# The effects of the pre-emptive oral gabapentin on post-anesthesia recovery criteria, acute post-thoracotomy pain and development of chronicity in pain with benign thoracotomy operations

Preemptif oral gabapentinin benign torakotomi ameliyatlarında anestezi sonrası derlenme kriterleri, torakotomi sonrası akut ağrı ve ağrının kronikleşmesi üzerine etkileri

# Müge Koşucu, Ersagun Tuğcugil, Engin Ertürk, Murat Topbaş, Ahmet Eroğlu, Hülya Ulusoy, Celal Tekinbaş

Department of Anaesthesiology and Reanimation, Medical Faculty of Karadeniz Teknik University, Trabzon, Turkey

*Background:* In this article, we evaluated the effects of preemptive oral gabapentin on post-anesthesia recovery criteria and acute and chronic post-thoracotomy pain.

*Methods:* This prospective, randomized, clinical comparison study included 60 ASA II-III class patients undergoing thoracotomy for segmentectomy. The patients were randomly divided into two groups: Group G (n=29) received pre-emptive gabapentin 1200 mg peroral while group C (n=31) received placebo. Anesthetic procedure and post-anesthetic analgesia protocol were standardized. Spontaneous respiration, extubation, swallowing, spontaneous eye opening and verbal cooperation times, sedation, agitation and activity levels and modified Aldrete scores were evaluated. Time to first analgesic requirement, acute post-thoracotomy pain, and postoperative total morphine and additional analgesic consumption were recorded. The chronicity of post-thoracotomy pain was questioned using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) at the end of one year follow-up.

**Results:** Shorter verbal cooperation times (p=0.012), less agitation (at 15 min, p=0.001, and 30 min, p=0.001) and earlier recovery times (p<0.0005, at 15 and 30 min), despite greater sedation (at 15 min, p<0.0005, and 30 min, p=0.016) were observed in the gabapentin group. The time to first analgesic requirement was delayed (p<0.005 for all follow-up) and, total morphine and additional analgesic consumptions (p<0.0005 for all follow-ups) were consistent with the numerical rating scale scores. Gabapentin reduced persistent post-thoracotomy pain during the first year (at two, three, six, and 12 months; p=0.040, p=0.031, p=0.001 and p=0.001, respectively).

*Conclusion:* Pre-emptive oral gabapentin 1200 mg may improve the quality of recovery and reduce acute and chronic post-thoracotomy pain.

Keywords: Gabapentin; pain; thoracotomy.

*Amaç:* Bu çalışmada pre-emptif oral gabapentinin anestezi sonrası derlenme kriterleri ve torakotomi sonrası akut ve kronik ağrı üzerine etkileri değerlendirildi.

*Çalışma planı:* Bu prospektif, randomize, klinik çalışmaya segmentektomi yapılmak üzere torakotomi yapılan ASA II-III sınıf 60 hasta alındı. Hastalar rasgele iki gruba ayrıldı: Grup G'ye (n=29) oral yolla 1200 mg preemptif gabapentin verilirken, grup C'ye (n=31) plasebo kapsül verildi. Anestezi prosedürü ve anestezi sonrası analjezi protokolü standardize edildi. Spontan solunum, ekstübasyon, yutkunma, spontan göz açma ve sözel kooperasyon zamanları, sedasyon, ajitasyon ve aktivite düzeyleri ve modifiye Aldrete skorları değerlendirildi. İlk analjezik ihtiyacına kadar geçen zaman, torakotomi sonrası akut ağrı ve ameliyat sonrası total morfin ve ek analjezik tüketimi kaydedildi. Torakotomi sonrası ağrının kronikleşmesi Nöropatik Bulgu ve Belirtilerin Leeds Değerlendirme skalası (LANSS) ile bir yıllık takip sonunda sorgulandı.

**Bulgular:** Gabapentin grubunda sözel kooperasyon zamanı daha kısa (p=0.012), ajitasyon daha düşük (15. dk. p=0.001 ve 30. dk. p=0.001) ve daha fazla sedasyona rağmen (15. dk. p<0.0005 ve 30. dk. p=0.016) daha erken derlenme zamanları (15. ve 30. dk, p<0.0005) gözlendi. İlk analjezik ihtiyaç zamanı gecikti ve total morfin ve ek analjezik kullanımı (p<0.0005, tüm takipler için) sayısal değerlendirme ölçeği skorları ile uyumlu idi (p<0.005, tüm takipler için). Gabapentin, torakotomi sonrası kronik ağrıyı ameliyatı takip eden bir yıl boyunca azaltmıştı (sırasıyla iki, üç, altı ve 12. aylarda; p=0.040, p=0.031, p=0.001 ve p=0.001).

*Sonuç:* 1200 mg pre-emptif oral gabapentin derlenme kalitesini artırabilir ve torakostomi sonrasında akut ve kronik ağrıyı azaltabilir.

Anahtar sözcükler: Gabapentin; ağrı; torakotomi.



Available online at www.tgkdc.dergisi.org doi: 10.5606/tgkdc.dergisi.2014.7707 QR (Quick Response) Code Received: September 17, 2012 Accepted: May 13, 2013 Correspondence: Müge Koşucu, M.D. Karadeniz Teknik Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, 61080 Trabzon, Turkey. Tel: +90 462 - 377 59 04 e-mail: mugekk73@hotmail.com Gabapentin, a structural analog of gammaaminobutyric acid that mainly has antinociceptive and antihyperalgesic properties, is an anticonvulsant drug which also suppresses the release of noxious stimulus-induced excitatory amino acid in the spinal cord.<sup>[11]</sup> In addition, it is an oral non-opioid analgesic that is used pre- or postoperatively to prevent acute pain in different types of surgery.<sup>[2,3]</sup> In addition, the preoperative administration of this drug reduces opioid analgesic consumption and anxiety.<sup>[1,3,4]</sup>

Effective pain management and quality of recovery are some of the most important issues in the care of thoracic surgery patients. Intensity of pain and anxiety can persist long after surgery and limit normal lung function,<sup>[4]</sup> and patients with these symptoms often also demonstrate increased morbidity and mortality.<sup>[4,5]</sup> Furthermore, those who undergo a thoracotomy are very likely to develop chronic post-thoracotomy pain, with incidence rates ranging between 50 and 80% having been reported.<sup>[6,7]</sup> For this reason, minimizing acute pain intensity is important to help reduce the incidence of chronic pain,<sup>[6]</sup> and different protocols, including preemptive and multimodal strategies, have been used to reduce both of these types of pain.

We hypothesized that the preemptive use of oral 1200 mg gabapentin might accelerate recovery by reducing acute post-thoracotomy pain. Moreover, it might also have a positive effect on persistent chronic post-thoracotomy pain in the long-term. Therefore, our primary objective was to evaluate the effects of preemptive gabapentin on the recovery criteria and acute post-thoracotomy pain. The secondary objective was to evaluate the efficacy of gabapentin on persistent chronic post-thoracotomy pain.

# PATIENTS AND METHODS

After gaining the approval of the institutional ethics committee and obtaining the written informed consent from the study participants, 62 patients with an American Society of Anesthesiologists (ASA) physical status classification of 2/3 who were scheduled for open posterolateral or lateral thoracotomies along with a segmentectomy but not pneumonectomy or chest wall resection, were enrolled in this double-blind study in 2010. The study was then completed in 2011. The segmentectomy was to be performed due to the presence of bronchiectasis. All of the patients underwent a standard posterolateral or lateral thoracotomy. In the posterolateral thoracotomy, the skin incision was between 15 and 20 cm long, depending on the patient's adiposity, and the latissimus dorsi, serratus anterior, and intercostal muscles were incised. However, in the lateral thoracotomy, the skin incision was between 12 and 15 cm long, and the serratus anterior and intercostal muscles were incised. Furthermore, none of the patients underwent a pneumonectomy or chest wall resection and none developed rib fractures. Any patients with cancer, central nervous system diseases, diabetes mellitus (DM), psychiatric disorders, a history of opioid or gabapentin use 24 hours prior to surgery, or a history of chronic alcohol or anti-epileptic use were excluded from the study along with those with chronic pain syndromes or known allergies to opioids or gabapentin. In addition, patients who were unable to apply patient-controlled analgesia (PCA) were also not included.

The evening before surgery, the patients were instructed how to use the 10-point numerical rating scale (NRS) in our study in which 0 represented no pain and 10 the worst imaginable pain and were also told how to use the PCA device (Abbott, New York, USA). They were then premedicated with intramuscular midazolam 0.07 mg/kg the night before the surgery and one hour before. The patients were allocated randomly by sealed envelope into one of two groups. Blinded investigators gave the control group (group C, n=31) oral identicallooking placebo capsules (prepared by the pharmacy department) and the gabapentin group (group G, n=29) received oral gabapentin 1200 mg (Neurontin<sup>®</sup>, Pfizer, Freiburg, Germany) one hour before the surgery.<sup>[8]</sup> The patients' heart rates (HRs), non-invasive mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO<sub>2</sub>), and end-tidal partial pressure of carbon dioxide (EtCO<sub>2</sub>) were monitored and recorded. Additionally, venous access was achieved in all of the patients, and a saline crystalloid solution was started. Anesthesia induction and muscle relaxation were performed with propofol 2 mg.kg<sup>-1</sup>, intravenous (i.v.) fentanyl 1-1.5 µg/kg<sup>-1</sup>, and cisatracurium 0.15 mg/kg<sup>-1</sup>. The anesthesia was initially maintained with sevoflurane 1.7% inspired at a fresh gas flow rate of 3 L/min<sup>-1</sup> in combination with air 50% in oxygen and repetitive doses of cisatracurim 0.7 mg/kg<sup>-1</sup>. Furthermore, an i.v. infusion of remifentanil 0.5<sup>-1</sup> µg/kg<sup>-1</sup> per hour was used as an analgesic during the intraoperative period. The patients were mechanically ventilated to maintain the EtCO<sub>2</sub> values at between 34 and 38 mmHg, and the sevoflurane and remifentanil infusions were switched off when the last suture was inserted. At the start of spontaneous respiration, iv morphine 4 mg and diclofenac 75 mg were administered, and we recorded the return of spontaneous respiration, extubation, swallowing, spontaneous eye opening, and verbal cooperation times.

After tracheal extubation and upon awakening from anesthesia, the patients were transferred to the

postanesthesia care unit (PACU) where they remained for a minimum of one hour to be evaluated in terms of sedation, agitation, activity, and acute postoperative pain levels. Sedation and agitation were assessed using a five-point scale (Tables 1 and 2),<sup>[9,10]</sup> while activity was assessed with a four-point scale (Table 3)<sup>[11]</sup> at the postoperative 15<sup>th</sup>, 30<sup>th</sup>, and 60<sup>th</sup> minutes. The patients with a modified Aldrete score of >9 were transferred to the ward at the end of the first hour,<sup>[12]</sup> whereas the patients who were connected to a PCA device or those with postoperative analgesia were started on 2 mg bolus injections of morphine for a maximum of four hour limits of 40 mg and a lockout interval of 10 minutes. An anesthesiologist blinded to the group allocations performed the assessments for pain, opioid usage, and side effects at 2, 4, 6, 8, 12, 24, 36 and 48-hour intervals. In the postoperative first hour, when a patient had an NRS score of >3, the bolus morphine was increased to 3 mg. Furthermore, for the patients with an NRS score of >5 the first 48 hours after surgery, additional doses of intramuscular meperidine 50 mg and/or diclofenac 75 mg were administered with a minimal allowed interval of six hours for each. At the end of the first 48 hours on the ward, the PCA was concluded, and analgesia was provided via diclofenac 75 mg and 50 mg of meperidine on an as needed basis. We first recorded the time until the first analgesic requirement, total morphine consumption, and NRS values, which is our standard ward analgesic protocol for all patients following major thoracic surgery. We do not routinely use epidural analgesia in our patients following this type of surgery. In these cases, we also particularly evaluated the potential side effects, including lightheadedness, drowsiness, pruritus, headaches, decreased coordination, visual disturbances, nausea and vomiting, and respiratory depression by questioning the patient and the nurse.

Following discharge, the scores on the Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale<sup>[13]</sup> were evaluated via examinations done in the hospital at the second, third, and sixth months and at the end of the first year, and those with a score of >12, were regarded as "chronic pain patients" or "patients with chronicity". The statistics associated with the chronic process were then recorded for analysis.

## **Biostatistical analysis**

The sample size was determined prospectively using data from previous studies<sup>[4,7]</sup> in our institution's power and precision analysis program. For purposes of the priori power calculation, a 15% reduction in the NRS acute pain scores in group G was considered to be significant. Based on this pain reduction estimate [and an average standard deviation (SD) of 1.49], we calculated that a sample size of 26 patients would provide a power of 80%.<sup>[4]</sup> Again, for priori power calculation, a 10% reduction in the LANSS chronic pain scores in group G was considered to be significant. Based on this pain reduction estimate (and an average SD of 3.5), we calculated that a sample size of 25 patients would provide a power of 80%.<sup>[7]</sup> There were 29 patients in group G and 31 in group C in our study.

The compatibility of the normal distribution of the measured data was analyzed using the Kolmogorov-Smirnov test. A between-group comparison of the normally distributed data was performed using Student's t-test, and the Mann-Whitney U test was used to compare non-normally distributed data. In addition, a chi-square test was used to compare qualitative data. Cochrane test was used for chronicity of pain analyzed. The measured data was expressed as mean $\pm$ SD, the score values as median (minimummaximum), and the qualitative data as percentages. A *p* value of <0.05 was considered to be significant.

## RESULTS

Two of 62 patients from group G were excluded postsurgically, and the study was completed with the remaining 60 patients. One of them had been uncooperative during the departmental follow-ups,

#### Table 1. Sedation scale

- 0 No sedation; can initiate speech
- 1 Light sedation; eyes open; can not initiate speech
- 2 Eyes closed; answers immediately when asked a question
- 3 Responds with a few sounds or tactile responses
- 4 Difficulty in being awakened; very powerful stimuli needed

#### Table 2. Agitation scale

- 0 Sleeping
- 1 Awake and calm
- 2 Irritable; crying
- 3 Crying and cannot be pacified
- 4 Severe agitation and orientation impairment

### Table 3. Activity scale

- 1 Minimal activity
- 2 Limited activity
- 3 Mildly restricted activity
- 4 Normal activity

	Group G (n=29)		Group C (n=31)			
	n	Mean±SD	n	Mean±SD	р	
Age (years)		55.4±13.3		54.3±12.1	0.605	
Gender						
Female	15		16 [	]	0.993	
Male	14		15 [	J	0.995	
American Society of Anesthesiologists						
2	14		15 <u>[</u>	1	0.002	
3	15		16	-] T	0.993	
Operation duration (min)		135.6±37.2	L	131.8±33.1	0.418	

#### Table 4. Demographic and surgical data

SD: Standard deviation; p>0.005, for all values.

and the other could not be contacted after the postoperative first month.

There were no differences between groups G and C regarding the demographic and surgical data (Table 4) or the MAP, HR, SpO<sub>2</sub>, and EtCO<sub>2</sub> values. Moreover, no differences were detected related to spontaneous respiration, extubation, swallowing, or spontaneous eye opening times, but the verbal cooperation time was shorter in group G (p=0.012) (Table 5).

At the postoperative PACU follow-up, an elevated sedation score was observed in group G at 15 (p<0.0005) and 30 minutes (p=0.016) following extubation, but this difference disappeared by the  $60^{\text{th}}$  minute (Table 6). Furthermore, the agitation scores in group G were also lower at 15 and 30 minutes postextubation (p=0.001 and p=0.001, respectively), but there was also no difference at 60 minutes (Table 6). Furthermore, the modified Aldrete scores decreased in group G at the same times (p<0.0005 and p<0.0005, respectively), but no difference was seen at the  $60^{\text{th}}$  minute (Table 6). However, no statistically significant differences were observed regarding the activity levels (Table 6).

We also observed significant differences in terms of the NRS values at all of the time points, and these values were lower in group G than in group C at each interval [second hour (p<0.0005), fourth hour (p<0.0005), sixth hour (p=0.005), eighth hour (p=0.045),  $12^{th}$  hour (p=0.012),  $24^{th}$  hour (p=0.043),  $36^{th}$  hour (p<0.0005), and  $48^{th}$  hour (p<0.0005)] (Table 7).

The time until the first analgesic requirement in the postoperative period was highly statistically significant and prolonged in group G (p<0.0005) (Table 7). Similarly, the morphine levels consumed via the PCA method at the end of the postoperative  $24^{th}$ and  $48^{th}$  hours were lower in group G than in group C (p<0.0005 at both times) (Table 7). Additionally, the levels of additional meperidine at the end of the postoperative  $48^{th}$  hour were also significantly lower in group G (p<0.0005) (Table 7).

At the end of 48 hours, the most common side effect in both groups was nausea and vomiting, and there were no statistically significant differences (Table 8).

When comparing the chronicity of pain using the LANSS at the end of the second, third, and sixth months as well as at one year, the number of patients with pain chronicity was lower in group G compared with group C, and the differences were significant for these four assessments. The chronicity in group G fell from 37.9% to 3.4% by the  $12^{th}$  month (p<0.0005),

	Group G (n=29)	Group C (n=31)	
	Mean±SD	Mean±SD	р
Spontaneous respiration time	6.5±2.9	6.6±2.9	0.401
Extubation time	$11.9 \pm 4.4$	11.8±4.9	0.551
Swallowing time	16.1±3.8	16.5±4.8	0.722
Spontaneous eye opening time	24.3±5.1	26.0±6.3	0.273
Verbal cooperation time	25.2±4.3	30.2±7.1	0.012*

#### Table 5. Early recovery criteria

SD: Standard deviation; \* p<0.05; The early recovery criteria is given in minutes.

Koşucu et al. Preemptive oral gabapentin with benign thoracotomy operations

	Group G (n=29)				Group C (n=31)		
	Mean	Minmax.	Mean±SD	Mea	n Minmax.	Mean±SD	р
Sedation score at 15 minutes	3	3-4		3	0-4		< 0.0005*
Sedation score at 30 minutes	2	0-3		2	0-3		0.016*
Sedation score at 60 minutes	2	0-2		1	0-3		0.702
Agitation score at 15 minutes	2	0-4		2	0-4		0.001*
Agitation score at 30 minutes	1	0-2		2	1-3		0.001*
Agitation score at 60 minutes	1	0-2		1	0-2		0.215
Activity level at 15 minutes	1	1-2		1	1-3		0.884
Activity level at 30 minutes	2	1-3		2	1-3		0.054
Activity level at 60 minutes	3	1-4		2	1-4		0.106
Modified Aldrete at 15 minutes			7.3±1.0			6.4±0.6	<0.0005**
Modified Aldrete at 30 minutes			8.6±0.7			7.9±0.8	<0.0005**
Modified Aldrete at 60 minutes			9.4±0.8			9.6±0.6	0.713

Min.: Minimum; Max.: Maximum; SD: Standard deviation; \* p<0.05; \*\* p<0.005; A five-point scale was used for sedation and agitation while a four-point scale was used for the activity level and a 10-point scale for the modified Aldrete scores.

and it also gradually decreased in group C, falling from 67.7% at the second month to 38.7% at the  $12^{th}$  month (p=0.0001). Furthermore, the pain chronicity prevalence in group G was statistically significantly lower than that in group C for every month (second month p=0.040; third month p=0.031; sixth month p=0.001; and at the end of one year; p=0.001) (Table 9).

# DISCUSSION

Post-thoracotomy pain is very intense and features nociceptive and neuropathic properties. If postoperative pain is not treated appropriately, tissue and nerve damage can initiate sensitization in the peripheral and central nervous systems that can lead to pain chronicity. Many drugs and methods are used to alleviate postoperative pain, with preemptive analgesia being one such technique. The aim in preemptive analgesia is to protect the central nervous system against noxious stimuli and the patient against hyperalgesia, allodynia, and severe pain.

A single preoperative dose of gabapentin 1200 mg was chosen for our study since this is prescribed most often to alleviate acute pain and reduce the consumption of morphine and additional analgesics without significant side effects.<sup>[2,3]</sup>

The relationship between postoperative pain and cognitive functions has already been described.<sup>[14,15]</sup> In our study, there were no differences between the groups G and C in terms of either eye opening, swallowing, or

Table 7. Numerical rating	scale values	, time until f	first analgesic	requirement,	morphine	consumption, and
additional meperadine usa	ige					

	Group G (n=29)	Group C (n=31)	
	Mean±SD	Mean±SD	р
NRS 2 <sup>nd</sup> hour	4.1±3.4	5.6±2.4	<0.0005**
NRS 4 <sup>th</sup> hour	2.9±2.7	5.2±1.5	<0.0005**
NRS 6 <sup>th</sup> hour	2.9±1.2	4.2±2.1	0.005*
NRS 8 <sup>th</sup> hour	2.6±1.3	4.1±1.0	0.045*
NRS 12 <sup>th</sup> hour	$1.9 \pm 0.7$	3.3±1.0	0.012*
NRS 24 <sup>th</sup> hour	1.3±0.8	3.2±1.1	0.043*
NRS 36 <sup>th</sup> hour	1.0±0.3	2.2±0.8	<0.0005**
NRS 48 <sup>th</sup> hour	$0.2 \pm 0.4$	1.4±0.7	< 0.0005**
First analgesic requirement times (minutes)	130±25.2	72.5±25.6	<0.0005**
Morphine 24 <sup>th</sup> hour (mg)	25.9±8.3	44.0±11.0	< 0.0005**
Morphine 48 <sup>th</sup> hour (mg)	18.2±6.4	30.0±7.4	<0.0005**
Additional meperidine usage (mg)	$169.0 \pm 45.2$	266.1±43.6	<0.0005**

SD: Standard deviation; NRS: Numerical rating scale from 1 to 10; \* p<0.05; \*\* p<0.005.

Group parameter	Group	o G (n=29)	Group		
	n	%	n	%	р
Nausea	9	29.0	4	13.8	0.263
Vomiting	7	22.6	4	13.67	0.586
Drowsiness	2	9.7	1	3.4	0.613
Pruritus	3	9.7	4	13.8	0.702
Constipation	3	9.7	3	10.3	

Table 8. Side effects

The data is expressed as a number of patients; p>0.005, for all values.

extubation times, although the verbal cooperation time was shorter and the agitation scores (at 15 and 30 minutes) were lower in group G, which is contrary to the findings in some studies.<sup>[16]</sup> We interpreted these results as the demonstration of the possible positive impact of gabapentin on cognitive functions through its anxiolytic effect.<sup>[17]</sup> Postoperative pain and agitation may be related to perioperative anxiety, so taking this medication may have lowered the stress levels of the patients, thereby reducing their postoperative pain.<sup>[11]</sup>

Sedation is one of the most commonly reported side effects of gabapentin,<sup>[18-20]</sup> and we observed a significant elevation in the postoperative sedation scores in both of our groups 30 minutes after the surgery. However, this difference did not lead to an unwanted prolongation of sedation, and it disappeared by the 60<sup>th</sup> minute. The modified Aldrete scores were higher in group G compared with group C at 15 and 30 minutes, and we attributed this to the ability of gabapentin to reduced agitation. However, the effect of this drug on the sedation and agitation scores was not affective to alter the activity levels.

In addition to its other benefits, gabapentin may also increase the analgesic effect of morphine and prevent the development of resistance to opioids and/or reduce opioid tolerance.<sup>[12,16,20-22]</sup> Moreover, the combination of gabapentin and morphine is known to be more effective than morphine alone, especially for neuropathic pain. Many studies have investigated the effect of preoperative gabapentin on postoperative pain and have shown that it reduces postoperative opioid consumption parallel to postoperative pain in surgery other than thoracotomies.<sup>[6,23,24]</sup> In this study, we also observed that a preemptive dose of gabapentin 1200 mg in thoracotomy surgery can reduce the total morphine and additional analgesic consumption. In addition, the time until the first analgesic requirement almost doubled in group G, and we identified lower NRS values in group G at all time intervals. There are two metaanalyses that focused on the role of gabapentin in the treatment of acute postoperative pain,<sup>[3,16]</sup> and they determined that it was effective preoperatively in reducing the pain scores, opioid consumption, and the opioid-related adverse effects in the first 24 hours after surgery.<sup>[16]</sup> Ho et al.<sup>[2]</sup> also suggested that future trials should investigate the effect of perioperative gabapentin on the chronicity of postsurgical pain. Another study by Huot et al.<sup>[18]</sup> investigated the levels of ipsilateral chronic shoulder pain after a single dose of gabapentin in thoracotomy operations, but they found no significant results.<sup>[18]</sup> To the best of our knowledge, in the English medical literature, the first prospective study that assessed the use of gabapentin for post-thoracotomy pain in cardiothoracic surgery was by Sihoe et al.<sup>[25]</sup> and they found that pain reduction could not be attributed to

	Group G (n=29)			Group C (n=31)			
	Chroni	icity (+)	Chronicity (-)	Chronicity (+)		Chronicity (-)	
	n	%	n	n	%	n	$p\dagger$
Month 2	11	37.9	18	21	67.7	10	0.040*
Month 3	7	24.1	22	17	54.8	14	0.031*
Month 6	3	10.3	26	15	48.4	16	0.001*
Month 12	1	3.4	28	12	38.7	19	0.001*
p‡		< 0.0005			0.001		

Table 9. Leeds assessment of neuropathic symptoms and signs scores

† chi-square test; ‡ Cochrane test; \* p<0.05; The data is expressed as number of patients.

gabapentin treatment alone. However, their study was limited by a very heterogeneous cohort of patients in terms of the initial pathology or trauma and the kind of surgical approaches that were involved, including VATS and open thoracotomies. They also emphasized that further studies were needed in order to answer the question concerning which groups might benefit the most from gabapentin and how this might occur. Our study was conducted with one initial pathology and similar surgical groups; therefore, we were able to ascertain the effectiveness of gabapentin on a specific group. Kinney et al.<sup>[26]</sup> added a single preoperative oral dose of gabapentin 600 mg in the context of multimodal analgesia to thoracic epidural infusion<sup>[26]</sup> and found that this drug provided no additional benefits to the epidural analgesia. In our study, we used preemptive gabapentin 1200 mg as a part of a multimodal analgesia technique and employed meperidine and diclofenac supplementary to the postoperative PCA (morphine). In contrast to Kinney et al.,<sup>[26]</sup> our results showed that gabapentin had a positive effect. Thoracic epidural analgesia is regarded as the most effective technique in thoracic surgery,<sup>[4,6,9]</sup> but routine epidural anesthesia/analgesia may not always be possible. Hence, gabapentin could be used to help overcome the acute postoperative pain that arises after thoracic surgery in these cases.

Studies exist regarding the treatment protocols for chronic post-thoracotomy pain. For example, Şentürk et al.<sup>[27]</sup> found that the prevention of chronicity of postthoracotomy pain is the most common approach when seeking to control late-stage thoracotomy pain and that the intensity of acute postoperative pain seems to be a good predictor of chronicity. For this reason, the use of thoracic epidural morphine has frequently been investigated. There are also studies concerning the use of gabapentin related to the chronicity of postoperative pain in non-thoracotomy surgery, and it has been shown to be superior to naproxen and amitriptyline in this context.<sup>[4,7]</sup> Furthermore, gabapentin administered before and after breast cancer surgery had no effect on third and sixth-month pain in a study by Fassoulaki et al.,<sup>[20]</sup> but it was used in another study for 10 days for patients with acute pain following breast cancer surgery and was able to prevent the chronicity of pain at the third month postoperatively.<sup>[21]</sup> In our study, a single dose of preemptive gabapentin was associated with a tendency toward a statistically significant reduction in the incidence of chronic post-thoracotomy pain during the first year. We think that alleviating acute pain may also help prevent chronicity of postthoracotomy pain, and this was the most crucial point to emerge from our study.

Group G had shorter verbal cooperation times, less agitation, and earlier recovery times, despite receiving more sedation. Their time to the first analgesic requirement was delayed and the NRS values were lower as was the consumption of total morphine and additional analgesics. In addition, gabapentin reduced persistent post-thoracotomy pain during the first year, and preemptive oral gabapentin 1200 mg may improve the quality of recovery and decrease acute and chronic post-thoracotomy pain after this type of surgery.

The main limitation of this study was that although our results were significant in terms of both acute surgical and chronic pain, studies with greater patient numbers (power above 90%) are now needed, particularly with regard to chronic pain development, because a difference of just one or two patients in a group can make it appear to be statistically significant in clinical terms, despite not having a large enough sample size. In addition, we did not include cancerassociated surgeries, the most important group in terms of severity of acute surgical pain and chronicity. We believe that studies with broader patient participation that would include cancer surgeries are needed to clarify the correlation between gabapentin and chronic post-thoracotomy pain.

# Conclusion

By simply giving patients oral doses of preemptive gabapentin 1200 mg, they may receive a reduction in acute thoracotomy pain and have a decrease in the need for postoperative morphine and additional analgesics. The patients may also simultaneously have an enhanced recovery if they take this drug. Even more importantly, gabapentin at this dosage may reduce the chronicity of post-thoracotomy pain.

# **Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

## Funding

The authors received no financial support for the research and/or authorship of this article.

## REFERENCES

- 1. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394-9.
- Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain 2006;126:91-101.

- 3. Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth 2006;53:461-9.
- 4. Ochroch EA, Gottschalk A, Augostides J, Carson KA, Kent L, Malayaman N, et al. Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. Anesthesiology 2002;97:1234-44.
- Turan A, White PF, Karamanlioglu B, Memis D, Tasdogan M, Pamukçu Z, et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. Anesth Analg 2006;102:175-81.
- 6. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009;36:170-80.
- Solak O, Metin M, Esme H, Solak O, Yaman M, Pekcolaklar A, et al. Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. Eur J Cardiothorac Surg 2007;32:9-12.
- Sen H, Sizlan A, Yanarateş O, Senol MG, Inangil G, Sücüllü I, et al. The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009;26:772-6.
- Seo IS, Seong CR, Jung G, Park SJ, Kim SY, Kim MM. The effect of sub-Tenon lidocaine injection on emergence agitation after general anaesthesia in paediatric strabismus surgery. Eur J Anaesthesiol 2011;28:334-9.
- Uysal HY, Takmaz SA, Yaman F, Baltaci B, Başar H. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. J Clin Anesth 2011;23:53-7.
- Köner O, Türe H, Mercan A, Menda F, Sözübir S. Effects of hydroxyzine-midazolam premedication on sevoflurane-induced paediatric emergence agitation: a prospective randomised clinical trial. Eur J Anaesthesiol 2011;28:640-5.
- Uysal HY, Takmaz SA, Yaman F, Baltaci B, Başar H. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. J Clin Anesth 2011;23:53-7.
- Maguire MF, Ravenscroft A, Beggs D, Duffy JP. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006;29:800-5.
- Laalou FZ(1), Jochum D, Pain L. Postoperative cognitive dysfunction (POCD): strategy of prevention, assessment and management. Ann Fr Anesth Reanim 2011;30:e49-53.
- 15. Ji MH, Yuan HM, Zhang GF, Li XM, Dong L, Li WY, et

al. Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery. J Anesth 2013;27:236-42.

- Serpell MG. Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain 2002;99:557-66.
- 17. Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders. Am J Psychiatry 1998;155:992-3.
- Huot MP, Chouinard P, Girard F, Ruel M, Lafontaine ER, Ferraro P. Gabapentin does not reduce post-thoracotomy shoulder pain: a randomized, double-blind placebocontrolled study. Can J Anaesth 2008;55:337-43.
- 19. Mao J, Chen LL. Gabapentin in pain management. Anesth Analg 2000;91:680-7.
- 20. Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. EMLA reduces acute and chronic pain after breast surgery for cancer. Reg Anesth Pain Med 2000;25:350-5.
- 21. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95:985-91.
- 22. Matthews EA, Dickenson AH. A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy. Anesthesiology 2002;96:633-40.
- Ochroch EA, Gottschalk A, Troxel AB, Farrar JT. Women suffer more short and long-term pain than men after major thoracotomy. Clin J Pain 2006;22:491-8.
- 24. Turan A, Karamanlioğlu B, Memiş D, Hamamcioglu MK, Tükenmez B, Pamukçu Z, et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004;100:935-8.
- 25. Sihoe AD, Lee TW, Wan IY, Thung KH, Yim AP. The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients. Eur J Cardiothorac Surg 2006;29:795-9.
- 26. Kinney MA, Mantilla CB, Carns PE, Passe MA, Brown MJ, Hooten WM, et al. Preoperative gabapentin for acute postthoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. Pain Pract 2012;12:175-83.
- 27. Sentürk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalçin S, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002;94:11-5.