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# Preoperative Oral Pregabalin Reduces Acute Pain after Thoracotomy

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## Abstract

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

**BACKGROUND:** Nowadays pain control is one of the most important challenges for physicians, surgeons and anesthesiologists. New drugs and procedures to control pain have always been a major topic for researches.

**AIM:** In this study, we evaluated the effects of preoperative pregabalin administration on relieving postoperative pain after thoracotomy surgery.

**MATERIALS AND METHODS:** This study is a randomised, double-blind clinical trial, performed on 60 patients who underwent thoracotomy at Afzalipoor hospital in Kerman, Iran. They were divided into case and control groups. Two hours before surgery an oral capsule of 300 mg pregabalin or placebo was given to patients. All patients similarly underwent general anaesthesia. Pain, nausea and vomiting were evaluated based on the visual analogue scale (VAS) and frequency. This study was verified and obtained the ethics committee code of K/92/489 from Kerman University of Medical Sciences.

**RESULTS:** The average age of the pregabalin group was  $39.7 \pm 5.8$  years and the control group  $41.3 \pm 6.1$  years. The average pain score after regaining consciousness was  $6.1 \pm 0.2$  in the case group and  $7.9 \pm 0.1$  in the control group, and there was a significant difference between the 2 groups ( $p$ -value = 0.002). In the control group, 2 patients and the intervention group 3 patients, experienced nausea and vomiting. There was a significant difference between the overall average pethidine consumption and the average visual analogue scale in both groups.

**CONCLUSION:** Pregabalin administration before thoracotomy is effective to reduce postoperative pain in patients. More research is needed to determine the optimal dose of pregabalin for preoperative administration.

## Introduction

Postoperative pain is a problem that can cause various complications if it is not controlled efficiently. Proper postoperative pain control is of great importance in preventing complications such as; tachycardia and hypertension, myocardial ischemia, decreased alveolar ventilation and poor wound healing [1].

Thoracotomy procedure provides access to intra-thoracic organs (heart, lungs, oesophagus, thoracic aortic), is associated with severe postoperative pain which is considered to be excruciating. Besides pain, it has adverse

physiological and pathological effects on surgery and disease outcome and prognosis. Postoperative pain causes patients to become less mobile and try to relieve their pain by taking shallow breaths and having fewer chest movements. As a result, this reduction can cause hypoxia and pulmonary dysfunction that can lengthen wound healing. On the other hand, the patient's immobility can cause atelectasis and predispose that can lead to infection and respiratory failure [2]. This pain can cause an increase in neuroendocrine and sympathetic tone systems activity, immunosuppression, hyper-coagulation; increased catabolism, restricted movement, breathing problems, and delay in getting out of bed. Consequently opioids are usually recommended to

suppress this pain. However, opioids have side-effects like respiratory suppression, sedation, gastrointestinal symptoms, and urinary retention. Nowadays attempts have been made to use alternative substances for postoperative pain reduction [3] [4]. It seems that in many cases pain is not controlled efficiently, considering the necessity of pain control especially when it is too severe [5]. Therefore, the need to assess various methods which can reduce postoperative pain is evident. By searching in the academic literature, pregabalin seems to have postoperative pain controlling and preventive properties, and this could reduce the need to administer opioids after surgery [6].

Pregabalin is a drug which binds to the  $\alpha$ -2- $\delta$  subunit of presynaptic calcium channels and prevents calcium from entering. This blocks the release of excitatory neurotransmitters like glutamate, noradrenaline, serotonin, dopamine, and substance p. The central sensitisation syndrome in dorsal horn neurons and centres with high-density synaptic connections such as the amygdala, neocortex and hippocampus is responsible for the increase in postoperative pain. Increase production of  $\alpha$ -2- $\delta$  subunits probably plays a role in central sensitisation. It seems that pregabalin reduces pain by reducing this syndrome [7] [8].

The studies mentioned above show that other researchers have conducted similar studies on the effects of pregabalin as a postoperative pain reliever such as limbs and abdominal surgeries. Since thoracotomy is one of the most common surgeries in medical fields and has one of the most excruciating postoperative pains, the necessity of pain control and reducing opioids consumption to reduce side-effects after this surgery is quite evident. However, no study was conducted on this type of surgery, hence; we decided to study the effects of preoperative pregabalin administration on relieving postoperative pain after thoracotomy operation.

## Materials and Methods

This research is an interventional clinical trial study. After getting approval from the ethics committee and obtaining a written informed consent, 60 male and female patients' between the age of 20 to 30 years old with ASA class I and II who were candidates for thoracotomy surgery at Afzalipour Hospital affiliated to Kerman University of Medical Sciences were selected. It is worth stating that the same surgical procedure (Lobectomy) through thoracotomy was performed for all patients.

The sample size was calculated based on results from similar studies and using the same sample size formula with type 1 error ( $\alpha$ ) of 0.05 for 30

patients in each group with the total of 60 patients.

Criteria for exclusion was; pregnancy, history of allergy to pregabalin, history of treatment with pregabalin or gabapentin, history of chronic pain syndromes and consuming painkillers, addiction to alcohol or drugs, allergy to pethidine, psychiatric drugs consumption, surgery lasting more than 4 hours, uncontrolled blood pressure, history of convulsion and patients who had preoperative pain based on the visual analogue scale (VAS).

Patients were randomly divided into two groups of intervention and control (the first one receiving pregabalin and the second one placebo). Neither the patients nor the drug administrators and the person in charge of recording pain scores based on the visual analogue scale (VAS), knew which type of drug was being administered. 300 mg of oral pregabalin was administered 2 hours before surgery as a premedication for pain relief. The control group received placebo (a similar looking capsule without any active pharmaceutical ingredients). VAS was explained to everyone before anaesthesia.

Method of anaesthesia was similar for all patients. First, 0.05 mg/kg midazolam and 3  $\mu$ g/kg fentanyl as premedication 3 min before induction and then 5mg/kg thiopental and 0.5 mg/kg atracurium and 5 mg/kg sodium thiopental were injected intravenously and then patients were intubated with double lumen tubes. Anaesthesia was maintained with 100% O<sub>2</sub> and 1/2% (one MAC) isoflurane. During surgery, 0.2 mg/kg atracurium injections were repeated once every half an hour and 50  $\mu$ g fentanyl injections were repeated once an hour to keep blood pressure and heart rate between 20% standard limits. After surgery when they were transferred to recovery, the patients' experienced pain scores were recorded using VAS every 15 minutes during the first hour after regaining consciousness and every four hours in the first 24 hours after being transferred to the ward.

Twenty-five mg of opioids (pethidine) were administered intravenously in case of having a higher pain score of 3 or more.

All information including the patients' demographic information, pain scores at different intervals and the amount of administered opioids were recorded. The obtained data were analysed with SPSS software version 21 using descriptive statistics indices. To determine the relationship between age, height, weight, amount of pethidine consumption, and experienced postoperative pain levels (VAS) in the two groups, a t-test was used.

In this study, in addition to collecting a written informed consent from the participants, two phone numbers were given to them to call the project executive and the department of research and technology of Karman's University of Medical Sciences to ask any questions or to report any complaint. All ethical principles for medical research in

the 2009 declaration of Helsinki were observed. At the same time if any patient was unwilling to participate, they were assured that this would not affect their treatment process.

## Results

This study was conducted on 60 patients who were admitted to Afzalipour academic medical centre for thoracotomy surgery. Each group consisted of 30 patients (Figure 1).

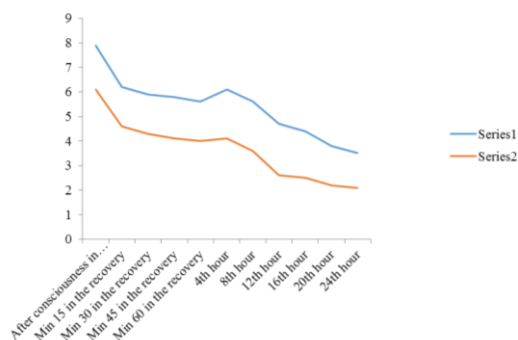


Figure 1: Pain level changes based on VAS

Table 1 shows each group's demographic characteristics. The patients' age, height and weight variables were evaluated, and based on these demographic characteristics; there were no statistically significant differences between the two groups ( $P > 0.05$ ).

Table 1: Demographic characteristics of the groups

	Pregabalin	Control	P-value
Age (year)	39.7 ± 5.8	41.3 ± 6.1	0.08
Weight (kg)	72.4 ± 10.2	74.6 ± 14	0.2
Gender	17male/13female	14male/16female	0.26
Height (cm)	165.1 ± 9.4	170.4 ± 12.9	0.09

Evaluating pain VAS scores in the recovery room (after regaining consciousness), average pain scores were  $7.9 \pm 0.1$  for the control group and  $6.1 \pm 0.2$  for the pregabalin group, which showed a statistically significant relationship between the two groups ( $P$  value = 0.002). Table 2 presents the data. Based on this chart, pain score was significantly different between the two groups during the first 15 minutes in the recovery room, at which time some patients received pethidine (patients with a pain score of 3 or higher). During the next 24 hours, pain scores were generally on a diminishing course for both groups. In comparison, pain scores were lower in the pregabalin group during each evaluation times, and a significant difference was observed between the two groups.

Table 2: Comparing pain VAS scores at all evaluation times

	Control	Pregabalin	P-value
After consciousness in the recovery	0.1 ± 7.9	6.1 ± 0.2	0.002
Min 15 in the recovery	6.2 ± 0.3	4.6 ± 0.4	0.01
Min 30 in the recovery	5.9 ± 0.2	4.3 ± 0.3	0.01
Min 45 in the recovery	5.8 ± 0.2	4.1 ± 0.2	0.01
Min 60 in the recovery	5.6 ± 0.3	4.0 ± 0.2	0.01
4th hour	6.1 ± 0.1	4.1 ± 0.4	0.002
8th hour	5.6 ± 0.1	3.6 ± 0.3	0.001
12th hour	4.7 ± 0.2	0.1 ± 2.6	0.001
16th hour	4.4 ± 0.1	2.5 ± 0.1	0.001
20th hour	3.8 ± 0.4	2.2 ± 0.2	0.001
24th hour	3.5 ± 0.3	2.1 ± 0.1	0.003

Average pethidine consumption changes during the first 24 hours of evaluation are presented in Table 3. All in all, there was a significant difference, considering pethidine consumption between the two groups during evaluation times.

Table 3: Average pethidine consumption (mg) changes in the 2 groups during evaluation hours

	control	pregabalin	p-value
First 15 minutes in the recovery	43.3±2.1	37.5±2.3	0.02
4th hour	33.3±2.2	26.6±1.2	0.001
8th hour	23.3±1.1	15.00±2.2	0.0001
12th hour	21.6±1.6	5.8±1.9	0.0001
16th hour	17.5±2.1	4.1±1.7	0.001
20th hour	15.0±2.2	3.3±1.5	0.001
24th hour	12.5±1.7	2.5±1.3	0.001

These changes were in a way that average pethidine consumption levels were higher in the control group while on average the pregabalin group received less pethidine. Also, Figure 2 shows that pethidine consumption was decreasing more dramatically in the intervention group.

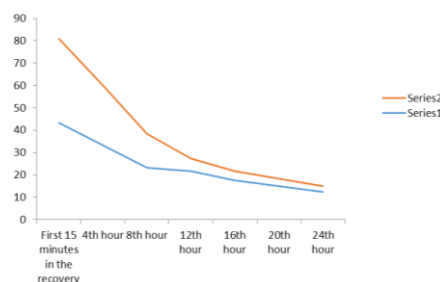


Figure 2: Average pethidine consumption (mg) changes in the 2 groups

Considering the side-effects of pregabalin which was expected based on the drug's pharmacodynamics, our evaluations showed that only three cases of nausea and vomiting were reported in the pregabalin group, whereas only two cases were reported in the control group. Hence, this was not statistically significant. This showed that these symptoms were probably caused by anaesthetics or had other causes. In our other evaluations in the first 24 hours, no other side-effects than the two were observed and all of the patients responded well to supportive treatment and made a full recovery. Of course, pregabalin's side-effects may occur after 24 hours or in the long term, which was not evaluated in this study.

## Discussion

In this study, observation showed that pregabalin significantly lowers postoperative pain VAS scores. It also lowers postoperative pethidine consumption levels. The Akhavan Akbari et al., the study showed that administering 150 mg of pregabalin before orthopaedic surgery can cause better pain control and by decreasing pethidine consumption, it can reduce the drug's side-effects [9].

The Entezary et al., a study on preemptive effects of pregabalin vs placebo on acute pain after abdominal hysterectomy showed that a 300 mg administration of pregabalin before surgery could reduce postoperative pain and malaise and also reduces the need for opioids. However, side-effects like dizziness increased in the pregabalin group [10].

The Imani et al., study on the effects of a single dose of pregabalin before surgery on postoperative pain after minor surgery revealed that even a 150 mg administration of oral pregabalin before minor surgeries could reduce pain score and opioids consumption in the first 24 hours after surgery. It is well worth mentioning that this amount of pregabalin had no side-effects [11].

The Imani et al., study on the effects of adding oral pregabalin to patient-controlled intravenous analgesia (PCIA) on pain levels after orthopaedic surgery showed that oral consumption of 300 mg pregabalin during the day after surgery could reduce pain score and opioids consumption in the next 48 hours after operation [12].

In their study titled "Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy", Agarwal et al., concluded that a single 150 mg preoperative dose of pregabalin significantly reduced pain levels and opioids consumption after laparoscopic cholecystectomy. Also, the side-effects were similar to the control group [13].

Experimental models of neuropathic and inflammatory pains have shown that aminobutyric acid analogues such as gabapentin and pregabalin have analgesic and anti-nociceptive components [14]. It is believed that hypersensitivity of central nerves may lead to a more severe postoperative pain. Preoperative administration of gabapentin, before inflammatory trauma or surgical stimulation, might reduce central nerves hypersensitivity [15].

Compared to gabapentin, pregabalin is a lipid-soluble alternative and can cross the blood-brain barrier, and has better pharmacokinetics and less drug interaction due to a lack of hepatic metabolism.

In the present study, the occurrence of postoperative nausea and vomiting were evaluated. Results showed that there were similar minor side-

effects in both groups. In separate studies, side-effects amongst patients were different. In a study on patients who had undergone dental surgery [16] and gynaecological surgery [17], symptoms like vomiting, nausea and stomachaches were observed. However, in studies on patients who had undergone hysterectomy [18], laparoscopic cholecystectomy [19], and orthopedic surgeries [20], no side-effects were observed [21] [22]. In this study, pain levels were evaluated based on the visual analogue scale (VAS) and the observation was that this drug can significantly lower the average pain score. Most studies [19] [20] [21] [22] have achieved similar results. For example, in other studies pregabalin, consumption reduced postoperative pain, while in a minor gynecological surgeries [17]; 150 mg preoperative administration of pregabalin had no pain-relieving effects, which might have been due to its low dosage.

One property of this drug that was observed in many studies is the reduction of postoperative opioids and analgesics consumption levels in the groups receiving pregabalin. These include studies which showed that pregabalin significantly lowers postoperative opioids consumption levels and also reduces opioids side-effects like vomiting. Those studies also showed that pregabalin reduces opioids consumption in patients with acute neuropathic pain. Another study [23] [24] showed that pregabalin reduces opioids consumption after hip arthroplasty.

Considering the effects of pregabalin, we suggest further studies to be conducted on patients in various age groups and bigger sample size. We also suggest that types of surgery, patients' BMI and the pregabalin dosage to be considered as variables. Finally, the effects of this drug in major surgeries should be studied based to see if there are any interfering factors. Finally, more research is needed to determine the optimal dose of pregabalin for preoperative administration.

In conclusion, preoperative administration of pregabalin can yield better pain control, and since this drug reduces the need for analgesics consumption, it can reduce hospital costs and adverse drug reactions.

## Ethics Committee Approval

Ethics committee approval was received for this study from the ethics committee of Kerman University of Medical Sciences, Iran. Written informed consent was obtained from patients who participated in this study.

## Author Contributions

HS, MH, MRL, and HJ conceived and designed the experiments, performed the experiments, analysed the data, and wrote the paper: All authors have read and approved the final manuscript

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