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EFFICACY OF PREOPERATIVE PREGABALIN IN ACUTE POST-THORACOTOMY PAIN

EFIKASNOST PREOPERATIVNOG PREGABALINA KOD AKUTNOG BOLA NAKON TORAKOTOMIJE

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Abstract

Introduction. Acute post-thoracotomy pain remains a significant clinical challenge, potentially impairing recovery, increasing opioid consumption, and contributing to the development of chronic post-thoracotomy pain. Pregabalin is increasingly incorporated into multimodal perioperative analgesic protocols; however, the optimal timing of its administration remains uncertain. **Material and Methods.** This prospective, randomized, double-blind study included 40 patients undergoing elective thoracotomy for lung surgery. Patients were randomly allocated using a sealed-envelope method into two groups. Group A received pregabalin 150 mg orally the evening before surgery and 2 hours preoperatively. Group B received pregabalin 75 mg orally the evening before surgery and 2 hours preoperatively, followed by an additional 150 mg postoperative dose on the day of surgery. Postoperative pain intensity was assessed using the Numerical Rating Scale over 48 hours. Total opioid consumption, sedation scores, and adverse effects were also recorded. **Results.** Demographic and perioperative characteristics were comparable between groups. During the first 24 postoperative hours, pain scores and cumulative opioid consumption did not differ significantly. On postoperative day one, Group B demonstrated significantly lower pain scores at 36 hours ($p = 0.035$) and borderline statistical significance at 48 hours ($p = 0.061$). There were no statistically significant differences in total opioid requirements, sedation scores, or incidence of adverse effects between groups. **Conclusion.** Perioperative pregabalin administration including an additional postoperative dose provides superior analgesia during the first postoperative day compared with preoperative administration alone, without increasing opioid consumption or sedation. These findings suggest that dosing timing plays an important role in optimizing acute post-thoracotomy pain management.

Key words: Thoracotomy; Pregabalin; Analgesics; Postoperative Pain; Acute Pain; Pain Measurement; Perioperative Care

Sažetak

Uvod. Akutni posttorakotomijski bol predstavlja značajan klinički problem, koji može usporiti postoperativni oporavak, povećati potrošnju opioida i doprineti razvoju hroničnog bola. Pregabalin se sve češće primenjuje kao deo multimodalne perioperativne analgezije, ali optimalno vreme njegove primene još uvek nije jasno definisano. **Materijal i metode.** Ova prospektivna, dvostruko slepa studija obuhvatila je 40 pacijenata podvrgnutih elektivnoj torakotomiji zbog hirurškog lečenja plućnih oboljenja. Pacijenti su naizmenično raspoređivani u dve grupe. Grupa A je primala pregabalin u dozi od 150 mg per os veče pre operacije i dva sata pre operacije. Grupa B je primala pregabalin u dozi od 75 mg u istim vremenskim intervalima, uz dodatnu postoperativnu dozu od 150 mg na dan operacije. Intenzitet postoperativnog bola procenjivan je *Numeričkom skalom bola* tokom 48 sati. Takođe su praćeni potrošnja opioida, stepen sedacije i pojava neželjenih efekata. **Rezultati.** Nije uočena statistički značajna razlika između grupa u pogledu demografskih i perioperativnih karakteristika. Tokom prva 24 sata nakon operacije, vrednosti skora bola i kumulativna potrošnja opioida bile su uporedive. Tokom prvog postoperativnog dana, pacijenti u grupi B imali su statistički značajno niži skor bola u 36. satu ($p = 0,035$), kao i granično statistički značajnu razliku u 48. satu ($p = 0,061$). Potrošnja opioida, stepen sedacije i učestalost neželjenih efekata nisu se razlikovali između grupa. **Zaključak.** Perioperativna primena pregabalina uz dodatnu postoperativnu dozu obezbeđuje bolju analgeziju tokom prvog postoperativnog dana u poređenju sa isključivo preoperativnom primenom, bez povećanja potrošnje opioida ili sedacije, što ukazuje na značaj vremena primene u lečenju akutnog posttorakotomijskog bola.

Ključne reči: torakotomija; pregabalin; analgetici; postoperativni bol; akutni bol; procena bola; perioperativna nega

Introduction

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is inherently subjective and multidimensional, influenced by physiological and psychological factors, as well as prior experiences, cultural background, fear, and anxiety. In a broader clinical context, "pain is everything the patient says it hurts" [1]. Effective perioperative analgesia and attenuation of the surgical stress response are essential for improving postoperative outcomes and accelerating recovery. Early control of postoperative pain

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Abbreviations

VAS – Visual Analogue Scale
CSF – cerebrospinal fluid
ASA – American Society of Anesthesiologists
BMI – body mass index
NSAIDs – non-steroidal anti-inflammatory drugs
NRS – numerical rating sscale
POSS – Pasero Opioid-Induced Sedation Scale

not only enhances patient comfort and confidence but also reduces the risk of central sensitization and wind-up phenomena [2]. Acute post-thoracotomy pain is multifactorial. Contributing factors include skin incision, soft tissue trauma, rib retraction, rib resection or fracture, costovertebral joint dislocation, and the intercostal nerve injury. Additional nociceptor activation results from pleural irritation caused by surgical manipulation, chest tube placement, and pleural effusion. Intercostal nerve injury is considered the principal mechanism, occurring either through direct mechanical trauma from rib retractors or rib resection, or indirectly through sustained traction leading to ischemic nerve damage. Pain may also arise from nerve entrapment within scar tissue or improper rib healing. Afferent sensory transmission from thoracic dermatomes (C3-T10) travels via the intercostal, vagal, and phrenic nerves [3]. Gabapentinoids are widely used for the management of neuropathic pain conditions, including postherpetic neuralgia and as adjunctive therapy in epilepsy. Pregabalinis additionally indicated for fibromyalgia and neuropathic pain associated with diabetes mellitus and spinal cord injury. Evidence from multiple clinical trials suggests that perioperative gabapentinoid administration may reduce early postoperative pain intensity and opioid consumption [4]. Gabapentinoids are structural analogues of γ-aminobutyric acid. By binding to the α-2δ subunit of presynaptic voltage-gated calcium channels, they reduce calcium influx and inhibit the release of excitatory neurotransmitters involved in nociceptive transmission, thereby attenuating central sensitization [5]. Additional antinociceptive effects may involve activation of descending noradrenergic inhibitory pathways within the brain and spinal cord [6].

Key pharmacokinetic differences between gabapentin and pregabalin primarily relate to bioavailability. Pregabalin is absorbed throughout the small intestine and exhibits linear pharmacokinetics without saturation at therapeutic concentrations, whereas gabapentin demonstrates dose-dependent absorption [7,8]. The elimination of half-life of gabapentin ranges from 4.8 to 8.7 hours, while pregabalin has a half-life of approximately 5.5 to 6.3 hours [5]. Both agents require dose adjustment in renal impairment [9,10]. Gabapentinoids are generally well tolerated. The most frequently reported adverse effects of pregabalin include dizziness, headache, sedation, visual disturbances, and peripheral edema [11,12]. Even in cases of overdose, management is typically supportive [13–15]. Reduced perioperative opioid requirements associated with gabapentin use may decrease the incidence of opioid-related adverse effects, including postoperative delirium and vomiting [11,16].

Patients who received gabapentin either prior to surgery or immediately after surgical incision demonstrated consistently lower Visual Analogue Scale (VAS) pain scores at all assessed time points and required less fentanyl compared with placebo [17,18]. Regarding Pregabalin, its efficacy in combination with ibuprofen was evaluated in patients undergoing third molar extraction. Participants were divided in groups: placebo, pregabalin 75 mg and pregabalin 150 mg. Pain intensity was assessed for six postoperative days, and patients premedicated with 150 mg pregabalin reported significantly lower numerical pain scores compared with other groups [19]. Similarly, a study compared preoperative gabapentin alone versus combined preoperative and postoperative gabapentin administration in patients undergoing total knee arthroplasty found that those receiving postoperative gabapentin consumed less morphine via patient-controlled analgesia at 24, 36, and 48 hours. In addition, they demonstrated improved active knee flexion on the second and third postoperative days compared with patients who received only preoperative gabapentin [20]. Moreover, a Cochrane review that included data from four unpublished trials concluded that gabapentin is effective in the treatment of established acute postoperative pain, even when administered exclusively after surgery [21].

Pharmacokinetic data indicate that peak plasma concentrations occur approximately 2 hours after gabapentin administration and 1 hour after pregabalin administration. However, peak cerebrospinal fluid (CSF) concentrations may occur considerably later. For pregabalin, CSF peak levels have been reported up to 8 hours post-administration, suggesting that earlier dosing may enhance pre-emptive analgesic effects [22].

Several investigations have attempted to determine the optimal perioperative dosing of gabapentinoids. For both gabapentin and pregabalin, lower doses have generally been associated with insufficient analgesic efficacy [23]. Although gabapentinoids are included in recommended Prospect Working Group, clear guidance regarding optimal dosing strategies and the need for repeated preoperative administration remains lacking [24]. Furthermore, two studies demonstrated that pregabalin at a dose of 150 mg – but not 75 mg – was superior to placebo in reducing postoperative opioid consumption or pain intensity [25,26].

With respect to drug selection, definitive conclusions regarding the comparative efficacy of gabapentin and pregabalin in the management of acute postoperative pain remain limited due to insufficient and inconclusive evidence [27]. Although both agents have been investigated in thoracic surgery, no study to date has directly compared two gabapentinoids in this setting [28,29]. Pharmacokinetic considerations may further influence clinical effectiveness. Pregabalin reaches peak cerebrospinal fluid concentrations approximately eight hours after administration, whereas gabapentin requires approximately 4–6 hours to achieve similar levels. Therefore, administration the evening before surgery may theoretically provide greater pre-emptive analgesic benefit than dosing two hours preoperatively. However, earlier initiation may also increase the risk of dose-related adverse effects, including dizziness, sedation, and confusion [30].

Accordingly, the present study was designed to determine whether preoperative administration of pregabalin (150 mg 12 hours before surgery) or a perioperative regiment (75 mg 12 hours before surgery and 150 mg postoperatively) provides superior control of acute post-thoracotomy pain.

Material and Methods

This prospective, double-blind study included patients undergoing elective thoracotomy at the Clinic for Chest Surgery of the Institute of Pulmonary Diseases of Vojvodina in Sremska Kamenica. The study protocol was approved by the institutional Ethics Committee and Expert Council. Inclusion criteria: age ≥ 18 years, elective thoracotomy for lung disease, American Society of Anesthesiologists (ASA) physical status I-III. Exclusion criteria: known hypersensitivity to pregabalin, pre-existing acute or chronic, age > 70 years, body mass index (BMI) > 30 kg/m^2, neurological diseases, use of calcium channel blockers, analgesics, anxiolytics, sedatives, or antidepressants, and opioid or alcohol dependence.

Between January and June 2024, 52 eligible patients were screened. Two declined participation, and ten were excluded due to conversion of surgery to mediastinoscopy for advanced malignant disease. A total of 40 patients were enrolled.

Patients provided written informed consent after receiving detailed oral and written explanations regarding the study objectives, preoperative medication, and anesthetic management. Patients were alternately allocated, according to admission order, into two groups: Group A: Pregabalin 150 mg orally the evening before surgery and 2 hours preoperatively, and Group B: Pregabalin 75 mg orally the evening before surgery and 2 hours preoperatively, followed by 150 mg on postoperative day 0.

Premedication consisted of atropine 0.5 mg. General balanced anesthesia was induced and maintained with propofol, fentanyl, rocuronium and sevoflurane. Patients were intubated using a double-lumen tube. Mechanical ventilation was provided with a mixture of air and oxygen. Standard ASA monitoring was applied in all cases. Hemodynamic parameters were maintained within ± 30% of baseline values. Morphine was administered intravenously at a dose of 0.2 mg/kg approximately one hour before emergence from anesthesia.

Postoperative analgesia included morphine 0.1 mg/kg every 6 hours and Ketorolac 30 mg every 8 hours. For breakthrough pain (VAS > 5), patients received paracetamol 1 g IV, and if inadequate response persisted, morphine 2 mg IV every 10 minutes until analgesia was achieved.

Postoperative pain intensity was assessed using the Numerical Rating Scale (NRS) at 1, 4, 8, 12, 16, 20, and 24 hours postoperatively, and every 6 hours during the second 24-hour period. Cumulative opioid consumption was recorded. Sedation was evaluated using the Pasero Opioid-Induced Sedation Scale (POSS). Adverse effects monitored included nausea, vomiting, dizziness, headache, urinary retention, and visual disturbances.

Descriptive statistics included the mean, standard deviation, and relative frequencies. Inferential analysis was performed using the independent samples t-test, Mann-Whitney U test, or χ^2 test, depending on data type and distribution. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics are presented in **Table 1**. Group A included 20 patients with a mean age of 59.00 ± 7.77 years, while group B included 20 patients with a mean age of 60.70 ± 10.19 years (p = 0.557). The mean body weight was 75.30 ± 11.74 kg in Group A 75.05 ± 10.71 kg in Group B, with no statistically significant difference between groups (p = 0.944).

No statistically significant differences were observed between groups regarding sex distribution (p = 0.752), ASA physical status (p = 1.00), side of thoracotomy (p = 0.091), or type of surgical procedure (p = 0.857). Intraoperative fentanyl and morphine requirements were compatible between groups **(Table 2).** There were no statistically significant differences in cumulative morphine or paracetamol consumption during the first 48 postoperative hours. Analysis of NRS pain scores during the zero postoperative day **(Table 3)** demonstrated no statistically significant difference between groups at any measured time point. Similarly, no statistically sig-

Table 1. Patient characteristics by group

	Group				p value
	A (N=20)		B (N=20)		
	N	%	N	%	
Sex (male/female)	11/9	55/45	10/10	50/50	0.752
ASA I	1	5	1	5	
ASA II	15	75	15	75	1.00
ASA III	4	20	4	20	
Thoracotomy (right/left)	16/4	80/20	11/9	55/45	0.091
Type of operation					
Atypical resection of upper lung lobe	5	25	5	25	
Atypical resection of lower lung lobe	1	5	1	5	
Upper lung lobectomy	7	35	6	30	0.857
Lower lung lobectomy	2	10	4	20	
Lower lung bilobectomy	3	15	1	5	
Pneumonectomy	2	10	3	15	

Table 2. Fentanyl and Morphine administered during surgery

	Group	N	Mean value	Standard deviation	p value
Fentanyl (mcg)	A	20	373.7500	108.05548	0.763
	B	20	362.5000	125.52521	
Fentanyl (mcg/kg)	A	20	5.0490	1.51833	0.671
	B	20	4.8350	1.63588	
Morphine (mg)	A	20	6.9500	2.21181	0.227
	B	20	6.0500	2.41650	
Morphine (mg/kg)	A	20	0.1277	0.14987	0.170
	B	20	0.0799	0.03038	

Table 3. NRS scale mean values on postoperative day 0

	Group								p value
	A				B				
	Mean value	Minimum	Maximum	SD	Mean value	Minimum	Maximum	SD	
NRS 0 h	2.50	0.00	7.00	1.54	3.55	0.00	9.00	2.58	0.127
NRS 1 h	3.85	0.00	8.00	2.32	4.90	0.00	9.00	2.10	0.142
NRS 4 h	3.85	0.00	8.00	1.90	3.35	1.00	6.00	1.23	0.329
NRS 8 h	3.00	0.00	6.00	1.41	2.75	0.00	6.00	1.48	0.588
NRS12 h	2.75	0.00	7.00	1.48	2.35	0.00	4.00	1.18	0.351
NRS16 h	2.20	0.00	5.00	1.20	2.15	0.00	6.00	1.39	0.903
NRS20 h	2.35	0.00	6.00	1.50	1.60	0.00	5.00	1.43	0.113
NRS24 h	2.50	0.00	5.00	1.43	2.25	0.00	6.00	1.55	0.600

Table 4. Differences in the sedation scale mean values between groups during postoperative day 0

	Group								p value
	A				B				
	Mean value	Minimum	Maximum	SD	Mean value	Minimum	Maximum	SD	
POSS 1 h	1.55	0.00	3.00	0.94	1.60	0.00	3.00	0.68	0.884
POSS 4 h	1.25	0.00	3.00	0.97	1.15	0.00	2.00	0.75	0.808
POSS 8 h	1.00	0.00	3.00	0.92	.75	0.00	2.00	0.72	0.418
POSS 12 h	095	0.00	3.00	0.89	0.70	0.00	2.00	0.73	0.391
POSS 16 h	0.90	0.00	3.00	0.79	0.70	0.00	2.00	0.66	0.453
POSS 20 h	0.40	0.00	2.00	0.60	0.25	0.00	2.00	0.55	0.323
POSS 24 h	0.10	0.00	1.00	0.31	0.20	0.00	2.00	0.52	0.604

Table 5. Differences in the NRS scale average values between the groups during postoperative day 1

	Group								p
	A				B				
	Mean value	Minimum	Maximum	Standard deviation	Mean value	Minimum	Maximum	Standard deviation	
NRS 30 h	2.70	0.00	6.00	1.45	1.95	0.00	4.00	1.32	0.096
NRS 36 h	2.15	0.00	5.00	1.23	1.35	0.00	3.00	1.09	0.035
NRS 42 h	2.05	0.00	5.00	1.28	1.50	0.00	4.00	1.15	0.160
NRS 48 h	1.60	0.00	4.00	1.05	1.00	0.00	3.00	0.92	0.061

nificant differences were observed in sedation scores during the same period **(Table 4)**. With regard to adverse effects (nausea, dizziness, postoperative headache, urine retention, blurred vision), only one patient in each group reported dizziness. On the first postoperative day (**Table 5),** Group B demonstrated lower mean NRS scores compared with Group A at 36 hours (p = 0.035), which was statistically significant. At 48 hours, pain scores were also lower in Group B, reaching borderline statistical significance (p = 0.061).

Discussion

Pregabalin has previously been evaluated in thoracic surgery. Studies have shown that pregabalin 75 mg twice daily significantly enhances the analgesic efficacy of self-administered NSAIDs compared with multimodal continuous epidural analgesia in acute post-thoracotomy pain. Additionally, postoperative administration of 150 mg pregabalin combined with continuous epidural analgesia significantly reduced post-thoracotomy shoulder pain [31,32]. The present study aimed to determine whether preoperative administration alone (150 mg before surgery) or a perioperative regimen (75 mg before and after surgery) provides superior control of acute post-thoracotomy pain. Our findings indicate that continuation of pregabalin 75 mg with a single postoperative dose resulted in significantly better analgesia on the first postoperative day, without increasing opioid consumption or sedation.

Hill et al. reported that pregabalin 300 mg following dental surgery prolonged analgesia but was associated with a higher incidence of adverse events [33]. Even lower doses, such as 100 mg, have been associated with clinically significant dizziness and sedation in outpatient settings [34]. For this reason, considering concomitant postoperative morphine use – which shares a similar adverse-effect profile – this study evaluated lower pregabalin doses (75 mg and 150 mg) to balance efficacy and safety.

Gabapentin has been more extensively studied in acute postoperative pain and has consistently demonstrated reductions in pain intensity, opioid consumption, and opioid-related adverse effects [35]. In contrast, evidence regarding pregabalin remains inconsistent, likely due to heterogeneity in dosing regimens, timing of administration, surgical procedures, and multimodal analgesic protocols [36].

Some studies have shown no significant benefit from a single 100 mg preoperative pregabalin dose in minor gynecological surgery, with increased adverse effects observed within 24 hours [37]. White et al. demonstrated that pregabalin doses ranging from 75 mg to 300 mg did not reduce either preoperative anxiety or postoperative pain [38]. Other investigations demonstrated that doses between 150-300 mg significantly reduced postoperative pain and opioid consumption following total joint arthroplasty, with improved mobility by the third postoperative day, and acceptable safety profile and tolerability [39]. Similarly, a multimodal analgesic regimen consisting of pregabalin and diclofenac has been shown to reduce both resting pain intensity and pain on movement following hysterectomy. Comparative evaluation of different pregabalin dosages (75 mg, 150 mg, and 300 mg) and their associated adverse effects suggests that pre-emptive oral administration of 150 mg pregabalin provides the most favorable analgesic profile with least side effects [40]. A similar regimen has also demonstrated reductions in morphine consumption and postoperative pain following laparoscopic sleeve gastrectomy [41].

The present study specifically evaluated the timing and potential pre-emptive effect of pregabalin in thoracotomy. Given its half-life of approximately 6.5 hours, a single preoperative dose would be expected to cover the peak postoperative pain [42]. Any sustained analgesic benefit beyond this window might suggest a pre-emptive mechanism. However, in the present study, preoperative pregabalin alone did not improve analgesia nor prolong its duration, thereby questioning the clinical relevance of a purely pre-emptive strategy in post-thoracotomy pain. Statistically significant differences in pain intensity were observed only on the first postoperative day, with lower pain scores in the group that received an additional postoperative dos-

This study has several potential limitations. First, the administered pregabalin dose may have been insufficient to achieve a stronger analgesic effect. Nevertheless, doses below 300 mg have demonstrated efficacy in other surgical settings [11]. Evidence indicates that preoperative administration of 150 mg pregabalin improves analgesia following procedures such as mastectomy. Importantly, lower doses may reduce the incidence of adverse effects, particularly sedation, which is of special concern in thoracic surgery due to the potential risk of postoperative pulmonary complications [43]. Therefore, investigating lower pregabalin doses for acute post-thoracotomy pain management represents a clinically justified approach.

Second, the study was conducted with a multimodal analgesic framework. The concomitant use of opioid analgesics may have masked early differences between groups during the first 24 postoperative hours and potentially increased the risk of additive adverse effects. A plausible explanation to this effect is that analgesic effects of intraoperative opioids diminished after 24 hours, whereas the maintained pregabalin concentration in Group B contributed to improved analgesia at 36 hours and beyond. Future studies incorporating epidural analgesia – the gold standard for thoracotomy pain management – may yield more definitive conclusions.

Third, a relatively small sample size likely contributed to the borderline statistical significance observed across the entire first postoperative day. Larger randomized trials are required to confirm these findings. Additionally, long-term outcomes, including the development of post-thoracotomy pain syndrome, were not assessed. Further research should explore whether sustained perioperative pregabalin administration influences chronic pain development. Finally, contemporary literature distinguished between pre-emptive analgesia – aimed to prevent central sensitization before surgical incision – and preventive analgesia, which emphasizes maintaining effective perioperative drug concentration. The findings of this study suggest that maintaining stable pregabalin plasma levels (Group B) may be more clinically relevant than achieving a high preoperative peak concentration alone (Group A).

Conclusion

Preoperative administration of pregabalin 75 mg (first dose in the evening and second dose 2 hours before surgery), followed by a single 150 mg postoperatively, provided superior analgesia on the first postoperative day compared with a regimen of 150 mg pregabalin administered exclusively preoperatively (evening and 2 hours before surgery). However, opioid consumption and the degree of sedation were comparable between the two groups. These findings support the use of the combined pre- and postoperative pregabalin regimen for the management of post-thoracotomy pain.

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