Original Research Article

Effectiveness of pre-emptive thoracic epidural analgesia for acute post thoracotomy pain relief: a randomised blinded study

Anupananda Chowdhury, Dipika Choudhury, Upasana Majumdar*, Trina Sen

Department of Anaesthesiology and Critical Care, Gauhati Medical College and Hospital, Guwahati, Assam, India

*Correspondence:
Dr. Upasana Majumdar,
E-mail: upasana.majumdar@gmail.com

ABSTRACT

Background: Thoracotomy is one of the most damaging surgical insults on respiratory mechanics and management of post-thoracotomy pain is a challenge. This study was conducted to compare intensity of postoperative pain, measured by VAS, in patients receiving Pre-emptive TEA compared to patients receiving epidural analgesia during surgical closure.
Method: Group A comprised of patients receiving Pre-emptive TEA with 0.1%Ropivacaine and 2 μg/ml fentanyl, 20 minutes before incision. Group B comprised of patients receiving the same drug, during surgical closure.
Results: Demographic profile was comparable between both groups. Both groups offered good analgesia, but pre-emptive group took an upper hand upto4th postoperative hour (p<0.05), both at rest and coughing. Beyond 4thhour, analgesic efficacy of both groups was comparable.
Conclusion: Pre-emptive technique offered better analgesia over the postoperative technique up to 4th postoperative hour, both at rest and coughing.

Keywords: Pre-emptive, Ropivacaine, Thoracic epidural analgesia, Visual analogue scale

INTRODUCTION

Pain following surgery is a universal phenomenon. Post-operative pain is initiated by tissue injury which determines the natural process of healing. Thoracotomy is widely recognised as one of the most painful surgical procedures.[1-3] In addition to the unpleasant cognitive aspects of thoracotomy pain, nociceptive signals have several other harmful effects that can delay patient's recovery. The pain associated with thoracotomy incision can be difficult to target and quantify, and till date, several studies have evaluated chest tube pain, incisional pain, visceral pain, and post thoracotomy pain at rest and pain associated with coughing or movement. Suboptimal pain relief results in shallow breathing and impaired coughing that may lead to atelectasis and retention of secretions, both of which may result in hypoxemia, hypercapnia and respiratory failure.[1] Acute post thoracotomy pain, if untreated, may lead to chronic post thoracotomy pain which has a serious negative impact on the quality of life.[4] Several methods of post thoracotomy pain management have been tried over the decades which include thoracic epidural analgesia,intercostal nerve block, paravertebral nerve block, intravenous, intrathecal or epidural analgesics.[1,2] Out of the various methods, thoracic epidural analgesia (TEA) is regarded as the gold standard and a suitably planned and timed TEA decreases postoperative morbidity and mortality.[1,3,5] Furthermore, the idea of pre-emptive analgesia is gaining popularity. pain after surgery might be amplified by the noxious surgical incision and administration of opioids or local anaesthetics before surgery reduces the central effects of

the C-fibre induced injury and thereby reduce the intensity of postoperative pain. Thus pre-emptive analgesia decreases hyperalgesia and allodynia by altering central sensory processing.[6] This study evaluates the effects of pre-emptive TEA versus postoperative initiation of TEA in patients undergoing thoracotomy.

METHODS

The present study used a prospective, randomised, patient and observer blinded, placebo controlled design. After approval from the institutional ethical committee, the clinical study was conducted under the Department of Anaesthesiology and Critical Care at Gauhati Medical College and Hospital, Assam, India.

Inclusion criteria

- Aged 18 to 65 years
- American Society of Anaesthesiology (ASA) Physical status II and III
- Scheduled to undergo an elective thoracotomy of at least 3 inches (7.6 cm) of intercostal incisional length or requiring insertion of an inter-rib spreader/retractor, under general anaesthesia
- Able to provide informed consent, adhere to the study, and complete all the study assessments

Exclusion criteria

- Unwilling patients
- Contra indications to epidural anaesthesia
- Disorders of haemostasis
- Abnormalities of thoracic spine
- Systemic infections or patients having local sepsis at the site of injection
- Patients with hypertension (history of hypertension or two subsequent readings of blood pressure more than 140/90 mm of Hg on examination)
- Other major systemic illness
- History of allergy to study medications
- Patients having chronic pain
- Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin or duloxetine within 3 days of surgery
- Use of any of the following medications within the times specified before surgery: long -acting opioid medication, NSAID, or aspirin (except for low-dose aspirin used for cardio-protection or acetaminophen / paracetamol) within 3 days and any opioid medication within 24 hours
- Re-thoracotomy

Using block randomisation, 60 patients satisfying the inclusion criteria were randomly assigned into two groups: group A (pre-emptive TEA) and group B (postoperative TEA). Group A (n=30) (PRE group) received a pre-emptive epidural bolus of local anaesthetic

solution which comprised of 0.1% Ropivacaine with 2 μg /ml of fentanyl, in a dose of 0.15ml/kg, 20 minutes prior to skin incision followed by epidural infusion of the same, at the rate of 0.1ml/kg/hour, up to the 24th hour in the post-operative period.

Group B (n=30) (POST group) received an epidural bolus of local anaesthetic solution which comprised of 0.1% Ropivacaine with 2 μg /ml of fentanyl in a dose of 0.15ml/kg, at the time of rib approximation during surgical closure. This was followed by epidural infusion of the same, at the rate of 0.1ml/kg/hour , up to the 24th hour in the post-operative period.

In patients of both Group A and Group B, an epidural catheter was inserted in sitting position under aseptic precautions at the mid thoracic level (T4-T7) before the induction of general anaesthesia. The Patients were kept in sitting position. The back of the patients were sterilized with chlorhexidine 0.5% in alcohol 70% and then draped suitably and anatomical landmarks were identified. Either T5-6 or T6-7 or T7-8 interspace (whichever was better) was selected for 18G Tuohy epidural needle insertion. A skin wheal was made with 2- 3ml of 1% Lignocaine. 18G Tuohy needle was introduced in the selected interspace. The epidural space was identified using midline approach and by Loss of Resistance (LOR) to air technique at a depth of 4-6cm from the skin. The space was cannulated with 20G epidural catheter via the tuohy needle and after facing the bevelled tip of the needle in the cephalic direction, the needle was advanced 3-5cms. Tuohy needle was taken out over the catheter and the catheter was secured with Tegaderm.™ After a negative aspiration of CSF and blood, a 3ml test dose of 2% Lignocaine with 1 in 200,000 adrenalines was given after the placement of the epidural catheter, to detect unintentional intrathecal or intravascular placement of the catheter.

In the operation theatre, standard monitoring devices measuring Non- Invasive Blood Pressure (NIBP), Pulse Rate (PR), Percentage Oxygen Saturation (SPO_2) and Continuous Electrocardiograph (ECG) were attached and baseline recordings were taken before induction of anaesthesia. In both groups, anaesthesia procedures were standardised according to departmental protocol.

Patients of both the groups A and B were pre medicated with inj. Glycopyrrolate (0.2mg) IV, inj. Midazolam (1-2mg) IV, inj Ondansetron (4 mg) IV and inj. Fentanyl (1mcg/kg) IV. After 3 minutes of pre oxygenation , patients were induced with Propofol (2-3mg/kg) IV. Neuromuscular block was achieved with inj. Vecuronium bromide (0.1mg/kg) IV, followed by tracheal intubation with an adequately sized endotracheal tube. For patients in the pre-emptive group (Group A), 0.15 mL/kg of bolus standard epidural solution was administered 20 minutes, prior to surgical incision via epidural catheter. Epidural infusion of the same solution was started immediately after the bolus dose at the rate of 0.1ml/kg/hour and continued up to the 24th post-operative hour.

Anaesthesia was maintained with inhalational agents, isoflurane in nitrous oxide and oxygen (in a ratio of 4:2) along with intermittent doses of i.v. vecuronium bromide, which was titrated to achieve adequate level of muscle relaxation. Unilateral Thoracotomy was then performed through the fifth or sixth intercostal space via a posterolateral incision. Intraoperative analgesia was provided by infusion paracetamol 1000mg IV, infused over 15 minutes. Another resident was allotted as an observer of this study during the intra operative period.

In patients in postoperative TEA group (Group B), an equal volume of normal saline was administered as a bolus of 0.15ml/kg, 20minutes prior to surgical incision , followed by normal saline infusion at the rate of 0.1ml/kg/hour via epidural catheter during the operation, in the same way as it was done in group A.0.15 mL/kg of standard epidural solution (0.1% Ropivacaine and 2 μg/mL fentanyl) was administered as a bolus via epidural catheter at the time of rib approximation and surgical closure. Thereafter, the local anaesthetic solution, was started at the rate of 0.1ml/kg/hour and continued up to the 24th postoperative hour. After skin closure, the neuromuscular blockade was reversed with a combination of neostigmine (0.05mg/kg) and glycopyrrolate (0.001mg/kg). The patient was extubated and shifted to intensive care unit (ICU) for the maintenance of post-operative analgesia and monitoring up to the 24th post-operative hour.

After the completion of surgery, patients were managed in the cardio thoracic intensive care unit for 24 hours as per the departmental protocol. Analgesia was assessed at an interval of 2, 4, 6, 8, 12 and 24 postoperative hours respectively using a pre-validated non-invasive pain scoring system (Visual Analogue Scale), both at rest and during coughing. The data were collected as per a pre-defined proforma. Both the groups were given inj. Tramadol (50 mg, maximum 3 doses in first 24 hours postoperatively) if their pain was above VAS 4.

In addition to the VAS scores, vital signs which included, non-invasive blood pressure (NIBP), heart rate (HR), and respiratory rate (RR) were also recorded at an interval of 2, 4, 6, 8, 12 and 24 hours in the post-operative period.

Side effects like nausea, vomiting, pruritus and sedation were recorded. Any other complications like hypotension, bradycardia, urinary retention, shivering, ipsilateral shoulder tip pain, pruritus, sedation and respiratory depression were also being recorded.

The data were collected by the nursing staff in the CTVS I.C.U, who was blinded for the technique used for each patient.

Sample size calculation

Considering the mean (standard deviation) VAS of 2.6 (1.93) at 4rth post-operative hour, to detect a difference of

1.5 in VAS, 26 samples are required in each group with a power of 80% at the significance level of 0.05. Considering an attrition rate of 15%, 30 patients in each group is required in this study.[9]

Statistical analysis

The data were entered into MS Excel spread sheets and analysis was carried out. The procedures involved were transcription, preliminary data inspection, content analysis and interpretation. Parameters used to compare the groups statistically were demographic characteristics and analgesia (VAS score). For analysis, descriptive and inferential statistics were used. The statistical analyses were done by using the PSW software version 21.0

Data are present as mean±standard deviation, unless otherwise denoted. All the 60 patients who were included in the study were comparable in age, sex and weight.

RESULTS

Data are present as mean±standard deviation, unless otherwise denoted. All the 60 patients who were included in the study were comparable with respect to ASA status, age, sex, weight, height and side of thoracotomy (Figure 2).
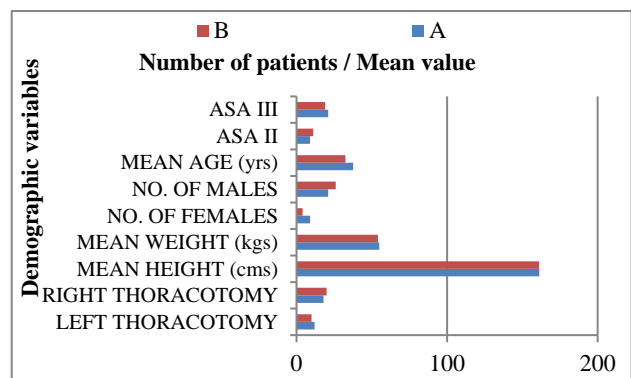

Figure 1: Demographic parameters.

To compare the VAS scores at rest (as depicted above in Table 1 and Figure 3) between the two groups A and B, authors applied the One-Sample Kolmogorov-Smirnov Test. The data did not follow normality, so authors used the Mann-Whitney Test.

It was found that, up to the 4th post-operative hour, there were highly significant statistical differences of VAS at rest (p value: 0.001 at 2nd hour and <0.001 at 4th hour) in between group A and group B. Beyond the 4th hour, there were no statistically significant differences of VAS at rest in between the two groups, up to the 24th post-operative hour.

To compare the VAS scores at coughing (Table 2 and Figure 4), between the two groups A and B, authors

applied the One-Sample Kolmogorov-Smirnov Test. The data did not follow normality, so authors applied the Mann-Whitney Test.
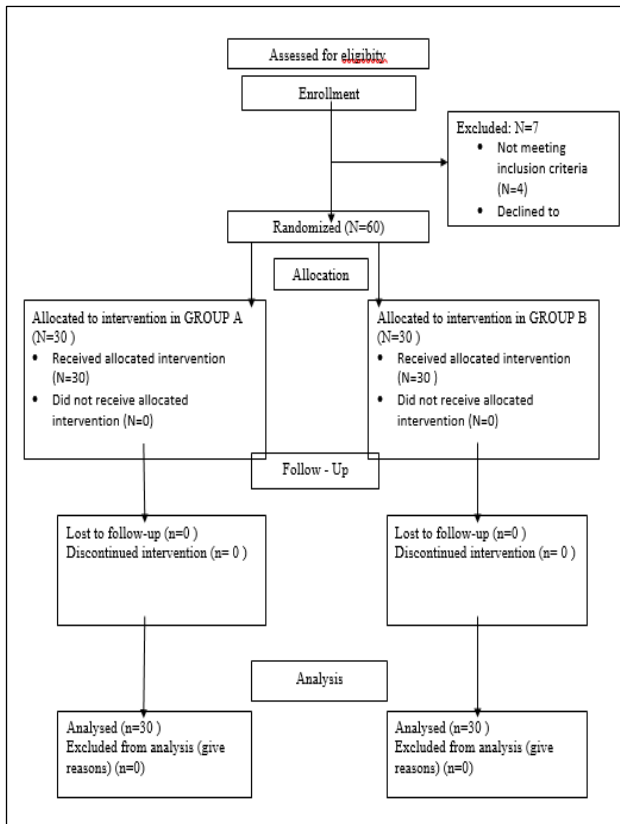

Figure 2: Consort flow diagram of study.

Table 1: Comparison of VAS between group A and B at rest.

VAS Score (Rest)	Group	Mean VAS	p Value
2 hr VAS	A	1.67	0.0013
	B	2.50	
4 hr VAS	A	1.83	0.0001
	B	3.07	
6 hr VAS	A	2.87	0.872
	B	2.83	
8 hr VAS	A	3.63	0.960
	B	3.57	
12 hr VAS	A	3.93	0.342
	B	3.53	
24 hr VAS	A	5.03	0.441
	B	4.73	

It was found that, up to the 4th post-operative hour, there are highly significant statistical differences of VAS at coughing (p value: <0.001 both at 2nd hour and 4th hour respectively) in between group A and group B. Beyond the 4th hour, there was no statistically significant differences of VAS at coughing in between the two groups, up to the 24th post-operative hour.
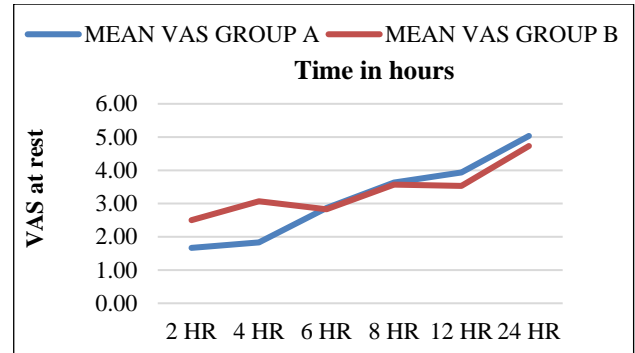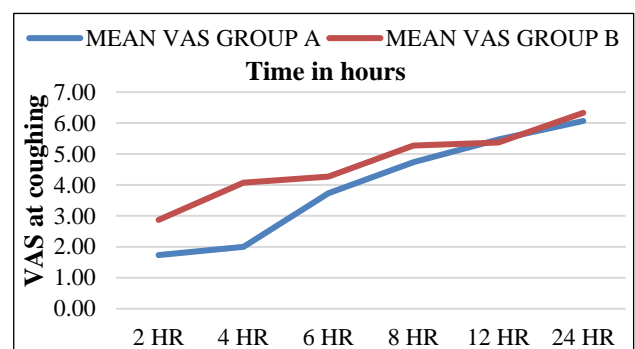

Figure 3: Comparison of VAS between group A and B at rest.

Table 2: Comparison

Vas score (coughing)	Group	Mean vas	P value
2 hr vas	A	1.73	0.00008
	B	2.87	
4 hr vas	A	2.00	<0.00001
	B	4.07	
6 hr vas	A	3.73	0.121
	B	4.27	
8 hr vas	A	4.73	0.152
	B	5.27	
12 hr vas	A	5.47	.872
	B	5.37	
24 hr vas	A	6.07	0.603
	B	6.33	

of VAS between group A and B on coughing.

Figure 4: Comparison of VAS between groups during coughing.

On comparing the VAS scores at rest and at coughing within group A (as shown above in Table 3), there was no statistically significant difference (p >0.05) up to the 4th post-operative hour. Beyond the 4th hour, there was highly significant difference up to the 24th post-operative hour (p value <0.001).

On comparing VAS at rest and at coughing within group B (Table 4), there were highly significant differences (p

<0.001) at all subsequent time intervals, up to the 24[th]post-operative hour.

Table 3: Comparison of VAS at rest and at coughing in Group A.

Time/Variable	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
VAS at rest (mean±SD)	1.67±0.884	1.83±0.913	2.87±1.042	3.63±1.066	3.93±1.413	5.03±1.712
VAS at coughing (mean±SD)	1.73±0.868	2.00±0.910	3.73±1.143	4.73±1.285	5.47±1.655	6.07±1.741
Significance	0.161	0.057	0.001	0.001	0.001	0.001

Table 4: Comparison of VAS at rest and at coughing in Group B.

| Time/Variable	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
VAS at rest (mean±SD)	2.50±0.900	3.07±1.143	2.83±1.147	3.57±1.331	3.53±1.592	4.73±1.780
VAS at coughing (mean±SD)	2.87±1.008	4.07±1.311	4.27±1.230	5.37±1.810	5.37±1.810	6.33±1.788
Significance	0.001	0.001	0.001	0.001	0.001	0.001
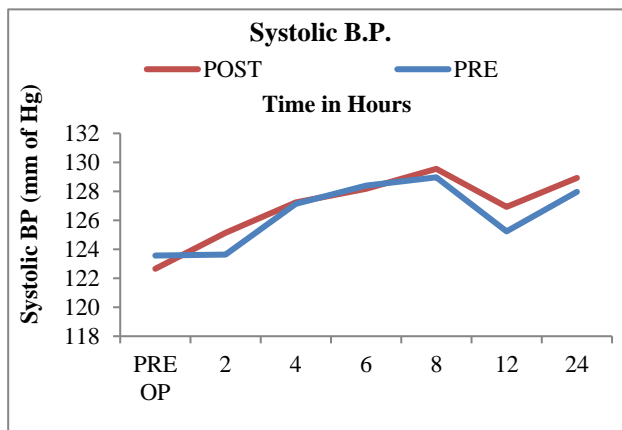
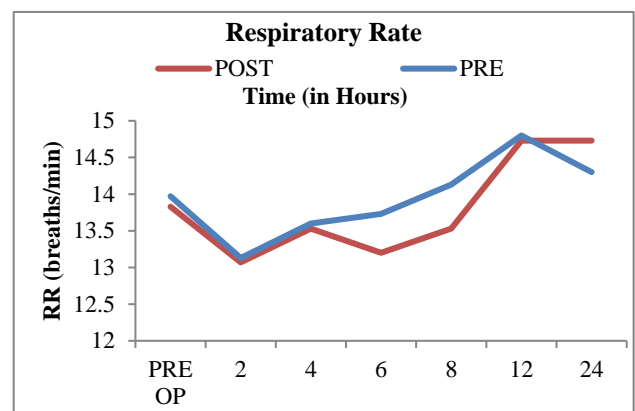**Figure 5: Comparison of Systolic B.P. between Groups A and B.**
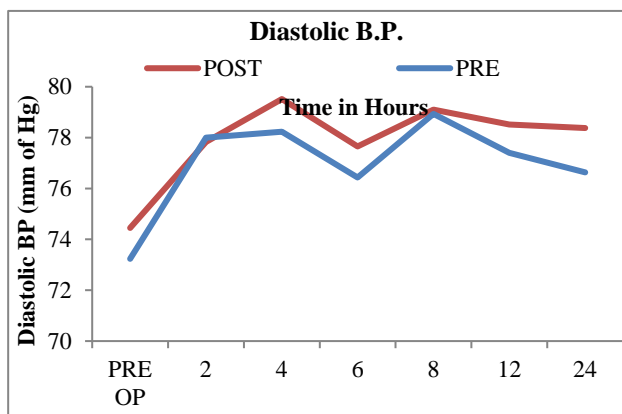
Figure 6: Comparison of Diastolic B.P. between Groups A and B.

It was found that only 3 patients in group A required rescue analgesic (intravenous tramadol) whereas 12 patients in group B requested rescue analgesic during the first 24 post-operative hours (p<0.05).
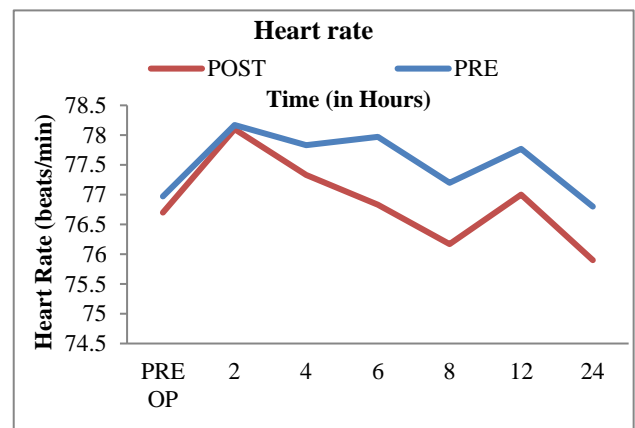
Figure 7: Comparison of Heart rate between Groups A and B.

Figure 8: Comparison of respiratory rate between groups A and B.

There were no statistically significant differences (p>0.05), between the two groups A and B, in terms of systolic B.P. (Figure 5), diastolic B.P. (Figure 6), heart rate (Figure 7) and respiratory rate (Figure 8). The incidence of adverse effects between patients of group A and B were also comparable.

DISCUSSION

Thoracic epidural anaesthesia (TEA) has been widely established as a cornerstone in the perioperative care after thoracic and major abdominal surgery providing very effective analgesia.[7,8] Thereby, in absence of contraindications for TEA, all patients posted for major thoracic surgical procedure should have a thoracic epidural catheter placed preoperatively.

It is important to cite that Pre-emptive analgesia refers to pain therapy given before the surgical incision and noxious stimulus.

In this study, the post-operative extent of sensory blockade was comparable in both the groups as assessed by pin prick. While comparing the VAS scores at rest and at coughing, it was found that VAS in the group A were lower and highly significant (p value <0.001) as compared to group B at the 2nd and 4th post-operative hour. Beyond the 4th hour, there was no significant difference in VAS scores up to the 24 hours.

For the pre-emptive group (group A), authors found that there was no significant difference between pain scores at rest and pain scores at coughing at the 2nd and 4th hour (Table 3). Beyond the 4th post-operative hour, pain scores at rest were lower and highly significant than pain scores at coughing. For the initial post-operative period, especially up to 4 hours, patients in the pre-emptive TEA group were quite comfortable, as evident from their lower pain scores, and their pain was not aggravated even on coughing. For the post incisional group (group B), pain scores at rest were found to be lower and highly significant than pain scores at coughing at 2nd, 4th, 6th, 8th, 10th, 12th and 24th post-operative hour, i.e., at each subsequent interval (Table 4). In addition to this, the use of rescue analgesics was significantly lower in the pre-emptive TEA group as compared to the post-operative TEA group. This further testifies to the beneficial effects of pre-emptive TEA in providing early post-operative analgesia.

Our findings are consistent with the findings by Erturk et al, 2014 (Biomed Res Int) who had conducted a similar study in 40 patients posted for thoracotomy.[9] They found that pain scores at rest and at coughing were significantly lower in the pre-emptive group than in the postoperative group in the 1st, 2nd and 4th postoperative hour. Though their study was based on an infusion of 0.1% levobupivacaine and fentanyl while authors carried out our study using 0.1% ropivacaine and fentanyl infusion, similar observations were made in both the studies.

Senard M, et. al. on comparing the analgesic efficacy of 0.1% levo bupivacaine and 0.1% ropivacaine infusion in lower abdominal surgery, found that both drugs were comparable. At the time of our study levo bupivacaine was not available, so authors used ropivacaine. Opioids reduce the need for local anaesthetic by 19-31%.[10] Fentanyl was preferred among the other opioids for its rapid onset and a relatively lower risk of respiratory depression.[11]

Another study by Neustin and his associates in 2002, found significantly lower pain scores in the pre-emptive group as compared to the post-operative group for the first 6 hours with 0.1% bupivacaine and fentanyl.[12] The equipotent doses of bupivacaine and ropivacaine has not been evaluated in thoracic surgery but it has been evaluated in the obstetric population by Anand LK et al.[13] Ropivacaine is preferred because of its reduced toxic potential as compared with bupivacaine, not only at equivalent, but also at equipotent doses.[14]

Similar study was conducted by Arif Yegin et al.[15] in 2003 and they found significantly lower pain scores in the pre-emptive TEA group than the post-operative TEA group till the first 12 hours in 61 patients undergoing thoracotomy. Epidural solution of 0.25% bupivacaine and fentanyl was used in their study and the longer duration of analgesia maybe attributed to the fact that post-operative analgesia was maintained by patient controlled epidural analgesia (PCEA) while authors used epidural infusion. PCEA offers improved analgesia along with patient satisfaction and safety as compared with conventional epidural infusion or bolus techniques, but as PCEA is not available in our set up, it could not be used in our study. Amr et al.[16] carried out a study in 2010 and showed significantly reduced pain scores up to the 48th postoperative hour in the pre-emptive group. The extended pre-emptive benefit was probably due to the use of basal epidural infusion with superimposed PCEA boluses.

In contrast to our findings, there has been studies that have found no analgesic benefit of pre-emptive TEA in post thoracotomy pain relief. The study by Aguilar et al.[17] in 1996 found that, there was no significant difference between groups, either in PCEA requirements or in pain scores (either at rest, during mobilization of the ipsilateral arm of surgery, or after cough) by using a bolus dose of 0.5% bupivacaine and adrenaline, followed by PCEA with 0.125% bupivacaine and fentanyl. They concluded that thoracic epidural block with bupivacaine did not produce significant pre-emptive beneficial effect as compared with the placebo group. Similar observations were made by Atashkhoyi et al. in 2012 who concluded that the postoperative epidural analgesia offered better analgesia than pre-emptive epidural analgesia, up to the 3rd post-operative hour in major gynaecological surgery.[18] The findings of their studies are sharply contrasting to our study probably because they have opted for a single bolus dose of local anaesthetic while authors have opted

for a pre-emptive bolus followed by continuous epidural infusion till the 24th post-operative hour. Postoperative epidural analgesia is usually administered via a continuous infusion to maintain a level of analgesia and to minimize the cardiovascular and respiratory effects of bolus doses of LA and opioid respectively.

A potential consequence of omitted epidural infusion is the additional requirement of intravenous opioid analgesics to treat breakthrough post-operative pain. Supplemental doses of intravenous analgesics might prevent the transmission of the painful impulses, but it does not completely block the pain pathways. Also, the use of additional intravenous opioid is associated with an increased incidence of opioid related side effects such as nausea, vomiting and pruritus.[19] Thereby, it can be very conceptually said that the best way to alleviate perioperative pain is the use of bolus dose of analgesic, which is to be given even before the surgical incision and it should be followed by continuous epidural infusion during the intra operative and immediate post-operative period.

It was also found that pre-emptive TEA provides similar haemodynamic stability as compared to the post incisional group. It has been shown that lower doses of continuous infusion of local anaesthetic and opioid combinations do not alter haemodynamics unlike single large bolus doses.[20] This might be the reason behind similar haemodynamic stability of the pre-emptive group although they have received the analgesic drug infusion for a longer duration of time.

There are several limitations of our study. Firstly, it is a single hospital study, but for the purpose of evaluation of parameters that authors have used in our study (VAS scores, Cardio-respiratory parameters and incidence of adverse effects), a multi hospital study is considered to be better. Secondly, this study was limited to the assessment of post-operative analgesia only up to 24 hours postoperatively. Also, the study population was not large enough to assess safety of the two differently timed perioperative analgesic techniques and no recommendations can be made regarding the safety profile of the two groups.

ACKNOWLEDGEMENTS

REFERENCES

1. Hughes R, Gao F. Pain control for thoracotomy. ContinEduc Anaesthesia, Crit Care Pain. 2005;5(2):56-60.
2. Bong CL, Samuel M, Ng JM, Ip-Yam C. Effects of Preemptive Epidural Analgesia on Post-thoracotomy Pain. J Cardiothorac Vasc Anesth. 2005;19(6):786-93.
3. Ng A, Swanevelder J. Pain relief after thoracotomy: is epidural analgesia the optimal technique? Br J Anaesth. 2007;98(2):159-62.
4. Ochroch EA, Gottschalk A. Impact of acute pain and its management for thoracic surgical patients. Thorac Surg Clin. 2005;15(1):105-21.
5. Kolettas A, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, Kioumis I, et al. Postoperative pain management. Journal of thoracic disease. 2015 Feb;71):S62.
6. Wilder-Smith OHG. Pre-emptive analgesia and surgical pain. In: 2000:129:505-24.
7. Pöpping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data†. BJA Br J Anaesth. 2008;101(6):832-40.
8. Benedetti F, Amanzio M, Casadio C, Filosso PL, Molinatti M, Oliaro A, et al. Postoperative pain and superficial abdominal reflexes after posterolateral thoracotomy. The Annals of thoracic surgery. 1997 Jul 1;64(1):207-10.
9. Erturk E, Aydogdu Kaya F, Kutanis D, Besir A, Akdogan A, Geze S, et al. The effectiveness of preemptive thoracic epidural analgesia in thoracic surgery. BioMed research international. 2014;2014.
10. D'Angelo R, Gerancher JC, Eisenach JC RB. Epidural fentanyl produces labor analgesia by a spinal mechanism. Anesthesiol. 88:1519-23.
11. Liu S, Angel JM, Owens BD, Carpenter RL, Isabel L. Effects of epidural bupivacaine after thoracotomy. Reg Anesth Pain Med. 1995 Jul 1;20(4):303-10.
12. Neustein SM, Kreitzer JM, Krellenstein D, Reich DL, Rapaport E, Cohen E. Pre-emptive epidural analgesia for thoracic surgery. Mt Sinai J Med. 2002 Jan-Mar;69(1-2):101-4.
13. Anand LK, Sarna R, Mitra S. A comparison of 0.1% ropivacaine and 0.1% bupivacaine plus fentanyl with patient-controlled epidural analgesia for labor: a double blind study. Anaesth Pain Intensive Care. 20(3):278-84.
14. Dony P, Dewinde V, Vanderick B, Cuignet O, Gautier P, Legrand E, et al. The comparative toxicity of ropivacaine and bupivacaine at equipotent doses in rats. Anesth Analg. 2000;91(6):1489-92.
15. Yegin A, Erdogan A, Kayacan N, Karsli B. Early postoperative pain management after thoracic

surgery; pre- and postoperative versus postoperative epidural analgesia: a randomised study. Eur J Cardio-Thoracic Surg. 2003;24(3):420-4.

16. Amr YM, Yousef AAA-M, Alzeftawy AE, Messbah WI, Saber AM. Effect of Preincisional Epidural Fentanyl and Bupivacaine on Postthoracotomy Pain and Pulmonary Function. Ann Thorac Surg. 2010;89(2):381-5.

17. Aguilar JL, Rincón R, Domingo V, Espachs P, Preciado MJ, Vidal F. Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery. Br J Anaesth. 1996;76(1):72-6.

18. Atashkhoyi S, Jafari Shobeiri M, Azari Kalejahi A, Hatami Marandi P. A comparison of pre-emptive with preventive epidural analgesia in the patients undergoing major gynecologic surgery. African J Pharm Pharmacol. 2013;7(6):245-9.

19. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesthesia and analgesia. 2005; 101(5):1343-8.

20. Curatolo M, Scaramozzino P, Venuti FS, Orlando A, Zbinden AM. Factors associated with hypotension and bradycardia after epidural blockade. Anesth Analg. 1996 Nov;83(5):1033-40.