmark-based	0.78	0.27, 0.90	0.05	0.78	0.27, 2.26	0.64
Intra-operative IV morphine addition; ref=no	0.25	0.07, 0.77	0.02	0.27	0.07, 0.92	0.04
Type of intra-operative LA; ref=not used						0.51
1% lidocaine	0.85	0.20, 3.58	0.82	0.67	0.13, 3.58	
2% lidocaine	0.84	0.28, 2.41	0.75	0.44	0.10, 1.74	
0.1-0.2% bupivacaine	0.52	0.17, 1.54	0.24	1.32	0.24, 7.46	
Dose of intra-operative epidural bupivacaine (mg/hr)	0.93	0.87, 1.00	0.05	0.93	0.80, 1.06	0.30
Dose of intra-operative epidural lidocaine (mg/hr)	1.01	1.00, 1.02	0.09	1.01	0.99, 1.03	0.20

CI=confidence interval, LA=local anesthetic, OR=odd ratio, PACU=post-anesthetic care unit, TEA=thoracic epidural analgesia, TEP=thoracic epidural placement

Table 3 Univariate and multivariate mixed-effects models of factors associated with ineffective TEA over time during PACU stay

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Technique of TEP; real-time ultrasound-guided vs. landmark-based	0.14	0.02, 0.86	0.03	0.36	0.03, 4.78	0.44
Number of TEP attempts; ≥3 attempts vs. <3 attempts	3.43	0.54, 21.9	0.19	3.38	0.37, 30.7	0.28
Intra-operative lidocaine epidural administration dose (mg/hr)	1.02	0.99, 1.04	0.20	1.01	0.98, 1.04	0.63
Intra-operative bupivacaine epidural infusion does (mg/hr)	0.86	0.74, 1.01	0.07	1.01	0.79, 1.28	0.96
Post-operative epidural bupivacaine dose (mcg/kg/hr)	0.96	0.93, 0.99	0.04	0.97	0.92, 1.01	0.12
Number of co-analgesic drugs (lag 10 minutes)	0.60	0.36, 1.00	0.05	0.67	0.35, 1.28	0.23
Cumulative fentanyl equivalent dose (per 10 mcg)	0.99	0.98, 1.00	0.06	0.87	0.77, 0.97	0.02

CI=confidence interval, LA=local anesthetic, OR=odds ratio, PACU=post-anesthetic care unit, TEA=thoracic epidural analgesia, TEP=thoracic epidural placement

Table 4 Univariate and multivariate logistic models of factors associated with severe pain at discharge from PACU

Characteristic	Univariate analysis					Multivariate analysis		
	N	Event N	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Sex; female vs. male	69	13	1.89	0.74, 5.08	0.18	1.57	0.56, 4.59	0.40
Technique of TEP; real-time ultrasound-guided vs. conventional technique	40	2	0.23	0.04, 0.85	0.03	0.38	0.04, 2.18	0.32
Intra-operative epidural lidocaine infusion dose (mg/hr)	142	21	1.01	1.00, 1.02	0.15	1.00	0.99, 1.02	0.60
Intra-operative epidural bupivacaine infusion dose (mg/hr)	142	21	0.91	0.79, 1.02	0.11	1.03	0.85, 1.22	0.76
Effectiveness of TEA at PACU arrival; ineffective vs. effective	74	17	4.77	1.65, 17.30	<0.01	4.77	1.57, 18.1	0.01
Post-operative epidural bupivacaine dose (mg/hr)	142	21	0.56	0.32, 0.89	0.01	0.62	0.30, 1.13	0.15
Cumulative fentanyl equivalent dose (per 10 mcg of fentanyl)	142	21	0.99	0.93, 1.05	0.69	0.99	0.91, 1.06	0.73
Cumulative number of co-analgesia administrations	142	21	1.03	0.51, 1.98	0.92	1.04	0.48, 2.18	0.92

CI=confidence interval, PACU=post-anesthetic care unit, TEA=thoracic epidural analgesia, TEP=thoracic epidural placement, OR=odd ratio

Figure 2 shows the distribution of VNRS scores measured over multiple time points. Overall, the at-rest pain score was lower than that during physical activity across all time points; however, both of them decreased over time. The median VNRS scores at arrival were 5 and 6 at rest and during physical activity, respectively; they dropped to 3 and 4 at 30 minutes after arrival.

Figure 3 demonstrates the classification of the participants according to their levels of pain at rest and during physical activity across time points. At 30 minutes, severe pain (VNRS>6) was experienced by 12.3% and 22.6% of participants at rest and during physical activity, respectively.

The incidence of iTEA on PACU arrival and at 10, 20, and 30 minutes after arrival were 53.4%, 51.4%, 50.7%, and 36.3% respectively; this indicates that iTEA incidence dropped significantly over time (chi-square for trends; p-value=0.005).

The association between intra-operative analgesia and iTEA at PACU arrival is presented in Table 2 The univariate logistic regression analysis found three variables associated with iTEA. However, after adjusting for other variables, only intra-operative morphine supplementation was found to significantly reduce the risk of iTEA at PACU arrival (adjusted OR 0.27; 95% CI 0.07-0.92; p-value= 0.035).

Table 3 reports the variables associated with iTEA over time points. The univariable mixed-model analysis indicated that using the real-time ultrasound technique for the TEP procedure, a higher dose of post-operative epidural bupivacaine, and a higher number of co-analgesic medications reduced the risk of iTEA in a statistically

significant manner. However, after adjusting for covariates, only the cumulative dose of fentanyl remained statistically significant. For each 10-microgram of fentanyl-equivalent dose, the risk of iTEA decreased by 13% (adjusted OR 0.87; 95% CI 0.77-0.97; p-value=0.015).

Of the 146 participants, 4 cases did not record pain score at 30 mins, hence remaining 142 participants. Among those participants 21 patients (14.3%) experienced severe pain at discharge from PACU. We found that iTEA at PACU arrival was associated with severe pain at PACU discharge (adjusted OR 4.77; 95% CI 1.57-18.1; p-value= 0.011) (Table 4).

Discussion

This prospective cohort study aimed to evaluate the effectiveness of TEA and the associating factors determining immediate post-operative iTEA during PACU stay in patients undergoing major abdominal and thoracic surgery. We have shown that the incidence of iTEA at PACU arrival and at 10, 20 and 30 minutes after arrival was 53.4%, 51.4%, 50.7% and 36.3% respectively; a significant gradual reduction in its incidence over the period of PACU stay was observed. In addition, we found that supplementing intra-operative TEA with IV morphine reduced the risk of iTEA at PACU arrival. Moreover, the iTEA on PACU arrival is a strong factor in predicting severe pain when discharged from PACU. We believe our results highlight the fact that the incidence of iTEA immediately after surgery occurs at substantially higher rates than expected, which emphasizes the need for aggressive epidural management in patients undergoing major thoracic and abdominal surgery.

The current study showed that the incidence of iTEA at PACU arrival was 53.4%, and that at 30 mins after PACU arrival was 36.3%. The decrease in the incidence of iTEA over time is explained by the interventions performed at the PACU, especially the onset of the effect of epidural drugs administered after the patient's PACU arrival. The delayed onset of the effect of epidural drugs can explain this phenomenon. The mixture of 0.0625% or 0.1% bupivacaine with fentanyl 2 mcg/ml (lipophilic opioid) or morphine 0.03 mg/ml (hydrophilic opioid) was the common epidural therapy used. It is well-established that the combination of local anesthetic drugs with opioids for epidural analgesia is more efficacious, has fewer side effects, and offers more favorable post-operative pain control than the use of a local anesthetic or opioids alone[18-19], and that TEA is a safe technique for in-patient pain management[20-21]. This study did not discriminate between morphine and fentanyl as factors of iTEA because the authors believed that the addition of both drugs to epidural bupivacaine provides equal analgesic effects. This was confirmed by a previous study, which reported that the differing of fentanyl dosages (lipophilic opioids) did not lead to any clinical benefits (analgesic efficacy, side effects, and safety) apart from reducing the onset of analgesia compared to morphine (hydrophilic opioid)[22].

Though the incidence of iTEA reported by our study is similar to those of prior studies[13,16,23], the earlier studies usually evaluated the effectiveness of TEA during 24-72 hours after the operation. Anderson et al[23]. reported that 30-50% of patients receiving TEA after trans-abdominal surgery had insufficient pain control during coughing on post-operative days 1 to 3. Wongyingsinn et al[13]. reported that up to 50% of patients experienced at least one episode of moderate pain at rest during the first 48 hours after surgery, and 24.5% suffered severe pain at rest after major surgery even though epidural analgesia was used. Motamed et al[16]. reported that 24.8% of patients experienced TEA failure. Further investigation found that, in 50% of cases, catheter-related leakage or catheter placement outside of the epidural space were the causes, whereas 32% of failures could be attributed to an insufficient epidural dose, even though the dose was properly adjusted. On the contrary, a UK cohort study reported that only 5.2–7.5% of their patients received inadequate analgesia during post-operative days 1–3[24]. Moreover, the epidural catheter

can migrate from the epidural space through intervertebral foramen, and it produces unilateral blockade[25].

The comparison of the incidence of iTEA is difficult for two reasons. First, several terms are commonly used to described iTEA, e.g., TEA failure, inadequate TEA, and insufficient TEA[13,14,23]. Second, the definition of iTEA varies between studies; such definitions include 1) an acceptable level of pain control was not achieved[14,16], 2) inability to locate the sensory blockade after epidural bolus injection[26-27], and 3) any reasons causing the premature removal of the epidural catheter[16,28] or the need for epidural catheter re-insertion[26]. TEA failure can be classified into primary and secondary causes. Hermanides et al[8]. defined primary failure as an inability to insert or correctly place the epidural catheter. Tran and colleagues[29] classified primary failure into two different etiologies, which are the misidentification of the epidural space and the misplacement of the epidural catheter. Secondary failure occurs due to any causes that results in inadequate pain control by epidural analgesia; such causes include catheter-related issues such as migration, obstruction, disconnection, or any cause of premature catheter removal and inadequate dose of local anesthetic drug (clinically anticipated)[8]. We report a secondary failure rate of 11.6%. It is comparable to the rate of 9% reported by Ganapathi et al[28]. and 16% by Andersen et al[23]. Strategies to reduce TEA failure such as the use of the real-time ultrasound-guided TEP technique that improves the success rate of TEP[30], the performance of the pressure waveform analysis to confirm the epidural space[31-32], the employment of fiberoptic-guided epidural insertion[33], and the maintenance of an epidural protocol to prevent suboptimum dose should be implemented in centers providing acute pain service.

Regarding the factors associated with iTEA over time during PACU stay, we found that higher doses of intra-operative and post-operative epidural bupivacaine (mcg/kg/hr) decreased the risk of iTEA, but this decrease was not statistically significant. Increasing the number of participants would improve the significance levels, and it would enhance the effects of the dose of epidural bupivacaine. On the other hand, the use of adjunct IV opioids significantly deterred the risk of iTEA (adjusted OR 0.87; p-value=0.015). It is reasonable to argue that adjunct analgesic medications provide an analgesic synergistic effect with TEA. Previous studies have found that the bupivacaine dose determines the efficacy of TEA rather than its volume or concentration[34-35]. Moreover, a literature review stated that the dose of the local anesthetic is the most important factor determining the effectiveness for post-operative analgesia[36].

We found that 14.3% of participants experienced severe pain at discharge from PACU. The multivariate analysis found that iTEA at PACU arrival was a significantly associated factor of severe pain at discharge from PACU and admission to the ward (adjusted OR of 4.77) compared to patients with effective TEA at PACU arrival. This result is similar to that a study by Shah et al[6]., which demonstrated that intra-operative epidural management predicted pain level, PACU length of stay, and PACU opioid use.

Our study is unique in several aspects. First, we integrated VNRS scores of both at rest and during physical activity to define the effectiveness of TEA. Second, we assessed the patient at regular 10-minute intervals for a period of 30 minutes from the time of PACU arrival, which offered a vivid representation of the physiology of pain as well as the dynamic change of the pain score immediately after surgery. To our knowledge, such close assessment has not been reported previously, and the data in the published literature pertinent to this topic remains obscure. Third, we used the mixed-effects model analysis for the repeated measurements of pain scores after surgery, which is an appropriate statistical technique for the measurement of a repeated outcome. Finally, we employed the concept of lag time to ascertain the effect of the analgesic drugs

considering their onset as well as their peak and cumulative effect on pain score at the next time interval.

However, this study had several limitations that are relevant to clinical practice. First, we did not control for any co-interventions in the study, which resulted in information heterogeneity. Some factors seemed to be associated with iTEA during the univariate analysis, e.g., TEP technique, multimodal analgesia technique, number of attempts to TEP success, and intra-operative epidural administration (administration vs. none, and bolus vs. continuous infusion). However, the significance of these factors disappeared after adjustment for other factors. Second, this study did not use objective evidence to confirm the correct placement of the thoracic epidural catheter. We used the clinical evidence of sensory blockade after the bolus dose of 2% lidocaine as an indication of correct catheter placement. The use of the sensory blockade to ascertain whether the position of the epidural catheter is in the correct or incorrect space is controversial. Therefore, we could not determine a definitive cause for iTEA; this requires an investigation to verify the location of the epidural catheter. Finally, our sample size was limited because of the COVID-19 pandemic; this fact compromises the power of our results.

In conclusion, this cohort study demonstrated that the incidence iTEA immediately after surgery is substantially higher than expected, which emphasizes the need for more aggressive intra-operative epidural management in patients undergoing major abdominal and thoracic surgery. Intravenous opioid supplementation during and after surgery was shown to reduce the risk of ineffective TEA. Moreover, ineffective TEA at PACU arrival was found to be a strong predictor of severe pain at discharge from PACU. Future studies should focus on the intra-operative epidural catheter management factors that could influence the effectiveness of TEA, both immediately and at days 2-3 after surgery.

Funding sources

This study was supported by the Research Fund of the Faculty of Medicine, Prince of Songkla University.

Conflict of interest

There is no conflict of interest to declare on the part of all the authors of this article.

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