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The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients☆

Alan D.L. Sihoe*, Tak-Wai Lee, Innes Y.P. Wan, Kin-Hoi Thung, Anthony P.C. Yim

Division of Cardiothoracic Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China

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Abstract

Objective: The pain following thoracic surgery and trauma is often refractory to conventional analgesic strategies. However, it shares key characteristics with neuropathic pain which gabapentin, an anticonvulsant, has been proven to effectively treat. To our knowledge, this is the first prospective study assessing the use of gabapentin in cardiothoracic surgery patients. **Methods:** Gabapentin was prescribed to 60 consecutive out-patients with refractory pain persisting at four weeks or more after thoracic surgery or trauma. Follow-up of 45 patients (75%) was performed for a median of 21 months (range: 12—28), and clinical data collected prospectively. The mean age of these patients was 51.6 years (range 22—83). Of these 45 patients, 22 had received video-assisted thoracic surgery (VATS), 8 had received thoracotomy, 3 had received median sternotomy, and 12 were treated for blunt chest trauma. **Results:** The mean duration of pre-treatment refractory pain was 5.76 months (range 1—62). The mean duration of gabapentin use was 21.9 weeks (range 1—68). No deaths or major complications were encountered. Minor side effects—mostly somnolence and dizziness—occurred in 18 patients (40.0%), causing 3 patients (6.7%) to discontinue gabapentin. Overall, 33 patients (73.3%) noted reduction of pain. Chest wall paresthesia distinguishable from wound pain was relieved in 24 (75.0%) of 32 affected patients. Severe initial pain was significantly correlated with pain relief using gabapentin ($p = 0.009$). No other demographical or clinical variable correlated with benefit or side effects. Satisfaction with gabapentin use was expressed by 40 patients (88.9%). Side effects were not a source of dissatisfaction in any patient. **Conclusions:** Gabapentin appears safe and well tolerated when used for persistent post-operative and post-traumatic pain in thoracic surgery patients, although minor side effects do occur. Gabapentin may relieve refractory chest wall pain in some of these patients, particularly those with more severe pain. Further studies are warranted to define the role of gabapentin in cardiothoracic surgical practice.

Keywords: Chest wall; Gabapentin; Pain; Thoracotomy; Video-assisted thoracic surgery (VATS)

1. Introduction

Pain occurring in the chest wall following thoracic surgery or trauma remains a significant clinical problem, contributing to increased post-operative complications and reduced quality of life after surgery. Persistent dysesthetic burning pain or aching can occur in up to 50—70% of patients at two months or more after thoracotomy [1,2]. In 5% of these patients, the pain has been described as 'severe and disabling,' and over 40% of patients may still have some degree of pain at one year after surgery.

Many strategies have been described to reduce such pain. These have included parenteral opiates, nonsteroidal anti-inflammatory drugs (NSAIDs), epidural and paravertebral infusions of local anesthetics, intercostal and phrenic nerve blockades, and cryotherapy. However, results have been mixed and no single strategy has been shown to be effective in all patients. Video-assisted thoracic surgery (VATS) has been advocated as a minimally invasive approach which may alleviate post-operate pain. Nevertheless, chronic discomfort is still reported to afflict up to 63% of patients after VATS procedures, and can persist for up to several years after surgery [3—6]. The difficulty in treating post-operative pain in thoracic surgical patients may be partly explained by its multifactorial nature. It has been previously suggested that rib spreading, costo-chondral dislocation, muscle division, use of diathermy, pleural trauma, subsequent neuroma formation, and so on may all play a part in the development of post-thoracotomy pain [1,2].

It is now increasingly recognized that intercostal neuralgia is one of the key components in the pain experience following thoracic surgery and trauma. Patients with post-thoracotomy pain typically describe their pain as being burning, aching, electrical and/or shock-like in quality [1,7], and responding

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* Corresponding author. Tel.: +852 2632 2629; fax: +852 2647 3512.
E-mail address: adls1@lycos.com (Alan D.L. Sihoe).

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poorly to the use of opiates [8]. These characteristics are the same as those of recognized neuropathic pain syndromes, such as post-herpetic neuralgia and diabetic peripheral neuropathy [9,10]. We have recently shown that even if elements, such as rib spreading, costo-chondral dislocation, muscle division and so on are minimized by performing VATS as opposed to open thoracotomy, 52.9% of patients may still experience paresthetic chest wall discomforts distinct from classical localized wound pain [11]. This chest wall paresthesia again shares the characteristics of neuropathic pain syndromes. The incidence and nature of the paresthesia remains similar even if the level of surgical trauma is further reduced by performing needlescopic VATS [12]. It may be hypothesized therefore that chest wall paresthesia may represent a form of neuropathy following thoracic surgery that requires specific treatment by nonconventional means or agents.

Neuropathic pain syndromes have been shown to be effectively controlled by the novel anticonvulsant drug gabapentin (Neurontin, Pfizer Inc., New York, NY, USA) [9,10]. To our knowledge, the use of gabapentin for post-thoracotomy pain has only previously been reported once in a case report of a 12-year-old girl with post-thoracotomy pain [13]. There have otherwise been no prospective studies reporting the use of gabapentin in thoracic surgery.

Herein we report the first clinical study of the use of gabapentin in the treatment of persistent pain following thoracic surgery or trauma. The primary objective was to evaluate the safety and potential adverse effects of the use of gabapentin in this role. The secondary objective was to obtain preliminary data on the efficacy of gabapentin in palliating such pain.

2. Methods

We studied 60 consecutive patients who presented at the out-patients clinic of our institution between 1 January 2003 and 30 April 2004 complaining of refractory pain following thoracic surgery or trauma. Patients were eligible for inclusion to the study if they had had any major general thoracic surgical procedure at our hospital or required initial in-patient treatment at our hospital for blunt thoracic trauma, and who presented to our clinic at four weeks or more after the initial operation or trauma with persistent chest wall pain or paresthesia which was refractory to conventional analgesics.

Our standard analgesics regime on discharge for all patients following major thoracic surgery or blunt chest trauma consists of 650 mg of paracetamol with 65 mg of dextropropoxyphene given orally five times a day. We do not routinely use epidural analgesia in all patients following surgery or trauma.

We rigorously excluded patients who had had initial pathology which invaded or involved the chest wall (such as locally invasive lung cancer, empyema thoracis necessitans, intercostal neural lesions, pathological rib fractures), surgery involving extensive parietal pleural trauma (such as pleurodesis, pleurectomy, extrapleural tumour resection), post-operative complications which may affect the pain experience (such as pleural space infection), history of analgesic dependence or abuse, history of epilepsy or any neurological condition for which the drug treatment may be affected by gabapentin, any known contraindications for gabapentin use, and any previous allergy or adverse effect from gabapentin. Patients were also excluded if they were mentally unable to respond to the required study questioning, if they refused to enter study, or if they requested withdrawal from the study.

All patients who met the above criteria gave informed signed consent. The study protocol was approved by our Institutional Research Ethics Committee.

Upon enrollment to the study, each patient was commenced on regular oral gabapentin at a dose of 300 mg nocte. The day of enrollment was designated as Day 1. All other regular analgesics were stopped, but the above paracetamol/dextropropoxyphene preparation was taken on an as required basis for 'breakthrough' pain. The dose of gabapentin is titrated up to 300 mg bd on Day 4, and 300 mg tds on Day 7 if the pain relief was inadequate and no adverse effect from the gabapentin was noted. Each patient is then maintained on the final titrated dose of gabapentin on Day 7 for the remainder of the treatment period.

Upon recruitment, patients were also asked to subjectively grade the severity of their chest wall pain or paresthesia on a 10-point analog scale (with 1 being minimal discomfort and 10 being the worst discomfort imaginable). We regard a severity of 1–3 on the 10-point scale to be 'mild,' 4–7 to be 'moderate,' and 8–10 to be 'severe.' For the purposes of this study, 'paresthesia' has been defined as any numbness or disordered sensation causing chest wall discomfort which the patient can distinguish clearly from the wound pain. Affected patients were also questioned regarding the perceived effect of the discomfort on their daily lives, and how they responded to the discomfort if at all.

Patients were followed up regularly at our out-patients clinic. Gabapentin treatment was stopped if the pain had fully resolved, if there were any serious adverse effects attributable to gabapentin use, if the treatment proved ineffectual, or if the patient refused to continue treatment for any reason.

Patients were subsequently interviewed on out-patients follow-up and by telephone using a standardized questionnaire, and clinical data was collected prospectively. Pain and paresthesia were documented using the same 10-point analog scale as above throughout the study. Patients were asked about any adverse effects or benefits from gabapentin treatment, and about their satisfaction with use of the drug. Statistical analyses of the collected data were performed by Spearman correlation analyses or Pearson exact chi-square tests using StatXact Version 4 software (Cytel Software Corporation). We regard a p-value of less than 0.05 as being significant.

3. Results

The median observation time was 21 months (range 12–28 months). Of the 60 patients initially recruited, 1 died from recurrent lung cancer, 1 required chemotherapy for recurrent lung cancer, 7 defaulted follow-up and could not be contacted by telephone or post, and 6 claimed they could no

longer recall or articulate their pain experience adequately to participate in this study. After excluding these patients, the 45 remaining patients included 28 males and 17 females. They had a median age of 52 years and a mean age of 51.6 years (range 22—83 years). None refused to participate in this study, giving an overall response rate of 75.0%.

Of these 45 patients, 22 had major surgery by a VATS approach, 8 had open thoracotomy, 3 had median sternotomy, and 12 had blunt chest trauma. At the time of enrollment to the study, the mean duration of their chest wall pain had been 5.76 months (range 1—62 months). The pain was described as severe (7—10 on the 10-point analog scale) by 24 patients (53.3%). Chest wall paresthesia distinct from sharp wound pain was reported by 32 patients (71.1), of whom 18 described the symptoms as severe (56.3%). The pain or paresthesia affected work in 11 patients (24%), reduced perceived exercise tolerance in 7 patients (16%), affected sleep in 7 patients (16%), and noticeably affected normal activities of daily life in 10 patients (22%).

At the close of this study, the 45 surveyed patients had taken gabapentin for a mean duration of 21.9 weeks (range 1—68 weeks).

3.1. Pain

At the close of study, 33 of the 45 patients (73.3%) reported a reduction of their pain scores on a 10-point analog scale compared to their scores prior to gabapentin treatment. There were 19 patients (42.2%) who reported a reduction in their pain scores of 50% or more.

The data relating pain reduction to the initial type of operation or trauma, the initial severity of pain, and the final daily dose of gabapentin used (after titration during the first seven days of the treatment) is summarized in Table 1. No correlation can be found between pain reduction and operation or trauma type, or between pain reduction and the final daily dose of gabapentin used. However, more severe levels of initial pain were significantly associated with improvement in pain following gabapentin treatment.

Further subgroup analyses failed to detect any association between pain reduction with gabapentin use and the age, sex, or occupation of the patients. There was similarly no correlation between pain reduction and the underlying pathologies necessitating surgery in the first place.

Note was taken of other medications taken concurrently by the patients during the study period. The aforementioned paracetamol/dextropropoxyphene preparation was used by 17 patients occasionally on an 'as required' basis, and 2 patients used forms of traditional Chinese herbal medications for their chest wall discomforts. Neither of these treatments was found to correlate with pain reduction with gabapentin use.

3.2. Paresthesia

At the time of enrollment to the study, 32 patients (71.1%) described having chest wall paresthesia that they could distinguish from the sharp wound-related pains. Numbness of the chest wall was described by 14 patients, pins and needles by 12, chest wall 'bloating' sensations by 8, electric shock-like sensations by 2, and burning and hyperesthesia by 1 each. These incidences and characteristics of chest wall paresthesia following thoracic surgery are similar to those we have previously reported [11,12].

At the close of study, 24 of these 32 patients (75.0%) reported a reduction of their paresthesia scores on a 10-point analog scale following gabapentin treatment. The data relating paresthesia reduction to the initial type of operation or trauma, the initial severity of pain, and the final daily dose of gabapentin used (after titration during the first seven days of the treatment) is summarized in Table 2. No correlation can be found between paresthesia reduction and any of these factors, although there was a trend for more of those with initially severe paresthesia to benefit from gabapentin treatment. Subgroup analyses failed to correlate paresthesia reduction after gabapentin use with the age, sex, or occupation of the patients, or with the underlying pathologies necessitating surgery in the first place.

3.3. Adverse effects

None of the patients in this study died or had any major adverse event as a result of gabapentin use.

Minor side effects related to use of gabapentin are summarized in Table 3. Overall, 18 patients (40.0%) reported at least one minor side effect. The most common such side effects were somnolence and dizziness. The incidence of side effects was found not to correlate with any patient

Table 1
The effect of gabapentin on pain following thoracic surgery or trauma

	Number of patients	Pain improved	*p*-value
Operation/trauma			
VATS	22	14 (63.6%)	
Thoracotomy	8	7 (87.5%)	
Sternotomy	3	3 (100%)	
Blunt trauma	12	9 (75.0%)	NS
Initial pain severity			
Mild (1—3)	9	3 (33.3%)	
Moderate (4—6)	12	9 (75.0%)	
Severe (7—10)	24	21 (87.5%)	0.009
Final titrated dose of gabapentin used			
300 mg nocte	21	16 (76.2%)	
300 mg bd	10	7 (70.0%)	
300 mg tds	14	10 (71.4%)	NS

Table 2
The effect of gabapentin on paresthesia following thoracic surgery or trauma

	Number of patients	Paresthesia improved	*p*-value
Operation/trauma			
VATS	15	9 (60.0%)	
Thoracotomy	8	7 (87.5%)	
Sternotomy	2	1 (50.0%)	
Blunt trauma	7	6 (85.7%)	NS
Initial pain severity			
Mild (1—3)	5	3 (60.0%)	
Moderate (4—6)	9	5 (55.6%)	
Severe (7—10)	18	16 (88.9%)	NS
Final titrated dose of gabapentin used			
300 mg nocte	14	9 (64.3%)	
300 mg bd	6	6 (100%)	
300 mg tds	12	9 (75.0%)	NS

Table 3
Side effects relating to gabapentin use following thoracic surgery or trauma

Side effect	Number of patients
Somnolence	11 (24.4%)
Dizziness	3 (6.7%)
Diarrhea	2 (4.4%)
Nausea/dyspepsia	2 (4.4%)
Palpitations	1 (2.2%)
Headache	1 (2.2%)

demographic factor, the initial type of operation or trauma, the initial severity of pain or paresthesia, or the final daily dose of gabapentin used.

In three patients (6.7%), use of gabapentin was discontinued because of intolerance of side effects. These included dizziness in two patients and diarrhea in the third.

3.4. Discontinuation of treatment

At the close of the study, 11 patients (24.4%) were still taking gabapentin and claimed that attempts at stopping the drug resulted in recurrence of the neuropathic discomforts. Gabapentin was stopped after complete resolution of the pain or paresthesia in 22 patients (48.9%). In four patients (8.9%), gabapentin was stopped after its use resulted in no perceived improvement in the discomforts. As mentioned above, in three patients (6.7%), gabapentin was discontinued because of the side effects caused.

In five cases (11.1%), the patients refused to continue treatment with gabapentin despite improvements in their pain or paresthesia levels and despite lack of any adverse effects. The reason they gave was generally that they believed that prolonged use of 'Western' medications was 'bad for the body.' Such views are not uncommon among the local Chinese community in Hong Kong.

3.5. Patient satisfaction

Table 4 shows the overall satisfaction with gabapentin treatment as expressed by the patients on a 10-point analog scale. Defining a score of '5' as a pass mark, 40 patients (88.9%) were satisfied with gabapentin treatment for their pain following thoracic surgery or trauma. A score of '7' or more was given by 21 patients (46.7%).

Patient satisfaction was found not to correlate with any patient demographic factor, the initial type of operation or trauma, the initial severity of pain or paresthesia, or the final daily dose of gabapentin used.

Of the five dissatisfied patients giving a score of less than '5,' one belonged to the group that stopped taking gabapentin despite improvements in their pain and lack of any adverse effects. The other four were the same four patients for whom gabapentin was stopped after its use resulted in no perceived improvement. In none of these patients was the occurrence of side effects a source of dissatisfaction.

Table 4
Satisfaction with gabapentin in thoracic surgery patients

Satisfaction score	Number of patients
0–2	2 (4.4%)
3–4	3 (6.7%)
5–6	19 (42.2%)
7–8	16 (35.6%)
9–10	5 (11.1%)

4. Discussion

The fact that the pain following thoracic surgery often proves so difficult to treat may be due to its multifactorial nature. Our previous studies have suggested that chest wall paresthesia is one discrete component of the overall noxious experience following thoracic surgery [11,12]. This paresthesia appears to have characteristics resembling those of the neuropathic pain syndromes, including neuralgia, burning, electrical allodynia, and hyperalgesia which are poorly relieved by conventional analgesic treatments [9,10]. Intercostal neuropathy may result from injury to the intercostal bundles during thoracic surgery or trauma. Patients undergoing a posterolateral thoracotomy have been shown to have reduced superficial abdominal reflexes and impaired intercostal nerve neurophysiologic performance [7,8,14], suggesting that a physiologic basis for neuropathic pain in thoracic surgery patients may exist.

If this hypothesis is true, the use of an agent known to specifically treat neuropathic pain may presumably also reduce the pain and discomfort following thoracic surgery or trauma. Gabapentin was first developed as an anticonvulsant drug, but it has been proven to effectively treat neuropathic pain syndromes, such as post-herpetic neuralgia and diabetic peripheral neuropathy [9,10,15,16]. It appears to act on voltage-dependent calcium ion channels at the post-synaptic dorsal horn neurons [9,17]. As such channels have been associated with the responsiveness of the nociceptive system, it has been proposed that gabapentin may therefore block the influx of calcium as a secondary messenger in the nocireception experience, thereby interrupting the development of neuropathic pain.

Except for a single case report in 1998 [13], we know of no other reports in the literature describing the use of gabapentin for the treatment of pain in cardiothoracic surgery patients. To our knowledge, ours is the first study to document this use of gabapentin.

In this study, we achieved our primary objective of exploring the safety profile of gabapentin, finding it to be safe and well tolerated for use in pain relief in thoracic surgery patients. Although 40% of patients experienced at least one minor side effect, only three patients (6.7%) had to discontinue use of gabapentin because of the side effects and no patient expressed dissatisfaction with gabapentin use because of side effects. We can compare our results with the accumulated data for the first two major controlled trials for gabapentin use in post-herpetic neuralgia—with a total of 336 patients receiving gabapentin [15,16]. In those two studies, the overall incidences of dizziness, somnolence, and diarrhea were 28.0%, 21.4%, and 5.7%, respectively, and 16.0% of patients had to discontinue gabapentin therapy because of side effects. In our current study, the incidences of dizziness, somnolence, and diarrhea were 6.7%, 24.4%, and 4.4%, respectively, and only 6.7% of patients had to discontinue gabapentin therapy because of side effects.

With regard to our secondary objective, it was found that overall gabapentin reduced the perceived severity of pain in 73.3% of patients, and chest wall paresthesia in 75.0%. It would also appear that the benefits of gabapentin in reducing pain might be significantly greater in patients whose initial, pre-treatment pain was more severe. We found that 42.2% of our patients reported a reduction in pain scores of 50% or more after using gabapentin. This compares with rates of 29—34% in previous trials of gabapentin use for post-herpetic pain [15,16]. At the close of the study, around three quarters of patients perceived their pain as either completely resolved after finishing gabapentin therapy or under control by continued use of gabapentin. That close to 90% of patients expressed satisfaction with gabapentin overall as prescribed for their post-operative or post-traumatic chest pain further demonstrates its acceptability to patients in this role.

Despite these encouraging results, we would refrain from drawing overly strong conclusions or recommendations regarding the analgesic properties of gabapentin in thoracic surgery patients at this stage given the limitations of the current study. We acknowledge that short of a randomized placebo-controlled trial, it would not be possible to attribute the pain reductions observed to the gabapentin treatment alone. In addition, our study is limited by a very heterogeneous cohort of patients in terms of initial pathology or trauma, and the surgical approaches used. We appreciate that the mechanisms of chest wall insult varies considerably between VATS, thoracotomy, sternotomy and blunt chest trauma, and that studies with larger cohorts will be required to determine which groups may benefit most from gabapentin and how. Given the small size of our study, we would refrain from speculating with regards the different rates of response amongst patients with different initial sources of pain. Our present study suggests only that use of gabapentin may be safe in thoracic surgical practice regardless of the initial painful stimulus. We have also not yet established a fixed set of criteria for the cessation of gabapentin treatment. Previous trials involving gabapentin for post-herpetic neuralgia typically restricted treatment to a seven- or eight-week course [15,16]. In contrast, in this study, some patients have been taking gabapentin for considerably longer, based, in most cases, on the patients' own reports that discontinuation resulted in recurrence of the pain. Whether this represents a form of psychosomatic dependence, and whether there may be detrimental effects from prolonged usage remains to be elucidated.

Nevertheless, we believe our study has demonstrated the safety profile of using gabapentin in thoracic surgery patients for the first time, paving the way for future studies. We are currently embarking on a randomized controlled trial to further investigate the analgesic efficacy of this drug in specifically treating refractory post-thoracotomy pain. We also envisage that future studies will be necessary to define the cost-effectiveness of gabapentin therapy vis-à-vis more conventional analgesic strategies, and to identify the patient groups that may benefit most.

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