Open Access Maced J Med Sci **electronic publication ahead of print,**
published on June 30, 2019 as https://doi.org/10.3889/oamjms.2019.556

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.556
eISSN: 1857-9655
Clinical Science

Role of Perioperative Pregabalin in the Management of Acute and Chronic Post-Thoracotomy Pain

Sara Gaber[1*], Emad Saleh[2], Somaya Elshaikh[2], Rafaat Reyad[2], Mohamed Elramly[2], Ismail Mourad[2], Mohamed Abdel Fattah[2]

[1]National Heart Institute, Cairo, Egypt; [2]National Cancer Institute, Cairo University, Cairo, Egypt

Citation: Gaber S, Saleh E, Elshaikh S, Reyad R, Elramly M, Mourad I, Fattah MA. Role of Perioperative Pregabalin in the Management of Acute and Chronic Post-Thoracotomy Pain. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.556

Keywords: Pregabalin; Post-thoracotomy pain syndrome; Thoracic tumour; Neuropathic pain; Thoracotomy

***Correspondence:** Sara Gaber. National Heart Institute, Cairo, Egypt. E-mail: sara.gaber@hotmail.co.uk

Received: 14-Apr-2019; **Revised:** 19-Jun-2019; **Accepted:** 20-Jun-2019; **Online first:** 30-Jun-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Post-thoracotomy pain syndrome (PTPS) can be challenging to treat.

AIM: This study aimed to evaluate the efficacy of perioperative pregabalin in the prevention of acute and chronic post-thoracotomy pain.

METHODS: Sixty patients scheduled for thoracotomy for oncologic surgeries were randomly allocated to one of two groups; Pregabalin and Control. In the Pregabalin group, pregabalin 150 mg was administered one hour before thoracotomy and 12 hours later, then every 12 hours for five days. Pain intensity was assessed using the Visual Analogue Scale (VAS) at rest (VAS-R) and dynamic (VAS-D) in the ICU and during the next four days. Morphine consumption and the frequency of side effects were recorded. Assessment of PTPS was done using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale at 1, 2, and 3 months.

RESULTS: The VAS-R and VAS-D scores and the total morphine consumption were significantly lower in Pregabalin group during days 0 through 4. Neuropathic pain, allodynia, and hyperalgesia were significantly lower in Pregabalin group after 1, 2, and 3 months.

CONCLUSION: Pregabalin is effective in the reduction of chronic neuropathic pain at 1, 2, and 3 months after thoracotomy and it also reduces pain and opioid consumption during the acute postoperative period with few adverse effects.

Introduction

Thoracotomy is recognised as one of the most painful surgical procedures [1]. Studies have shown that high levels of acute postoperative pain are associated with an increase in the likelihood of chronic pain [2]. The severity of acute postoperative pain has been linked to the development of persistent postoperative pain [3].

Post-thoracotomy pain syndrome (PTPS) is a common condition; its prevalence has been reported to reach 80% [4]. It is defined as pain that recurs or persists along a thoracotomy scar at least two months after the surgical procedure [5].

In general, postoperative pain after thoracotomy is burning and stabbing pain and shares many features of neuropathic pain [6]. It was found that tissue damage leads to sensitisation of dorsal horn neurons, which causes hyperalgesia or allodynia. This course may contribute to chronification of pain. Therefore, initiating analgesic treatment before tissue damage can reduce hyperexcitability of dorsal horn neurons and central sensitisation [7]. Hence, drugs that reduce postoperative hyperalgesia and control acute postoperative pain may be of clinical interest [8].

Pregabalin is one of these drugs that can reduce the excitability of the dorsal horn neurons. It is a γ-aminobutyric acid analogue that binds to α2-δ subunits of the voltage-gated calcium channels in the central nervous system [9]. It was first introduced as a potent anticonvulsant and anxiolytic drug [10]. Pregabalin is recommended as a first-line treatment for neuropathic pain conditions [11]. Because of its ability to block presynaptic voltage-gated calcium channels implicated in central sensitisation, perioperative use of pregabalin could be valuable in preventing the development of chronic pain [12], [13]. It has been successfully used perioperatively for controlling neuropathic pain during knee and laparoscopic surgery; therefore, similar positive results are expected for intercostal neuralgia in post-

thoracotomy pain [14].

The purpose of this study was to investigate the safety and efficacy of perioperative administration of pregabalin to control intercostal neuralgia after thoracotomy.

Patients and Methods

The study included 60 ASA physical status I and II patients between 25 and 60 years of age scheduled for elective open thoracotomy for thoracic oncologic surgeries. They were recruited from the National Cancer Institute, Cairo University from January 2017 to February 2018. The study was approved by the local ethical committee, and every patient provided an informed written consent to participate in the study.

Patients with renal insufficiency, history of congestive heart failure, major psychiatric disorder, body mass index > 40 kg/m², weight < 50 kg, pre-existing chronic pain in proposed surgical area or elsewhere requiring chronic analgesic use, hypersensitivity to opioids, tumors extending into chest wall, previous ipsilateral thoracotomy, chest tube in situ at time of surgery, patients on anticonvulsants, patients planned for postoperative ventilation, or those who cannot use patient-controlled analgesia (PCA) were excluded from the study.

Preoperatively patients were instructed how to use a visual analogue scale (VAS) (0 = no pain, 10 = worst pain) to express pain and use of the PCA device. Patients were randomly allocated to one of two equal groups. Pregabalin Group received pregabalin capsules, 150 mg (Lyrica, Pfizer, Egypt) while the Control group received placebo capsules (multivitamin capsules). A treatment schedule in the two groups was one capsule one hour before thoracotomy, 12 hours following operation (day zero postoperative), and then twice a day for 5 postoperative days.

All patients were premedicated with midazolam 0.05 mg/kg IV 30 minutes before the surgical procedure. A crystalloid IV infusion was established, and the baseline means arterial blood pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SO_2) were recorded. Anaesthesia was induced with fentanyl 2 µg/kg and propofol 2 mg/kg and atracurium 0.5 mg/kg IV and maintained with sevoflurane (2-3 vol%) and fresh gas flow rate of 2 L/min in combination with 50% oxygen/air. After endotracheal intubation, lungs were mechanically ventilated to maintain the end-expiratory CO_2 values between 32-36 mm Hg, then morphine 0.1 mg/kg was administered IV. With skin closure, the residual neuromuscular blockade was antagonised with IV neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. Ondansetron 4 mg IV was given to all patients.

Patients were then transferred to the intensive care unit (ICU) to start using the PCA device for 5 days (Accufuser PLUS M5015L WOO YOUNG MEDICAL CO.LTD, Korea). The PCA device contained a volume of 300 ml (60 mg morphine + 60 mg ketorolac + 2 mg Garnitryl). The basal rate was 5.0 ml/hr, and bolus 1.0 ml (0.2 mg) with a lockout interval of 15 min (limit of 1.8 mg/hr) and total opioid consumption were recorded. The pain was assessed using a VAS score at 0, and after 4, 8, 12, 16, 20, and 24 hours. The mean of VAS at rest (VAS-R) and during a cough or with movement or cough (dynamic) (VAS-D) were recorded. The occurrence of postoperative side effects (confusion, dizziness, headache, dry mouth, nausea, vomiting, and pruritus were recorded at follow up intervals.

Assessment of the incidence of chronic post-thoracotomy pain syndrome and pain quality (neuropathic versus other) using Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale was done at 1, 2, and 3 months postoperatively. Patients who suffered from symptoms of neuropathic pain, allodynia or hyperalgesia at first month received pregabalin 150 mg BID and were reassessed at 2nd and 3rd month. The LANSS pain scale consists of five items that document self-reported pain symptoms and two items that document the findings of a simple clinical examination conducted by the healthcare professional to assess the presence of allodynia and pin-prick threshold [15]. A LANSS score of 12 or more is an indication of chronic neuropathic pain; allodynia (assessed by gentle rubbing of the operated site by a piece of cotton) and hyperalgesia (gently applied pressure from the fingertip).

Statistical Analysis

Statistical Analysis was performed using SPSS 15.0 for Windows. Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, a comparison between two groups was made using independent sample t-test or Mann-Whitney test. A *p*-value of < 0.05 was accepted as statistically significant.

Results

Demographic data, duration of anaesthesia and surgery were comparable between groups (Table 1).

Table 1: Demographic data

Variables	Pregabalin (n = 30)	Control (n = 30)	p value
Age (years)	46.9 ± 10.1	41.0 ± 14.5	0.072
Weight (kg)	83.1 ± 9.9	77.1 ± 15.5	0.078
Height (cm)	176 ± 9	173 ± 11	0.246
Gender (M/F)	22/8	21/9	1.0
Duration of surgery (minutes)	188 ± 25	178 ± 10	0.066
Duration of anesthesia (minutes)	220 ± 28	211 ± 11	0.910
Type of surgery			
Lobectomy	9	3	0.117
Pneumonectomy	11	17	
Pleurectomy	10	10	

Data are expressed as mean ± SD (standard deviation), or number as appropriate; *P* value < 0.05 is considered significant; There were no statistical differences among groups.

VAS-R and VAS-D were significantly lower in Pregabalin group at 0, 6, 18 and 24 hours but were comparable between groups at 12 hours (Table 2).

Table 2: VAS-R and VAS-D. Data are expressed as mean ± SD

		Pregabalin (n = 30)	Control (n = 30)	*p* value
0 hour	VAS-R	2.9 ± 0.7	3.5 ± 1.0	0.022*
	VAS-D	6.0 ± 0.7	6.6 ± 1.0	0.016*
6 hours	VAS-R	3.3 ± 0.9	3.8 ± 0.7	0.042*
	VAS-D	4.4 ± 0.9	5.0 ± 0.7	0.023*
12 hours	VAS-R	2.6 ± 0.8	3.0 ± 0.9	0.125
	VAS-D	3.5 ± 0.8	3.9 ± 0.9	0.209
18 hours	VAS-R	2.1 ± 0.6	2.6 ± 0.8	0.022*
	VAS-D	3.3 ± 0.7	3.8 ± 0.9	0.020*
24 hours	VAS-R	1.6 ± 0.6	2.0 ± 0.6	0.037*
	VAS-D	3.1 ± 0.7	3.5 ± 0.8	0.039*

Data are expressed as mean ± SD (standard deviation); VAS-R = visual analogue score at rest; VAS-D = visual analogue score dynamic (during movement); * *P* value < 0.05 is considered significant.

The mean VAS-R and VAS-D during 24 hours on days 1, 2, 3 and 4 were significantly lower in Pregabalin group. There was no significant difference between groups in days 5 and 6 (Table 3).

Table 3: Mean of VAS-R and VAS-D during postoperative days 1, 2, 3, 4, 5 and 6

		Pregabalin (n = 30)	Control (n = 30)	*p* value
Day 1	VAS-R	2.1 ± 0.7	2.5 ± 0.6	0.047*
	VAS-D	4.1 ± 1.0	4.8 ± 0.8	0.014*
Day 2	VAS-R	2.0 ± 0.8	2.5 ± .8	0.031*
	VAS-D	3.1 ± 1.0	3.8 ± 0.8	0.021*
Day 3	VAS-R	1.4 ± 0.5	1.8 ± 0.6	0.027*
	VAS-D	2.5 ± 0.5	2.9 ± 0.7	0.043*
Day 4	VAS-R	2.4 ± 0.7	2.8 ± 0.8	0.022*
	VAS-D	3.3 ± 0.7	3.7 ± 0.8	0.029*
Day 5	VAS-R	2.8 ± 0.8	2.9 ± 0.8	0.981
	VAS-D	3.6 ± 0.8	3.8 ± 0.6	0.509
Day 6	VAS-R	1.8 ± 0.6	2.2 ± 1.1	0.163
	VAS-D	3.0 ± 0.8	3.5 ± 1.2	0.197

Data are expressed as mean ± SD (standard deviation); VAS-R = visual analogue score at rest; VAS-D = visual analogue score dynamic (during movement); * *P* value < 0.05 is considered significant.

Total morphine consumption during the postoperative period was significantly lower in Pregabalin group (Table 4).

Table 4: Total daily morphine consumption in (mg) with PCA device from day 0 to day 4 in the two studied groups

	Pregabalin (n=30)	Control (n=30)	*p* value
Day 1	34.8±2.2	35.9±1.3	0.028*
Day 2	30.9±2.7	32.3±2.2	0.033*
Day 3	28.3±2.2	29.6±2.0	0.022*
Day 4	26.4±2.0	27.5±1.9	0.035*

Data are expressed as mean ± SD (standard deviation); * *P* value < 0.05 is considered significant.

The frequency of neuropathic pain, allodynia, and hyperalgesia at the site of operation were significantly lower in Pregabalin group after 1, 2- and 3-months post-thoracotomy (Table 5).

Table 5: The proportion of post-thoracotomy chronic pain after 1, 2 and 3 months

	Pregabalin (n = 30)	Control (n = 30)	*p* value
Neuropathic pain			
At 1 month	3 (10.0%)	11 (36.7%)	0.015*
At 2 months	1 (3.3%)	8(26.7%)	0.011*
At 3 months	0 (0.0%)	5 (16.7%)	0.052*
Allodynia			
At 1 month	5 (16.7%)	13 (43.3%)	0.024*
At 2 months	2 (6.7%)	9 (30.0%)	0.020*
At 3 months	0 (0.0%)	6 (20.0%)	0.024*
Hyperalgesia			
At 1 month	3 (10.0%)	11 (36.7%)	0.015*
At 2 months	2 (6.7%)	9 (30.0%)	0.020*
At 3 months	0 (0.0%)	7 (23.3%)	0.011*

Data are expressed as number (proportion); * *P* value < 0.05 is considered significant.

Adverse effects were comparable between groups (Table 6). No cases of respiratory depression were recorded.

Table 6: Incidence of Adverse Effects

	Pregabalin (n=30)	Control (n=30)	*p* value
Confusion	2 (6.7%)	4 (13.3%)	0.671
Dizziness	5 (16.7%)	8 (26.7%)	0.347
Headache	3 (10.0%)	2 (6.7%)	1.000
Dry Mouth	1 (3.3%)	2 (6.7%)	1.000
Nausea	8 (26.7%)	3 (10.0%)	0.095
Vomiting	3 (10.0%)	1 (3.3%)	0.612
Pruritus	3 (10.0%)	1 (3.3%)	0.612

Data are expressed as number (proportion); * *P* value < 0.05 is considered significant.

Discussion

The results of this study demonstrated that perioperative administration of pregabalin reduced pain intensity and morphine consumption during the first postoperative 4 days in patients having oncologic surgery through a thoracotomy incision. The frequency of chronic neuropathic pain, allodynia and hyperalgesia was significantly reduced in pregabalin group one, two, and three months after surgery. The frequency of side effects like confusion, dizziness, headache, and dry mouth was not increased in the pregabalin group.

In this study, the first dose of pregabalin 150 mg is given 1 hour before surgery to provide analgesia immediately after surgery. The idea of the study was to test whether pregabalin will have better control of acute postoperative pain aiming at prevention of pain chronification [16]. The proposed action of pregabalin was suppression of hyperexcitability of the dorsal horn neurons and neuroplastic changes after surgery. Pregabalin has predominantly inhibitory effect during the first 24 hours; then it has an excitatory effect for 5 days after surgery [17]. The daily pregabalin dose of 300 mg used in this study was based on previous studies [14], [15].

In the current study, on postoperative day 0, the pain intensity was less in pregabalin group throughout the day. This can be contributed to the synergistic analgesic effect of pregabalin with morphine, which led to a decrease in opioid consumption in the first day. After that, pain intensity was lower in the pregabalin group from day 1 through day 4 with reduced total morphine consumption.

Previous studies reported similar results in different after different surgical procedures. Bornemann-Cimenti et al., [7] found that the preoperative administration of 300 mg pregabalin in patients undergoing transperitoneal nephrectomy reduces postoperative opioid consumption by 33% within the first 48 h. In video-assisted thoracoscopic surgery, a single dose of pregabalin 150 mg preoperatively was effective in reducing the pain intensity and need for additional analgesic drugs [19]. Another study reported adequate postoperative pain control after robot-assisted endoscopic thyroidectomy using one dose of 150 mg 1 h before surgery and another dose 12 hours after [20]. Similar results were reported [21].

In the current study, perioperative administration of pregabalin decreased the frequency of chronic neuropathic pain after one, two and three months after surgery. Similar results were obtained concerning allodynia and hyperalgesia in the pregabalin group.

By these findings, Fawzi and El-Tohamy found that perioperative pregabalin reduces the incidence of chronic post-thoracotomy pain at 3 and 6 months from 60 and 40% to 10 and 6.7%, respectively [22].

On the contrary, Brulotte et al. concluded that pregabalin did not reduce the incidence of PTPS. However, among pregabalin users who developed PTPS, pain intensity was less marked, required significantly fewer analgesics, and presented significantly less neuropathic characteristics compared to patients in the placebo group 3 months after surgery [13].

The limitation of our study is a relatively small sample size and short follow up, which is only three months. In conclusion, perioperative use of pregabalin reduces pain and opioid consumption during the acute postoperative period and the incidence of chronic pain at two and three months after thoracotomy.

References

1. Peng Z, Li H, Zhang C, Qian X, Feng Z, Zhu S. A retrospective study of chronic post-surgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on qualify of life. PLoS ONE. 2014; 9(2):e90014. https://doi.org/10.1371/journal.pone.0090014 PMid:24587187 PMCid:PMC3938555

2. El-Hag-Aly MA, Nashy MR. Double edge closure: a novel technique for reducing post-thoracotomy pain. A randomized control study. Interact Cardiovasc Thorac Surg. 2015; 21(5):630-5. https://doi.org/10.1093/icvts/ivv218 PMid:26254464

3. Maxwell C, Nicoara A. New developments in the treatment of acute pain after thoracic surgery. Curr Opin Anaesthesiol. 2014; 27(1):6-11. https://doi.org/10.1097/ACO.0000000000000029 PMid:24296973

4. Gerner P. Post-thoracotomy Pain Management Problems. Anesthesiol Clin. 2008; 26(2):355-vii. https://doi.org/10.1016/j.anclin.2008.01.007 PMid:18456219 PMCid:PMC2453516

5. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015; 156(6):1003-7. https://doi.org/10.1097/j.pain.0000000000000160 PMid:25844555 PMCid:PMC4450869

6. Koehler RP, Keenan RJ. Management of postthoracotomy pain: acute and chronic. Thorac Surg Clin. 2006; 16(3):287-97. https://doi.org/10.1016/j.thorsurg.2006.05.006 PMid:17004557

7. Bornemann-Cimenti H, Lederer AJ, Wejbora M, Michaeli K, Kern-Pirsch C, Archan S, et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. Br J Anaesth. 2012; 108(5):845-9. https://doi.org/10.1093/bja/aes004 PMid:22362672

8. Martinez V, Cymerman A, Ben Ammar S, Fiaud JF, Rapon C, Poindessous F, et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia. 2014; 69(1):46-52. https://doi.org/10.1111/anae.12495 PMid:24320856

9. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth. 2015; 114(1):10-31. https://doi.org/10.1093/bja/aeu293 PMid:25209095

10. Ogawa S, Satoh J, Arakawa A, Yoshiyama T, Suzuki M. Pregabalin treatment for peripheral neuropathic pain: a review of safety data from randomized controlled trials conducted in Japan and in the west. Drug Saf. 2012; 35(10):793-806. https://doi.org/10.1007/BF03261976 PMid:22967187

11. Freynhagen R, Serpell M, Emir B, Whalen E, Parsons B, Clair A, Latymer M. A comprehensive drug safety evaluation of pregabalin in peripheral neuropathic pain. Pain Pract. 2015; 15(1):47-57. https://doi.org/10.1111/papr.12146 PMid:24279736 PMCid:PMC4320770

12. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? Anesth Analg. 2011; 113(5):1242-53. https://doi.org/10.1213/ANE.0b013e31822c9a59 PMid:21965352

13. Brulotte V, Ruel MM, Lafontaine E, Chouinard P, Girard F. Impact of pregabalin on the occurrence of postthoracotomy pain syndrome: a randomized trial. Reg Anesth Pain Med. 2015; 40(3):262-9. https://doi.org/10.1097/AAP.0000000000000241 PMid:25899956

14. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesth Analg. 2010; 110(1):199-207. https://doi.org/10.1213/ANE.0b013e3181c4273a PMid:19910619

15. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001; 92(1-2):147-57. https://doi.org/10.1016/S0304-3959(00)00482-6

16. Dahl JB, Mathiesen O, Møiniche S. "Protective premedication": an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand. 2004; 48(9):1130-6. https://doi.org/10.1111/j.1399-6576.2004.00484.x PMid:15352959

17. Wilder-Smith OHG, Tassonyi E, Arendt-Nielsen L. Preoperative back pain is associated with diverse manifestations of central neuroplasticity. Pain. 2002; 97(3):189-94.

https://doi.org/10.1016/S0304-3959(01)00430-4

18. Singla NK, Chelly JE, Lionberger DR, Gimbel J, Sanin L, Sporn J, et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using different surgical models. J Pain Res. 2015; 8:9-20. https://doi.org/10.2147/JPR.S67841 PMid:25565885 PMCid:PMC4278776

19. Kim JC, Byun S, Kim S, Lee S-Y, Lee JH, Ahn S. Effect of preoperative pregabalin as an adjunct to a multimodal analgesic regimen in video-assisted thoracoscopic surgery: A randomized controlled trial. Medicine (Baltimore). 2017; 96(49):e8644. https://doi.org/10.1097/MD.0000000000008644 PMid:29245223 PMCid:PMC5728838

20. Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam K-H, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. Surg Endosc. 2010; 24(11):2776-81. https://doi.org/10.1007/s00464-010-1045-7 PMid:20376496

21. Chotton T, Singh NR, Singh LC, Laithangbam PS, Singh HS. The effect of pregabalin for relief of postoperative pain after abdominal hysterectomy. Journal of Medical Society. 2014; 28(1):18. https://doi.org/10.4103/0972-4958.135219

22. Fawzi H, El-Tohamy S. Effect of perioperative oral pregabalin on the incidence of post-thoracotomy pain syndrome. Ain-Shams Journal of Anaesthesiology. 2014; 7(2):143. https://doi.org/10.4103/1687-7934.133350