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Original Article

Perioperative pregabalin reduced fatigue scores after thoracoscopic pneumonectomy in a RCT of NSCLC patients

Yue Zhao[1,2*], Yan Li[1,2*], Lei Sun[1,2*], Fang Gao[1,2], Qin Yin[1,2], Wei Cheng[1,2,3], Zhiping Wang[1,2], Yinming Zeng[1,2]

[1]Xuzhou Medical University, Xuzhou 221002, Jiangsu, China; [2]Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, Jiangsu, China; [3]Huai'an First People's Hospital, The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University, Huai'an 223399, Jiangsu, China. [*]Equal contributors.

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Abstract: Postoperative fatigue is prevalent, but non-small cell lung cancer (NSCLC) patients receive poor treatment after video-assisted thoracoscopic surgery (VATS). The main objective of the present trial is to observe the anti-fatigue function of pregabalin in NSCLC patients after surgery. Patients requiring VATS pneumonectomy were randomized into two groups (n=33): the experimental and control groups. The results showed that the experimental group's Identity-Consequence Fatigue Scale (ICFS) scores on days 1, 3, 7, and 30 after the operation decreased more than those of the control group. On days 1, 2, and 3 following surgery, there were significant differences in the Visual Analog Scale (VAS) scores, the incidence rate of anxiety and depression, and the Athens Insomnia Scale (AIS) scores between the two groups. Furthermore, we discovered that the ICFS scores were positively related to the VAS scores, Hospital Anxiety and Depression Scale (HADS) scores, and AIS scores. Postoperative fatigue and pain, on the other hand, were more closely related. Finally, this analysis suggested that perioperative pregabalin can reduce postoperative fatigue in NSCLC patients by relieving postoperative pain, anxiety, and depression, improving postoperative sleep quality, and promoting early recovery.

Keywords: Pregabalin, postoperative fatigue, video-assisted thoracoscopic surgery, analgesia

Introduction

Postoperative fatigue (POF) is a group of symptoms including different degrees of muscle weakness, physical pain, insomnia, depression and immune dysfunction in patients after surgery [1]. In the perioperative period, postoperative fatigue is one of the most common complications. Due to severe pain, decreased body function, high psychological pressure and other reasons, patients with lung cancer are at risk of postoperative fatigue. A study on severe postoperative complications in lung cancer patients showed that approximately 51%-70% of patients still felt tired in the 4th month after surgery, which seriously hindered their postoperative recovery [2]. Cheville et al. also found that for lung cancer patients, fatigue not only seriously affects their quality of life but also plays an essential role in predicting their prognosis [3].

The high-risk factors for POF include postoperative pain, anxiety, depression, surgical type, anesthetic factors, stress response, and endocrine and metabolic disorders [1, 4]. The pain caused by pneumonectomy impedes patients from breathing hard and coughing after the operation, which affects postoperative expectoration and lung expansion, aggravates the patients' anxiety, insomnia and stress reaction. All these factors ultimately leads to postoperative fatigue. On the other hand, the physical discomfort caused by postoperative fatigue makes patients more anxious and less tolerant to pain, thus decreasing their sleep quality and leading to persistent postoperative fatigue. As symptoms such as fatigue, pain, harmful psychological factors and insomnia

often appear together, it is essential to treat all elements concurrently [5].

Pregabalin is a gabapentinoid, a γ-aminobutyric acid analog that binds to the CACNA2D subunit, licensed for adult neuropathy pain management [6]. Pregabalin is thought to improve its analgesic effects by inhibiting calcium influx and relieving central neuropathic pain [7, 8]. In addition, pregabalin can reduce the excitability of dorsal horn neurons by antagonizing the abnormal release of various excitatory neurotransmitters, thus relieving anxiety, depression and sleep disorders [9-11]. Recent literature has shown that pregabalin could significantly relieve neuropathic pain, anxiety and insomnia after pneumonectomy. As a result, applying pregabalin during the perioperative period is beneficial to shortening the hospitalization time of patients and promoting their early postoperative recovery [12-14].

To date, pregabalin has been widely used in perioperative analgesia, its anti-anxiety and insomnia effects have also been clinically verified. However, to our knowledge, no studies have been performed to demonstrate pregabalin's impact on postoperative fatigue. We hypothesized that perioperative pregabalin could reduce postoperative fatigue in NSCLC patients by relieving postoperative pain, anxiety and depression, improving sleep quality and promoting early postoperative recovery.

Methods

Study design

The trial was approved by the Medical Ethics Committee of the local hospital (XYFY2022-KL208-01) and then registered in the ChiCTR Center (ChiCTR2200063306). Patients who underwent VATS without contraindications were recruited from September 2022-October 2022. After signing the authorization consent form, they participated in the trial and underwent surgery. The following procedure and report adhere to the consort declaration [15].

Sample calculation

It was regarded as meaningful when the ICFS scores were reduced by 10 points (standard deviation =13) across groups in the previous study. Accordingly, the sample size calculated by the two-tailed test (α=0.05, β=0.8 and an effect size d=0.75) was 29 in G-power software. The 33 patients of each group were finally recruited, taking into account the 10% dropout rate.

Patient selection

The inclusion criteria were as follows: (a) Age ≥18 years old; (b) ASA grade I-II; (c) Patients who had been previously diagnosed with NSCLC and underwent video-assisted thoracoscopic surgery.

The exclusion criteria were as follows: (a) Patients with preoperative fatigue; (b) Patients who were allergic to or highly sensitive to the test drugs; (c) Patients who were taking gabapentin or pregabalin at the time of the trial; (d) Patients who had severe renal dysfunction; (e) Patients who were participating in long-term fasting; (f) Patients who had a recent history of surgery or radiotherapy and chemotherapy; (g) Patients with a history of chronic pain or taking analgesics every day; (h) Patients who had cognitive dysfunction and a history of epilepsy.

The rejection criteria were as follows: (a) Patients who refused or for whom the operation was canceled; (b) Patients who experienced serious complications that required a secondary operation or caused death.

Study procedures and interventions

According to a computer-generated randomization sequence, pregabalin or placebos were randomly distributed to eligible patients after they signed informed consent forms. Being blinded to the data collection, a researcher determined whether patients received pregabalin or a placebo according to the opaque and sealed envelope. The experimental group received pregabalin 150 mg orally 1-2 hours before the operation, and 75 mg of pregabalin was taken orally from the first day after the operation twice a day for 5 days. The control group received the placebo at the same time.

All patients entered the induction room 30 minutes before anesthesia induction. The monitor recorded electrocardiogram (ECG), invasive blood pressure (IBP), heart rate (HR) and oxygen saturation (SpO_2).

Intravenous anesthesia induction scheme: midazolam, 0.05 mg/kg; sufentanil, 0.5 ug/kg; etomidate, 0.3 mg/kg and rocuronium, 0.6 mg/kg. After the patient's consciousness disappeared and the muscle relaxation effect was satisfactory, tracheal intubation was performed under a visual laryngoscope. The parameters of volume control mode were as follows: tidal volume, 6-8 ml/kg; respiration frequency, 12-16 times/min; respiration ratio, 1:1.5; fractional inspired oxygen tension (FiO_2), 80%; end-tidal pressure of carbon dioxide ($PetCO_2$), 35-45 mmHg and positive end-expiratory pressure (PEEP), 5-10 cmH_2O.

Maintenance program: The various schemes of sevoflurane, remifentanil and propofol were adjusted to maintain stable life signs during the surgery. Sevoflurane was stopped 30 minutes before the end of the operation. All anesthetic drugs were stopped after the operation, and the patients remained intubated during transport to the postanesthesia care unit (PACU).

Postoperative management: ECG, IBP, HR and SpO_2 were continuously monitored after the patients entered the PACU. The endotracheal tube was pulled out when extubation was indicated. An analgesic pump was given to relieve pain, and a mask was used for oxygen inhalation. When the patient's modified Aldrete score was above 9, we sent him back to the ward.

All patients were given intravenous patient-controlled analgesia (PCA) after returning to the ward. The PCA device was sufentanil 2 ug/kg + tosetron 6 mg + physiological saline to 120 ml. The basal rate was 2 ml/h, and the bolus was 0.5 ml with a lockout interval of 15 minutes.

Outcome measure

Before the study was conducted, the outcomes were established. The primary outcome was the ICFS scores, which measured the patients' fatigue before surgery and on days 1, 3, 7 and 30 after surgery [16]. The ICFS is a multidimensional, scientifically validated measurement tool designed primarily to evaluate postoperative fatigue and recovery in surgical patients [17].

After evaluating the basic values, the VAS and HADS scores of the patients were recorded on days 1, 2, 3, 7 and 30 after the operation. The AIS was used to record patients' sleep quality on days 1, 2, 3 and 7 after the operation, and patients' sleep quality on day 30 after the operation was evaluated by using the Pittsburgh Sleep Quality Index (PSQI). The cumulative dose of morphine after surgery, the incidence of adverse events, the retention time of the drainage tube and the postoperative length of stay were also recorded.

Statistical analysis

The Windows version of the SPSS application, version 26.0, was used for statistical analysis. The mean ± standard deviation (SD) was used to present the quantitative variables showing a normal distribution (Kolmogorov-Smirnov test). Descriptive statistics for data showing a skewed distribution were expressed as median and range. Rates were used to describe binomial variables. Student's t test was selected to compare continuous data with a normal distribution. The Mann-Whitney U test was selected to analyze the continuous data with a skewed distribution. "Pearson's chi-square" or "Fisher's exact" analysis was selected for the categorical variables. The associations between postoperative fatigue, pain, anxiety, depression and sleep quality were assessed by Spearman's correlation.

A generalized estimated equation (GEE) analysis was performed to analyze the time trend in the ICFS, VAS, AIS scores and the incidence of anxiety and depression. The measurement data were all expressed as the mean ± standard deviation (SD). Bonferroni-corrected multiple comparisons were made for intergroup differences in mean values at each time point. For all tests, statistical significance was defined as a two-sided *P value of* <0.05.

Results

Baseline characteristics

As shown in **Table 1** and **Figure 1**, we initially assessed 66 eligible patients undergoing VATA, with 33 in the experimental group and 33 in the control group. All patients completed the study and signed informed consent forms. There was no significant difference in demographic information, including age (*P*=0.087), sex (*P*=0.618), BMI (*P*=0.120), ASA grade (*P*=0.314), ICFS score (*P*=0.063), incidence of

Table 1. Preoperative patient characteristics

	EG n=33 (100%)	CG n=33 (100%)	*P* value
Age, year	53.6±9.2	56.9±5.9	0.087
Sex			0.618
Male, n (%)	13 (39.4%)	15 (45.5%)	
Female, n (%)	20 (60.6%)	18 (54.5%)	
BMI, kg/m^2	24.3±2.5	25.4±2.8	0.120
ASA Grade, n (%)			0.314
I	15 (45.5%)	11 (33.3%)	
II	18 (54.5%)	22 (66.7%)	
ICFS score			0.063
Median	42.0	46.0	
Range	39.0-51.0	42.0-56.5	
HADS			
Anxiety, n (%)	24 (72.7%)	22 (66.7%)	0.592
Depression, n (%)	8 (24.2%)	12 (36.4%)	0.284
VAS score			0.089
Median	0.0	1.0	
Range	0.0-1.0	0.0-1.0	
PSQI score			0.481
Median	5.0	6.0	
Range	3.0-8.0	4.0-8.0	
AIS score	6.2±2.6	6.8±3.0	0.359
Comorbidities, n (%)			
Hypertension	7 (21.2%)	5 (15.2%)	0.523
Diabetes	4 (12.1%)	2 (6.1%)	0.669
Heart Disease	1 (3.0%)	3 (9.1%)	0.606
Lacunar Cerebral Infarction	2 (6.1%)	4 (12.1%)	0.669
Smoker, n (%)	3 (9.1%)	5 (15.2%)	0.706
History of Operation, n (%)	14 (42.4%)	11 (33.3%)	0.447

Abbreviations: EG, Experimental Group; CG, Control Group; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; ICFS, Identity-Consequence Fatigue Scale; HADS, Hospital Anxiety and Depression Scale; VAS, Visual Analog Scale; PSQI, Pittsburgh Sleep Quality Index; AIS, Athens Insomnia Scale.

anxiety (*P*=0.592), incidence of depression (*P*=0.284), VAS score (*P*=0.089), PSQI score (*P*=0.481), AIS score (*P*=0.359), hypertension (*P*=0.523), diabetes (*P*=0.669), heart disease (*P*=0.606), lacunar cerebral infarction (*P*=0.669), smoking (*P*=0.706), and history of operation (*P*=0.447).

Postoperative fatigue

Figure 2 and **Table 2** show differences in the ICFS scores on days 1, 3, 7 and 30 after the operation. The generalized estimation equation analysis of ICFS scores showed that the interaction effects between different time points, groups and time points were statistically significant (*P*<0.05). At each time point after surgery, the experimental group's total ICFS scores were less than the control group's. Both groups showed an increase in postoperative fatigue scores, and the ICFS scores on POD1 (EG: 100.0±8.7; CG: 115.5±8.4) were significantly higher than those on POD3 (EG: 80.1±12.7; CG: 95.4±8.1), POD7 (EG: 90.1±18.3; CG: 106.1±11.9) and POD30 (EG: 63.7±13.0; CG: 76.3±11.9). There was a significant difference in ICFS scores at different time points within the same group (*P*<0.05). The total ICFS scores in both groups did not return to the preoperative level 30 days after the operation.

Pain

The VAS scores of the two groups on POD1 (EG: 4.7±1.0; CG: 5.9±1.2), POD2 (EG: 3.6±0.7; CG: 4.8±0.9), POD3 (EG: 2.8±0.8; CG: 4.0±1.2) and POD7 (EG: 2.2±1.0; CG: 3.0±0.9) were statistically significant (*P*<0.05), but there was no significant difference on day 30 (EG: 1.4±0.7; CG: 1.6±0.7) between the two groups after surgery. The VAS scores of the two groups gradually decreased with time (*P*<0.05). However, there was no significant difference in VAS scores between the two groups on PRE (EG: 0.5±0.6; CG: 0.8±0.7) and POD30 (*P*>0.05) (**Table 3**).

The incidence of anxiety and depression

On days 1 (anxiety: EG: 20 (60.6%); CG: 28 (84.8%); depression: EG: 22 (66.7%); CG: 30 (90.9%)), 2 (anxiety: EG: 10 (30.3%); CG: 19 (57.6%); depression: EG: 12 (36.4%); CG: 24 (72.7%)) and 3 (anxiety: EG: 2 (6.1%); CG: 9 (27.3%); depression: EG: 2 (6.1%); CG: 8 (24.2%)) after surgery, the incidence rate of anxiety and depression were significantly different in the cases (*P*<0.05). Nevertheless, there were no significant differences on days 7 (anxiety: EG: 5 (15.2%); CG: 6 (18.2%); depression: EG: 3 (9.1%); CG: 6 (18.2%)) and 30 (anxiety: EG: 2 (6.1%); CG: 5 (15.2%); depression:

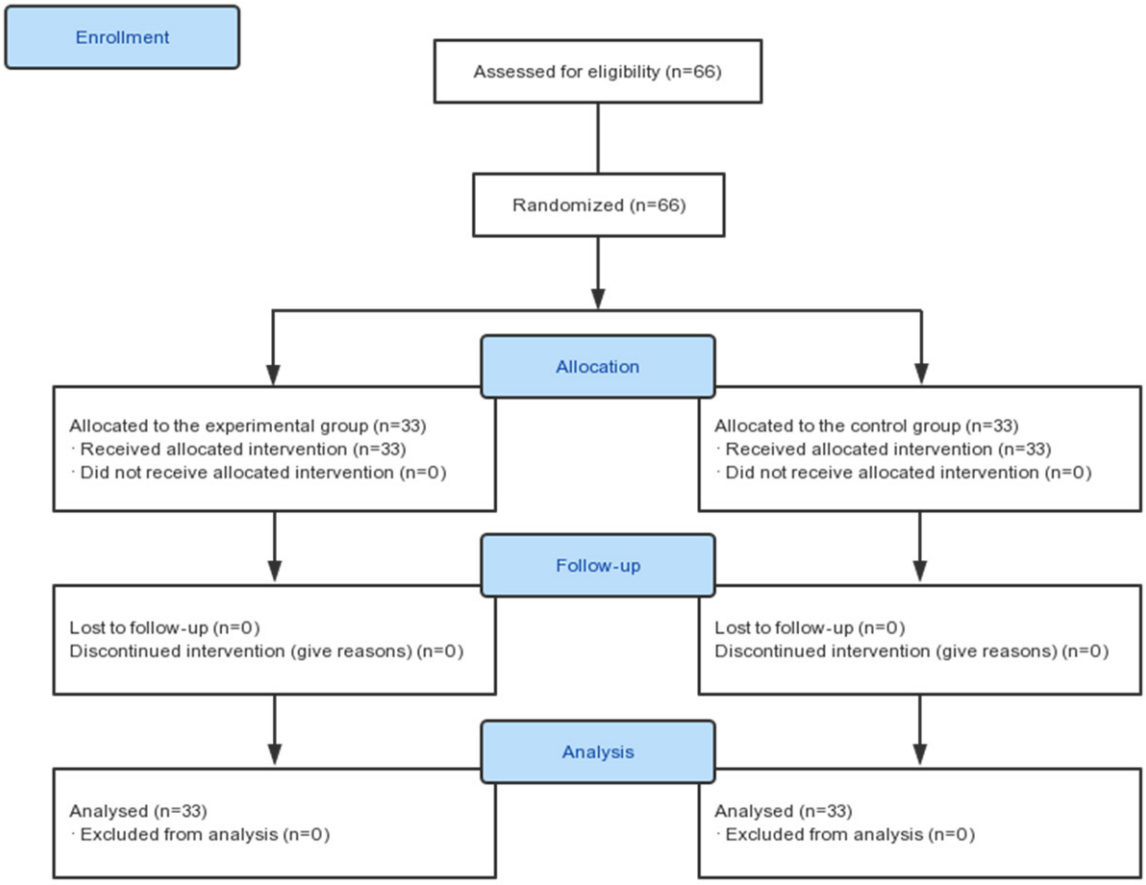

Figure 1. Flowchart of the patients enrolled in the study, including the overall changes in participants. A total of 66 eligible patients were divided into two groups based on intervention measures.

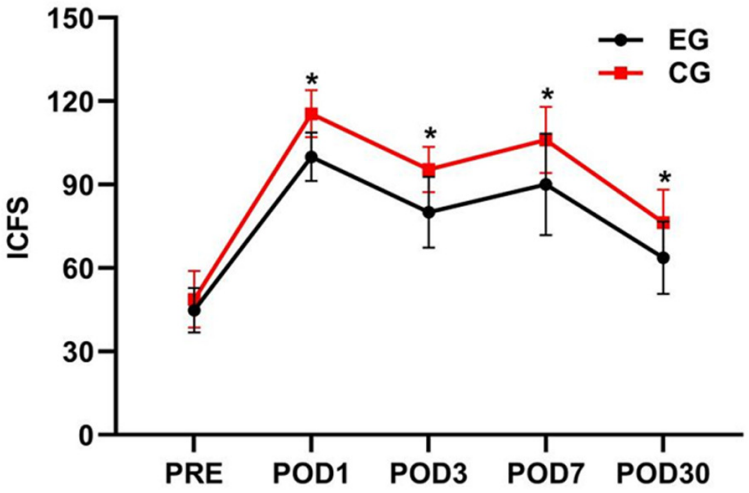

Figure 2. Fatigue scores in two cases. Generalized estimated equation analysis was performed to analyze the time trend in the ICFS scores. The horizontal axis is the time, and the vertical axis is the ICFS score. The measurement data were all expressed as the mean ± standard deviation (SD). *Compared with the EG group, $P<0.05$. Abbreviations: EG, Experimental Group; CG, Control Group; ICFS, Identity-Consequence Fatigue Scale; PRE, Preoperative; POD, Postoperative Day.

EG: 1 (3.0%); CG: 3 (9.1%)) after surgery between groups ($P>0.05$) (**Tables 4**, **5**).

Sleep quality

Both groups' AIS scores declined gradually on days 1 (EG: 13.6±4.1; CG: 17.0±3.7), 2 (EG: 9.2±2.7; CG: 11.3±3.2), and 3 (EG: 7.3±2.3; CG: 8.8±2.3) after surgery, and the differences were statistically significant ($P<0.05$). However, the experimental group's scores were less than those of the control group. There was no significant difference in the AIS scores on PRE (EG: 6.2±2.6; CG: 6.8±3.0), POD7 (EG: 7.6±2.7; CG: 7.9±2.6) or the PSQI scores on day 30 (EG: median 5.0, range 4.0 to 8.0;

Table 2. Fatigue scores

	EG (*n*=33)	CG (*n*=33)	*P value*
PRE	44.9±8.1	48.7±10.2	0.079
POD1	100.0±8.7[a]	115.5±8.4[a]	<0.001
POD3	80.1±12.7[a,b]	95.4±8.1[a,b]	<0.001
POD7	90.1±18.3[a,b,c]	106.1±11.9[a,b,c]	<0.001
POD30	63.7±13.0[a,b,c,d]	76.3±11.9[a,b,c,d]	<0.001
P value	<0.001	<0.001	-

Annotate: Wald χ^2_{time}=2317.363, *P*<0.001; Wald $\chi^2_{time*group}$=25.282, *P*<0.001; Wald χ^2_{group}=40.621, *P*<0.001. Abbreviations: EG, Experimental Group; CG, Control Group; PRE, Preoperative; POD: Postoperative Day; [a]Compared with PRE; [b]Compared with POD1; [c]Compared with POD3; [d]Compared with POD7, *P*<0.05.

Table 3. VAS scores

	EG (*n*=33)	CG (*n*=33)	*P value*
PRE	0.5±0.6	0.8±0.7	0.055
POD1	4.7±1.0[a]	5.9±1.2[a]	<0.001
POD2	3.6±0.7[a,b]	4.8±0.9[a,b]	<0.001
POD3	2.8±0.8[a,b,c]	4.0±1.2[a,b,c]	<0.001
POD7	2.2±1.0[a,b,c,d]	3.0±0.9[a,b,c,d]	0.001
POD30	1.4±0.7	1.6±0.7[a,b,c,d,e]	0.199
P value	<0.001	<0.001	-

Annotate: Wald χ^2_{time}=1306.311, *P*<0.001; Wald $\chi^2_{time*group}$=20.379, *P*=0.001; Wald χ^2_{group}=37.736, *P*<0.001. Abbreviations: EG, Experimental Group; CG, Control Group; PRE, Preoperative; POD, Postoperative Day; [a]Compared with PRE; [b]Compared with POD1; [c]Compared with POD2; [d]Compared with POD3; [e]Compared with POD7, *P*<0.05.

Table 4. The incidence of anxiety

	EG (*n*=33)	CG (*n*=33)	*P value*
PRE	24 (72.7%)	22 (66.7%)	0.591
POD1	20 (60.6%)	28 (84.8%)	0.022
POD2	10 (30.3%)[a,b]	19 (57.6%)	0.020
POD3	2 (6.1%)[a,b,c]	9 (27.3%)[a,b,c]	0.016
POD7	5 (15.2%)[a,b]	6 (18.2%)[a,b,c]	0.522
POD30	2 (6.1%)[a,b,c]	5 (15.2%)[a,b,c]	0.225
P value	<0.001	<0.001	-

Annotate: Wald χ^2_{time}=174.429, *P*<0.001; Wald $\chi^2_{time*group}$=11.568, *P*=0.041; Wald χ^2_{group}=4.710, *P*=0.030. Abbreviations: EG, Experimental Group; CG, Control Group; PRE, Preoperative; POD, Postoperative Day; [a]Compared with PRE; [b]Compared with POD1; [c]Compared with POD2, *P*<0.05.

CG: median 6.0, range 4.0 to 8.0) between the two groups (*P*>0.05) (**Table 6**).

Table 5. The incidence of depression

	EG (*n*=33)	CG (*n*=33)	*P value*
PRE	8 (24.2%)	12 (36.4%)	0.280
POD1	22 (66.7%)[a]	30 (90.9%)[a]	0.012
POD2	12 (36.4%)[b]	24 (72.7%)[a]	0.001
POD3	2 (6.1%)[b,c]	8 (24.2%)[b,c]	0.033
POD7	3 (9.1%)[b,c]	6 (18.2%)[b,c]	0.278
POD30	1 (3.0%)[a,b,c]	3 (9.1%)[b,c]	0.298
P value	<0.001	<0.001	-

Annotate: Wald χ^2_{time}=236.008, *P*<0.001; Wald $\chi^2_{time*group}$=8.984, *P*=0.110; Wald χ^2_{group}=12.198, *P*<0.001. Abbreviations: EG, Experimental Group; CG, Control Group; PRE, Preoperative; POD, Postoperative Day; [a]Compared with PRE; [b]Compared with POD1; [c]Compared with POD2, *P*<0.05.

Table 6. Sleep quality

	EG (*n*=33)	CG (*n*=33)	*P value*
AIS			
PRE	6.2±2.6	6.8±3.0	0.401
POD1	13.6±4.1[a]	17.0±3.7[a]	<0.001
POD2	9.2±2.7[a,b]	11.3±3.2[a,b]	0.003
POD3	7.3±2.3[b,c]	8.8±2.3[a,b,c]	0.007
POD7	7.6±2.7[a,b]	7.9±2.6[b,c]	0.636
P value	<0.001	<0.001	-
PSQI			
POD30			0.393
Median	5.0	6.0	
Range	4.0-8.0	4.0-8.0	

Annotate: Wald χ^2_{time}=304.364, *P*<0.001; Wald $\chi^2_{time*group}$=7.405, *P*=0.116; Wald χ^2_{group}=11.620, *P*=0.001. Abbreviations: EG, Experimental Group; CG, Control Group; PRE, Preoperative; POD, Postoperative Day; AIS, Athens Insomnia Scale; PSQI, Pittsburgh Sleep Quality Index; [a]Compared with PRE; [b]Compared with POD1; [c]Compared with POD2, *P*<0.05.

Correlation analysis

The correlation coefficient is defined as "r". This study revealed a positive correlation. The "r" values between the ICFS and VAS scores were 0.618 (POD1) and 0.611 (POD3) (*P*<0.01). The "r" values between the ICFS and anxiety scores were 0.409 (POD1) and 0.447 (POD3) (*P*<0.01). The "r" values between the ICFS and depression scores were 0.573 (POD1) and 0.504 (POD3) (*P*<0.01). The "r" values between the ICFS and AIS scores were 0.563 (POD1) and 0.587 (POD3) (*P*<0.01). Postoperative fatigue and pain, on the other hand, were more

Table 7. Correlation coefficient data

	r	*P* value
POD1		
The VAS Score	0.618	<0.01
The anxiety Score	0.409	<0.01
The depression Score	0.573	<0.01
The AIS Score	0.563	<0.01
POD3		
The VAS Score	0.611	<0.01
The anxiety Score	0.447	<0.01
The depression Score	0.504	<0.01
The AIS Score	0.587	<0.01

Abbreviations: POD, Postoperative Day; VAS, Visual Analog Scale; AIS, Athens Insomnia Scale; r, Spearman's rank correlation coefficient.

closely related (POD1: r=0.618; POD3: r=0.611, *P*<0.01) (**Table 7**).

Comparison of adverse events

Table 8 shows no severe side events in the two groups. The proportion of patients with side events in the experimental group was 36.4%, and that in the control group was 51.5% on POD1. On POD2, 4 patients in the experimental group and 6 in the control group reported adverse events. The proportion of patients with side events in the experimental group was 3.0%, and that in the control group was 9.1% on POD3. The minor side events showed no difference across patients three days after the operation (*P*>0.05).

Other variables

The operation duration, anesthesia duration, total morphine during surgery, urine output, blood loss, total fluid infusion, the occurrence of hypotension, type of surgery and retention time of drainage tube showed no significant difference (*P*>0.05). The experimental group required less total morphine (EG: median 15.0, range 10.0 to 22.5; CG: median 20.0, range 11.0 to 38.0) and spent less time in the hospital after surgery (EG: median 4.0, range 3.0 to 5.0; CG: median 5.0, range 3.5 to 7.0), the difference was statistically significant (*P*<0.05) (**Table 9**).

Discussion

Pregabalin is a gabapentinoid that reduces the central release of excitatory molecules, it has been approved for treating neuropathic pain in adults [18]. In this study, pregabalin relieved postoperative fatigue in patients within one month after VATS. At any measurement point, the experimental group demonstrated lower ICFS scores, a shorter postoperative hospital stay, and an insignificant increase in the incidence of postoperative adverse events, compared with the control group.

Table 8. Adverse events

	EG n=33 (100%)	CG n=33 (100%)	*P value*
POD1	12 (36.4%)	17 (51.5%)	0.215
POD2	4 (12.1%)	6 (18.2%)	0.492
POD3	1 (3.0%)	3 (9.1%)	0.606

Abbreviations: EG, Experimental Group; CG, Control Group; POD, Postoperative Day.

Postoperative fatigue is a common complication and seriously affects patients' quality of life. The first study to observe postoperative fatigue of lung cancer shows that an estimated 75%-90% of patients with lung cancer report fatigue after cancer treatment. Postoperative fatigue is closely related to pain, depression and sleep disorders, which seriously hinders the postoperative recovery of patients and imposes a severe burden on patients, families and society [4]. Considering that postoperative fatigue is a multidimensional disease, its management has important clinical significance.

As a first-line drug for neuropathic pain management, pregabalin has a good analgesic effect. It has been reported that the correlation between the pregabalin dose and the VAS score after surgery is negative [19]. According to multiple meta-analyses, pregabalin at 75-150 mg could improve postoperative analgesia, relieve anxiety and depression, and reduce the incidence of adverse events [20, 21]. Pregabalin is quickly absorbed by the body after oral administration, reaching the maximum plasma concentration within 1 hour. Therefore, the patients in our study received pregabalin 150 mg 1-2 hours before surgery and 75 mg the first day after surgery, twice a day for five days. Additionally, none of the recipients of pregabalin reported severe adverse events as predicted.

Regardless of whether thoracotomy or video-assisted thoracoscopic surgery, the incidence

Table 9. Other variables

	EG n=33 (100%)	CG n=33 (100%)	*P* value
Operation Duration, mins	113.7±37.5	127.9±55.4	0.227
Anesthesia Duration, mins	143.9±40.3	153.0±58.4	0.462
Total Morphine During Surgery, mg			0.302
Median	224.3	247.8	
Range	198.1-288.0	175.7-329.8	
Urine Output, ml			0.863
Median	220.0	300.0	
Range	150.0-300.0	110.0-300.0	
Blood Loss, ml			0.094
Median	50.0	50.0	
Range	30.0-50.0	50.0-50.0	
Total Fluid Infusion, ml			0.337
Median	1000.0	1000.0	
Range	750.0-1325.0	1000.0-1250.0	
Crystalloid Fluid, ml			0.179
Median	900.0	1000.0	
Range	650.0-1000.0	700.0-1000.0	
Artificial Colloid, ml			0.759
Median	0.0	0.0	
Range	0.0-250.0	0.0-225.0	
Occurrence of Hypotension, n (%)	18 (54.5%)	23 (69.7%)	0.205
Type of Surgery, n (%)			0.710
Segmental Resection	7 (21.2%)	6 (18.2%)	
Lobectomy	20 (60.6%)	23 (69.7%)	
Wedge Resection	6 (18.2%)	4 (12.1%)	
Total Morphine after Surgery, mg			0.013
Median	15.0	20.0	
Range	10.0-22.5	11.0-38.0	
Retention Time of Drainage Tube, day			0.242
Median	3.0	3.0	
Range	2.0-4.0	2.0-5.0	
Postoperative Hospital Stay, day			0.042
Median	4.0	5.0	
Range	3.0-5.0	3.5-7.0	

Abbreviations: EG, Experimental Group; CG, Control Group.

of postoperative neuropathic pain is high, which seriously affects patients' quality of life after the operation [22, 23]. The results of this experiment showed that the VAS score in the experimental group decreased significantly on days 1, 2, 3 and 7 after the operation, and there was a significant difference in the total morphine consumption after the operation between the two groups. This means that the application of pregabalin reduces the degree of acute postoperative pain and the consumption of morphine after the operation, which is consistent with previous findings [12, 24].

Interestingly, previous studies that evaluated the effect of pregabalin on postoperative pain yielded contradictory results [25, 26]. The first reported that six days of perioperative pregabalin did not affect pain during the nine months after thoracoscopic surgery. The different results may have come from the deviation caused by the different drugs used in the PCA

device, and whether the thoracoscopic port sites were infiltrated with local anesthetic. Indifferent use of incision local infiltration can partially block the transmission of neuropathic pain, this would weaken the analgesic effect of pregabalin and lead to a different conclusion. The second study reported that the available data do not support pregabalin for systematic prevention of chronic postsurgical pain (CPSP). Although CPSP has been described as predominantly neuropathic, it is more like a mixed neuropathic and nociceptive pain syndrome, compared with simple neuropathic pain [27]. The application of pregabalin interferes with the development of its neuropathy characteristics and changes the severity. However, pregabalin lacks the preventive efficacy of long-term chronic pain. Therefore, the conclusions will also differ at different time points of pain measurement.

A randomized controlled study of 94 patients who underwent thoracotomy showed that fatigue severity is closely related to pain [2]. In this study, through correlation analysis, we found that postoperative ICFS scores were positively correlated with VAS scores, which was consistent with previous findings. Following pneumonectomy, the nervous system activates the stress response and releases inflammatory factors into the blood, the activation of tryptophan metabolism through the NMDA receptor ultimately leads to postoperative fatigue [28, 29]. More recently, a study of 599 newly diagnosed patients with NSCLC reached the same conclusion. They found that inflammatory factors, especially IL-8 and IL-10, may be the main biological mechanism of fatigue, pain and depression [30]. Previous studies have proven that pregabalin combines with presynaptic voltage-gated calcium channels, which blocks the cascade amplification effect of central sensitization and inflammatory mediators, so it can effectively prevent pain and lessen the inflammatory response following pneumonectomy [12, 31, 32]. Based on these considerations, we speculate that pregabalin reduces the postoperative stress response and inflammatory mediators, relieves patients' postoperative pain, and then alleviates postoperative fatigue. This may be the possible mechanism for decreasing the postoperative fatigue scores in the experimental group.

In this randomized controlled trial, we found that patients in the experimental group had a lower incidence of anxiety and depression, higher sleep quality and lower fatigue score within one week after the operation. In recent years, much research that observed the risk factors for postoperative fatigue showed that postoperative fatigue was closely associated with negative emotion and sleep disorders [1, 4]. An altered psychological state, such as anxiety and insomnia, will lead to postoperative dyspnea and aggravate postoperative fatigue in patients undergoing pneumonectomy. This kind of fatigue will also incur more severe insomnia, anxiety and depression, thus forming a vicious cycle. Pregabalin has been shown to ameliorate sleep latency and wakefulness after sleep onset, increase deep sleep, and have adjunctive effects on depression and anxiety [33-35]. Therefore, according to our comprehensive analysis, pregabalin can effectively alleviate the anxiety and depression of patients and improve their postoperative sleep quality. At the same time, good mood and sleep quality can effectively alleviate patients' fatigue.

We also analyzed the association of postoperative fatigue with factors that included pain, depression, anxiety, and sleep quality. The results suggested a positive association between the ICFS scores and the VAS, HADS, and AIS scores. Additionally, there was a more vital link between postoperative fatigue and pain (POD1: $r=0.618$; POD3: $r=0.611$, $P<0.01$). Previous clinical data showed that the occurrence of early acute neuropathic pain after pneumonectomy is approximately 20%-30% [22]. If postoperative pain cannot be well controlled, patients will be in a state of anxiety and fear for a long time. This case will aggravate patients' insomnia, negatively affect their postoperative quality of life, and make them feel persistent fatigue [23, 36, 37]. As a result, we believe that effective perioperative analgesic management can relieve postoperative pain, anxiety, and depression, improve the quality of postoperative sleep, while also reducing postoperative fatigue. This has positive implications for postoperative rehabilitation. However, this effect is no longer appreciable on days 7, 30 after the operation, which may be related to the shift in mood, the restoration of sleep patterns, and the elimination of drug metabolism.

As a prospective, randomized controlled trial, this study found that pregabalin significantly reduced the fatigue scores of patients with NSCLC after VATS, without increasing the perioperative risk. What's more, the primary mechanism of pregabalin's anti-fatigue function might be related to its improvement in postoperative pain. This discovery adds to pregabalin's research on postoperative recovery, and provides a new idea for multimode relief of postoperative fatigue. The limitation of this study is that, for safety reasons, there was no higher dose of pregabalin to explore the dose-effect relationship. At the same time, there was no significant difference in the side events between groups, which may be due to the small dosage of our experiment. In addition, TNF, IL-1, and CRP are the early sensitive indexes of stress response intensity, but these indexes were not measured in this study. All of them require ongoing advancement through follow-up research.

Conclusions

Perioperative pregabalin can reduce postoperative fatigue in NSCLC patients by relieving postoperative pain, anxiety, and depression, improving sleep quality, and promoting early postoperative recovery.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei Cheng and Qin Yin, Xuzhou Medical University, Xuzhou 221002, Jiangsu, China. Tel: +86-18796205791; Fax: +86-0517-84907287; E-mail: 53974314@qq.com (WC); Tel: +86-13814446826; E-mail: 810780794@qq.com (QY)

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