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Low-dose oral pregabalin is not effective enough to control the acute post-thoracotomy pain

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ABSTRACT

Background: Acute post-thoracotomy pain (APTP) is severe and can lead to various respiratory complications if left untreated. Epidural (Ep) analgesia is the gold standard for APTP relief. **Aims and Objectives:** The aims and objectives of this study were to study the impact of low-dose oral pregabalin 75 mg on APTP. **Materials and Methods:** 100 patients were randomized into two groups (Group P and C). The Group P, study group received pregabalin 75 mg per oral preoperatively and for 2 days postoperatively. Group C received no medication. All the patients received thoracic Ep as a standard practice. Postoperatively Visual Analog Scale (VAS), modified Ramsay sedation scoring (RSS), number of Ep top-ups, and adverse effects were noted. **Results:** The age and gender of the patients in both the groups were comparable. No statistically significant difference was found between Group P versus Group C with regard to VAS score, RSS, number of Ep top-ups, and any adverse effects. VAS between the groups at 4 h, 36 h, and 48 h postoperatively were statistically significant differences ($P<0.05$). VAS score at 48 h was not statistically significant ($P>0.05$). Ep analgesia was sufficient in both the groups and no patient in either group required intravenous fentanyl as rescue analgesia. No adverse effects were reported in any groups ($P>0.05$). **Conclusion:** Oral Pregabalin 75 mg did not reduce the severity of acute postoperative pain after thoracotomy. Study with higher doses of pregabalin needs to be carried out to evaluate the benefits of pregabalin on APTP.

Key words: Post-thoracotomy pain; Pregabalin; Epidural analgesia; Visual analogue scale; Ramsay sedation scoring

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INTRODUCTION

Post thoracotomy pain is very severe and is often associated with severe respiratory complications such as atelectasis, and subsequent retention of respiratory secretions which can cause severe pneumonia if not optimally controlled.[1-3] Pain is also responsible for ineffective coughing and prevents deep breathing and patient's mobility. It also increases

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perioperative morbidity and may lead to chronic pain syndromes impairing patient quality of life.[4-6] Thoracic epidural analgesia (TEpA) is considered the gold standard for post-thoracotomy analgesia.[7] However, Ep analgesia increases the risk of spinal injury and the risk of bleeding in patients receiving antithrombotic therapy.[8-10] Long-term use of Ep catheters is not recommended because of the risk of spinal infection.[11] Therefore, the development of a safe pain management alternative to Ep analgesia which can be administered for extended periods is desirable. Pregabalin, a new class of oral therapeutic drug for neuropathic pain interacts with pre-synapses and would be anticipated to show an effect similar to Ep analgesia.[12-16] It has been reported that pregabalin is effective against post-thoracotomy pain[17-19] and has been in application for various types of pain, mainly for post-herpetic neuralgia.[20-22] Although limited evidence supports its analgesic efficacy for acute postoperative pain, it theoretically may reduce such pain.[22] Therefore, we evaluated the analgesic effects of perioperative oral pregabalin on acute post-thoracotomy pain.

Aims and objectives

This study aims to evaluate the efficacy and safety of low-dose oral pregabalin (75 mg) compared to standard treatment in reducing the incidence and severity of acute post-thoracotomy pain. By analyzing pain intensity, analgesic requirements, and potential side effects, the study seeks to determine whether low dose oral pregabalin offers a superior or equivalent alternative for post-thoracotomy pain management while maintaining an acceptable safety profile.

MATERIALS AND METHODS

This prospective, randomized study was conducted at a tertiary care referral and University teaching hospital for 2 years in the Division of Cardiovascular and Thoracic Anesthesia and Intensive Care of the Department of Anesthesiology and Critical Care. Patients with the physical status American Society of Anesthesiologist (ASA) I, II, and III of either sex in the age group of 20–60 years, admitted for elective unilateral posterolateral thoracotomy were included in the study. All the patients were informed about the purpose of the study and written informed consent was obtained from them after seeking approval from the Institutional Ethics Committee.

Patients who refused consent to participate in the study and those who were ASA IV, anticipated to need elective ventilation, hemodynamically unstable patients, undergoing bilateral thoracotomy and total pleurectomy, previous ipsilateral thoracotomy or chronic pain from any cause, conduction disturbances such as congenital heart block, atrioventricular blocks, hepatic and renal impairment, pregnancy, allergic to the drug used in the study, dementia or similar cerebral condition that makes the subject unable to interpret pain score, anticonvulsants, anti-depressants, or chronic analgesic use, alcohol and/or drug abuse, were excluded from the study. All the patients enrolled were reliable, cooperative, and mentally capable of adhering to the study protocol and agreed to provide the relevant study information for the whole study period. At the preoperative visit, patients were instructed about the evaluation of pain using 11 points Visual Analog Scale (VAS) of 0–10 cm. (0 cm=no pain, and 10 cm=the worst pain) and the target pain scoring as per VAS was ≤3.

All patients were clinically evaluated, assessed, and investigated a day before surgery. The patients were kept fasting as per the institutional protocol for a period of 6 h.

A total of 110 patients were selected for the study initially out of which 10 were excluded due to their refusal to consent and further participation in the study. The remaining 100 patients were randomized into two groups of 50 each (study group, Group P and control group, Group C) using a computer-generated table of random numbers. Both groups received TEpA with 5 mL/h of 0.2% ropivacaine as a standard for perioperative pain management.

Group P (Pregabalin group) received 75 mg pregabalin capsule 2 h before induction of anesthesia and was continued every 24 h for the next two postoperative days. The study drug was administered by an anesthesiologist not involved in the study while as Group C (control group) patients received no drug and acted as a control for comparison (Figure 1).

On arrival at the operating room (OR), the patients were reassured and explained the anesthesia plan. An intravenous (IV) catheter (16 G) was secured on the dorsum of the left hand after prior local anesthetic infiltration using 1–2 mL of lidocaine 2% for delivery of fluids and drugs. Standard monitoring was established such as electrocardiogram (for perioperative heart rate [HR] and rhythm analysis), non-invasive blood pressure (BP), temperature (T) in degree centigrade, and pulse oximetry (SpO_2). The patients were kept in a sitting position and then under all aseptic precautions, an Ep catheter was placed through the midline thoracic approach according to the desired level for analgesia. The Ep space was identified by the loss of resistance to saline technique. Ep catheter was inserted and fixed at 5 cm inside the Ep space. A test dose of 3 mL of freshly prepared preservative-free lidocaine plus adrenaline (1:100,000) was given to rule out intravascular or intrathecal placement of the catheter which was covered under the sterile transparent dressing. The patient was then

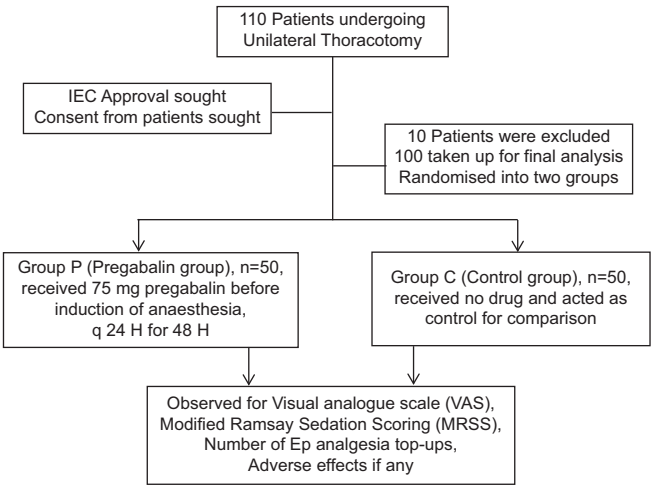

Figure 1: Consolidated standards of reporting trails diagram showing study design and methodology. EC: Institutional ethics committee, Ep: Epidural, H: Hours, n: Number of patients in a particular group, MRSS: Modified Ramsay sedation score

placed in a supine position with a pillow under the head for the administration of general anesthesia (GA). GA was administered using propofol after turning the patient to a supine position. Analgesia for the surgery was provided using 1.5 μg/kg of body weight (mcg/kg) of IV fentanyl, muscle relaxation for laryngoscopy and intubation was achieved with IV atracurium 0.5 μg/kg of body weight (mg/kg). Anesthesia was maintained with oxygen (50%) with compressed air and isoflurane with a minimum alveolar concentration of 1–1.5. Ep infusion of 0.2% ropivacaine was maintained at 5 mL/h for perioperative analgesia and was continued till the patient was shifted out of the OR. A muscle relaxant equal to 1/4th dose of atracurium used at induction was administered when required. Patients were given ondansetron hydrochloride 0.1 mg/kg to a maximum dose of 4 mg 15 min before the completion of surgery. HR, respiratory rate (RR), BP, end-tidal carbon dioxide, T, and digital co-oximetry (SpO_2) were recorded continuously till the end of the surgery and continued till in post-anesthesia care unit.

After the extubation, patients were interrogated for pain by the VAS scoring system at rest by an observer blinded to the study groups at 0 h (at extubation), thereafter at 4, 6, 12, 24, 36, and 48 h from extubation. In addition to VAS scoring at these intervals, HR, BP (systolic [SBP], diastolic [DBP] and mean arterial pressure], saturation (SpO_2), RR, Ramsay sedation score, incidence of postoperative nausea and vomiting or any other side effect (dizziness, somnolence, confusion, dry mouth, etc) and analgesic-sparing effect of pregabalin were noted. The time to first rescue analgesic was recorded for both the groups and the total consumption of rescue analgesics for the first 48 h was calculated.

In case of breakthrough pain (VAS ≥4) a top-of-rescue Ep injection of ropivacaine 0.2%–4 mL in 2 mL increments was given and a response was noted. In case of persistent pain, IV Fentanyl 0.5 mcg/kg was offered in addition and noted. This combination of Ep ropivacaine and IV fentanyl was repeated every 2 h in case of persistant breakthrough pains, i.e., VAS ≥4. The total number of rescue analgesics in 48 h post-extubation was recorded for both the groups.

RESULTS

The age in years, gender, and ASA physical status of the patients in both groups were comparable. The mean age of patients in Group P was 38.54 years and in Group C was 37.40 years (P=0.516) with an age range of 20–60 years. In Group P, 60% (n=30) patients were males and 40% (n=20) were female while in Group C, 62% (n=31) patients were male and 38% (n=19) were females (P=0.837). Patients included in the study belonged to ASA status I, II, and III. In Group P, 62% (n=31) patients belonged to ASA Class I, 38% (n=19) belonged to ASA Class II, and in Group C, 68% (n=34) patients belonged to ASA Class I, 28% (n=14) belonged to ASA Class II and 4.0% (n=2) patients belonged to ASA Class III with no statistical significance between the two groups (P=0.235). Similarly, no statistically significant difference was seen in comparing the preoperative vital parameters such as HR (P=0.942), SBP (P=0.163), DBP (P=0.057), and MAP (P=0.065), SpO_2 (P=0.175) and RR (P=0.448) between the two groups (Table 1).

Similarly, the postoperative HR (P=0.778), SBP (P=0.385), DBP (P=0.178) and MAP (P=0.246), SpO_2 (P=0.716), and RR (P=0.735) were also comparable between the two groups (Table 1).

With regard to pain assessment, the overall comparison between the two groups was statistically insignificant (P=0.089). However, the pain scores (VAS) at 4h (P=0.047), 36 h (P=0.038), and 48 h (P=0.027) postoperatively, were the only time intervals when statistically significant difference was observed (P<0.05) (Table 2).

With regard to sedation scores (Ramsey sedation scale) between the two groups, the comparison between the group was not statistically significant (P=0.310) (Table 3).

With regard to number of Ep top-ups required postoperatively, one patient (2%) required one Ep top-up, 19 patients (38%) were given 2 Ep top-ups, 24 patients (48%) received 3 Ep top-ups and 6 patients (12%) received 4 Ep top-ups in group P as per their VAS Score while in group C, 18 patients (36%) received two, 25 patients (50%) received 3 and 7 patients (14%) received 4 Ep top-

Table 1: Clinical and demographic profile of the patients

Clinico-demographic parameters	Group P, n=50	Group C, n=50	P-value
Age in years, n (%)			
20	1, (2)	5 (10)	0.093
21–30	13 (26)	13 (26)	1.002
31–40	13 (26)	10 (20)	0.478
41–50	16 (32)	14 (28)	0.664
≥51	7 (14)	8 (16)	0.780
Mean±SD	38.54	37.40	-
Gender, n (%)			
Male	30 (60)	31 (62)	0.838
Female	20 (40)	19 (38)	0.844
Surgical procedure (posterolateral thoracotomy) side, n (%)			
Right	28 (56)	28 (56)	-
Left	22 (44)	22 (44)	-
ASA, n (%)			
1	31 (62)	34 (68)	0.531
2	19 (38)	14 (28)	0.290
3	0	2 (4)	0.494
Preoperative clinical parameters, mean±SD			
HR	89.4±9.61	89.6±9.55	0.942
SBP	123.4±11.01	126.6±12.02	0.163
DBP	80.1±8.016	82.9±6.32	0.057
MAP	94.35±8.73	97.44±7.82	0.065
SpO_2	96.300±1.21	96.620±1.12	0.175
RR	20.74±2.38	21.08±2.06	0.448
Postoperative clinical parameters, mean±SD			
HR	89.03±4.79	88.74±5.55	0.778
SBP	119.26±6.19	120.47±7.51	0.385
DBP	76.02±6.22	77.68±5.82	0.178
MAP	90.45±6.02	91.8±6.22	0.246
SpO_2	96.14±0.92	96.21±0.91	0.716
RR	19.82±1.06	19.37±1.00	0.735

n: Number of patients in a particular group, %: Percentage, SD: Standard deviation, ASA: American society of anaesthesiology physical status, HR: Heart rate beats per minute, SABP: Systolic arterial blood pressure in mmHg, DABP: Diastolic arterial blood pressure in mmHg, SpO_2: Oxygen saturation, RR: Respiratory rate breaths per minute

Table 2: Over all pain score and its temporal trend

Post-operative pain severity	Time	Group P, n=50	Group C, n=50	P-value
Temporal trend of pain severity, VAS (Mean±SD)	0 h	0.18±0.038	0.10±0.030	0.253
	4 h	3.60±0.92	4.02±1.15	0.047
	6 h	3.70±0.95	3.62±1.02	0.687
	12 h	3.26±0.87	3.46±1.05	0.305
	24 h	3.62±0.90	3.90±0.90	0.125
	36 h	2.44±0.67	2.94±0.71	0.038
	48 h	2.14±0.49	2.42±0.73	0.027

n: number of patients in a particular group, SD: Standard deviation, VAS: Visual analogue scale, h: Time in hours

ups, respectively. A total of 135 and 139 Ep top-ups were given in Group P and Group C, respectively (P=0.236). Ep analgesia was sufficient in both the groups and no patient in either group required IV fentanyl as rescue analgesia (Table 3).

With regard to adverse effects, three patients (6%) in group P reported dizziness, but it was statistically insignificant when compared with group C (P=0.080), whereas confusion, somnolence, diplopia and blurred vision was not reported in any patient. Two Patients (4%) in group P and 3 patients (6%) in group C complained of nausea and vomiting (P=0.648). Two patients (4%) in group P complained of dry mouth, on comparing with the other group, the result was statistically insignificant (P=0.494). There were no cardiovascular (bradycardia, hypotension or any other) or respiratory complications (respiratory distress or any other) in any of the groups (Table 4).

Table 3: Number of epidural top-up and modified ramsay sedation scale

Ep Top-up's and MRSS	Group P, n=50	Group C, n=50	P-value
Number of Ep top-up, n (%)			
1	1/50 (2)	0	1.002
2	19/50 (38)	18/50 (36)	0.836
3	24/50 (48)	25/50 (50)	0.842
4	6/50 (12)	7/50 (14)	0.507
MRSS			
Mean±SD	2.003±0.019	2.008±0.385	0.310

n: Number of patients in a particular group, %: Percentage, SD: Standard deviation, Ep: Epidural, MRSS: Modified Ramsay sedation score

DISCUSSION

Acute post thoracotomy pain is the most important factor for development of pulmonary complications.[1-7] Shallow breathing and impaired coughing resulting from thoracotomy pain are a major cause of atelectasis and retention of secretions, both of which can lead to hypoxemia, hypercapnia and respiratory failure, especially in patients with pre-existing lung disease. It has been demonstrated that poor analgesia is associated with increased admissions and longer stays in intensive care unit and hospital overall.[7] Nociceptive transmission in thoracotomy pain is via C and Aδ fibres and can be considered in three discrete routes. Intercostal nerves carry impulses from the skin and intercostal muscles. Stimuli from the lung and mediastinum are carried by the vagus nerve. The visceral pleura is relatively insensitive, except to stretch. Parietal pleura, which is highly sensitive to noxious stimuli, receives innervation from intercostal and phrenic nerves. In addition, latissimus dorsi and serratus anterior are supplied by the thoracodorsal and long thoracic nerves, respectively. These arise from roots C5-C7 via the brachial plexus. Thoracotomy for lung resection usually involves a skin incision at the 5th Intercostal space, a variable degree of muscle cutting, and either excision or division of a rib. A posterolateral thoracotomy incision usually traverses around six dermatomal levels, starting at the 3rd thoracic

Table 4: Postoperative adverse effects

Post-operative adverse effects	Group P, n=50	Group C, n=50	P-value
CNS			
Dizziness, n (%)	3/50 (6)	0	0.080
GIT			
Nausea/vomiting, n (%)	2/50 (4)	3/50 (6)	0.648
Dry mouth, n (%)	2/50 (4)	0	0.494
CVS			
None, n (%)	0	0	-
Respiratory			
None, n (%)	0	0	-

n: number of patients in a particular group, %: Percentage, CNS: Central nervous system, GIT: Gastrointestinal tract, CVS: Cardiovascular system

dermatome posteriorly and extending to the 7th or 8th thoracic dermatome anteriorly. The chest wall muscles involved are latissimus dorsi, serratus anterior, pectoralis major, and the intercostal muscles.[23,24] Two or more chest drains may be inserted after thoracotomy in the 7th, 8th, or 9th Intercostal space which are may be outside the area covered by Ep analgesia and troubles the patients most. Furthermore, patients may well be extremely anxious after major thoracic surgery, exacerbating the perception of post-operative pain.[25] Analgesic approaches in thoracotomy pain include parenteral opioid infusion, intrathecal opioids, paravertebral block, intercostal nerve block, interpleural analgesia, erector spinae plane block, ryoprobe neurolysis, and balanced analgesic technique. Ep analgesia is considered gold standard for post-thoracotomy pain control but its bilateral effects on the sympathetic chain have been associated with increased rates of hypotension, itching, vomiting/nausea, urinary retention, and sometimes mental status changes and respiratory depression. Therefore, the development of a safe pain management alternative to epidural analgesia is desirable.

Pregabalin is a three-substituted derivative of the inhibitory neurotransmitter gamma amino butyric acid (GABA),[26] a potent gabapentinoid and a close structural analog of GABA that binds with high affinity to α2δ subunit-containing voltage-gated calcium channels and is a substrate of the system L-neutral amino acid transporter. Pregabalin modulates calcium influx at nerve terminals which may account for its therapeutic effect on neuropathic pain, anxiety, and seizures. It has been particularly used for neuropathic pain, such as diabetic neuropathy, post-herpetic neuralgia, complex regional pain syndrome,and certain other types of chronic pain. Sedative side effects are claimed to be less prominent, but poor concentration, rashes, and allergic reactions have been complained about. It possesses analgesic, anticonvulsant, and anxiolytic activities. Pregabalin increases the density of GABA transporter proteins and increases the rate of functional GABA transport. Pregabalin is 2–4 times more potent analgesic than gabapentin with 6 times more binding affinity.[27] It is rapidly absorbed when administered on an empty stomach, with peak plasma concentrations occurring within 1 h. Its oral bioavailability is estimated to be ≥90% and is independent of dose and is eliminated from the systemic circulation primarily by renal excretion as an unchanged drug.[28,29] Renal clearance of pregabalin is 73 mL/min.[30] It is generally well tolerated and associated with transient mild-to-moderate adverse effects which are dose-dependent. Dizziness and somnolence are most frequently reported (22–29%). Other less common adverse effects are dry mouth, peripheral edema, blurred vision, weight gain, and inability to concentrate.[28-30]

Homma et al. suggested pregabalin (50 mg/day) had a significant preventive effect on postoperative neuropathic pain after thoracic surgery, without side effects.[31] Similarly Yoshimura et al.[32] and Matsutani et al.[33] observed the role of oral pregabalin 75 mg is effective in controlling post-operative pain after thoracotomy. Obuchi et al.[34] and Fawzi and El-Tohamy[35] reported the role of pregabalin 75 mg orally reduces the incidence of post-thoracotomy and hospital stay besides decreasing the consumption of concomitant use of nonsteroidal anti-inflammatory drugs and opioids, respectively.

However, in our population, pregabalin in doses of 75 mg orally is not enough to control such pain after thoracotomies mandating dose escalation for its optimal effect as seen in other studies.

Limitations of the study

The limitations of the study were small sample size, short follow-up, and assessed only a 75 mg dose of pregabalin, which may not be optimal for post-thoracotomy pain management, necessitating further study with higher doses and more participants for optimal effect.

CONCLUSIONS AND RECOMMENDATIONS

Oral pregabalin in a dose of 75 mg is not sufficient enough to reduce the severity of acute postoperative pain after posterolateral thoracotomy, hence mandating future studies with higher doses of pregabalin to establish or refute its role in the management of post-thoracotomy pain in our population.

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