



# Preoperative Low-dose and High-dose Pregabalin and Cardiovascular Response to Endotracheal Intubation: A Prospective, Randomized, Single-blind, Controlled Study in China

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## ABSTRACT

**Purpose:** A prospective, randomized, single-blind, controlled clinical study was designed to evaluate the efficacy and tolerability of preoperative pregabalin on cardiovascular response to laryngoscopy and endotracheal intubation.

**Methods:** Patients aged 18–60 years with an American Society of Anesthesiologists scale score of I or II were recruited and randomly allocated to receive placebo (control), low-dose (150-mg) pregabalin, or high-dose (300-mg) pregabalin. The medications were orally administered 1 hour before general anesthesia. Heart rate, systolic and diastolic blood pressures, and mean arterial blood pressure were measured and recorded prior to the administration of placebo or pregabalin; before endotracheal intubation; and at 0, 1, 3, 5, 7, and 10 minutes after intubation. The sedation score was evaluated 1 hour after the administration of placebo or pregabalin.

**Findings:** A total of 90 patients were enrolled ( $n = 30$  per group). Pregabalin (150 or 300 mg) was associated with reduced blood pressure fluctuations after intubation, but with no significant differences between the 2 dose groups. Pregabalin was associated with an inhibitory effect on heart rate fluctuations and reduced hemodynamic complications after intubation, in a dose-dependent manner, but no effect on the required perioperative opioid dosage was found. Both doses were effective in reducing preoperative anxiety, but visual analog scale pain scores at 1 hour after surgery were reduced only in limb and spine as well as abdominal surgeries. A

pregabalin-related adverse reaction was dizziness, which was observed at 1 hour after surgery in both groups.

**Implications:** In this study, high-dose (300-mg) pregabalin effectively attenuated cardiovascular response after endotracheal intubation. [ClinicalTrials.gov](https://doi.org/10.1016/j.clinthera.2018.11.006) identifier: NCT03456947. (*Clin Ther.* 2019;41:68–77) © 2018 Elsevier Inc. All rights reserved.

**Key words:** blood pressure, cardiovascular responses, general anesthesia, laryngoscope and intubation, pregabalin, stress response.

## INTRODUCTION

Direct laryngoscopy and endotracheal intubation during general anesthesia are noxious stimuli that can cause mechanical injury to oropharyngeal tissues and provoke responses in the cardiovascular, respiratory, nervous, and other physiologic systems.<sup>1</sup> Although bronchospasm, intracranial and intraocular pressure elevation, hypertension, tachycardia, arrhythmia, and especially hemodynamic alterations occur transiently, the responses can be deleterious to patients with diseases of the cardio-/cerebrovascular and endocrine systems.<sup>2,3</sup> Various therapeutic medications and methods have been employed to reduce or suppress cardiovascular responses caused by endotracheal intubation,<sup>4</sup> including local

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anesthesia,<sup>5</sup> intravenous lidocaine,<sup>6</sup> drugs affecting adrenergic receptors (eg,  $\beta$ -adrenoceptor antagonists,<sup>7</sup>  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor agonists<sup>8</sup>), vasoactive agents (eg, glyceryl trinitrate,<sup>9</sup> calcium channel blockers,<sup>10</sup> sodium nitroprusside<sup>11</sup>), and a laryngeal mask.<sup>12</sup> However, the optimal medicine or method to avoid stress responses in these patients has not been unequivocally established.<sup>13</sup>

Pregabalin is a new generation of antiepileptic drug that interacts with the  $\alpha_2\text{-}\delta$  subunit of voltage-dependent calcium channels in the CNS and inhibits neuronal excitability.<sup>14</sup> Compared with that of gabapentin, another commonly used antiepileptic drug, the absorption of pregabalin in the gastrointestinal tract shows a better drug disposition, with peak plasma concentration occurring within 1 hour of administration in a dose-independent manner and without limitation of transport saturation.<sup>15</sup> Pregabalin is mainly used in the clinic to treat seizures, neuropathic pain, fibromyalgia, and anxiety disorders.<sup>16–18</sup> Recent studies have shown that perioperative oral administration of pregabalin can effectively reduce narcotic analgesic dosages during and after an operation, and also alleviate acute postoperative pain dose dependently.<sup>19–21</sup>

The present prospective, randomized, single-blind study was designed to establish the efficacy of premedication with pregabalin at 2 doses (150 and 300 mg) on cardiovascular responses induced by direct laryngoscopic endotracheal intubation in patients under general anesthesia.

## PATIENTS AND METHODS

### Patients and Groups

The study protocol was approved by the Research Ethics Committee of the Qingpu Branch of Zhongshan Hospital (affiliated with Fudan University, Shanghai, China), and written informed consent was obtained from each patient. The present prospective, randomized, single-blind trial was carried out from January 2017 to June 2017 in the Qingpu Branch of Zhongshan Hospital. The trial is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov) (identifier: NCT03456947; February 27, 2018).

Eligible patients were aged 18–60 years and scheduled for endotracheal intubation under direct laryngoscopic observation with general anesthesia and were evaluated before surgery. Patients were excluded from the study for the following reasons:

(1) American Society of Anesthesiologists scale score >II; (2) anticipated difficult intubation; (3) serious cardiopulmonary or hepatorenal disease; (4) obesity; (5) allergy to anesthetic drugs; and (6) use of sedative, hypnotic, or antihypertensive medication. In addition, patients were excluded from the study if the duration of intubation exceeded 22 seconds or if  $\geq 2$  intubation attempts were necessary.

Patients were recruited and randomly allocated, using random numbers generated by SPSS software version 22 (SPSS Inc, Chicago, Illinois), to 1 of 3 groups (30 in each): placebo (control), low-dose (150-mg) pregabalin (LDP), or high-dose (300-mg) pregabalin (HDP). The pregabalin was purchased from Pfizer Inc (New York, New York).

Corresponding premedications were administered orally with 20 mL of water at 1 hour before the induction of general anesthesia. The Ramsay sedation score (including status of anxiety and/or agitation; cooperative orientation and tranquility; response to commands; and sleep with brisk, sluggish, or no response to glabella or intensive sound stimuli) was recorded.<sup>22</sup>

On each patient's arrival in the surgical suite 1 hour after premedication, an intravenous infusion of crystalloid (6–8 mL/kg) was started lasting until completed anesthesia induction, and the cardiovascular activity was monitored by a routine 5-lead ECG and a noninvasive blood pressure monitor. Baseline systolic and diastolic blood pressure, mean arterial blood pressure (MABP), and heart rate were monitored, and Ramsay sedation scores were evaluated in each patient before the induction of general anesthesia.

### Operation Procedure

Fentanyl was administered at 1  $\mu\text{g}/\text{kg}$ , followed by a mask of 8 L/min of pure oxygen. Nitrogen oxides were discontinued for 3 minutes. Propofol was given at a dose of 2 mg/kg or was administered until the patient had no eyelash reflex. After intravenous injection of rocuronium 0.9 mg/kg for 90 seconds, endotracheal intubation was performed with the aid of a laryngoscope. Anesthesia was maintained by inhalation of sevoflurane and 60%  $\text{N}_2\text{O}$ , and the gases were continuously monitored. Mechanical ventilation maintained the  $\text{CO}_2$  partial pressure at 35–40 mm Hg at the end of exhalation. During the operation, 0.1 mg/kg of rocuronium was

continuously supplemented to maintain skeletal muscle relaxation. At the end of the operation, the residual muscle relaxant was antagonized by 0.05 mg/kg of neostigmine. The tracheal tube was removed after the patient's spontaneous breathing resumed.

During surgery, heart rate, mean arterial pressure, bispectral index, ECG, pulse oximeter levels, and exhaled CO<sub>2</sub> concentration were continuously monitored before and after the induction of general anesthesia; immediately after endotracheal intubation; and at 1, 3, 5, and 10 minutes after patient intubation. Specific values were recorded every 5 minutes until the end of the operation.

When patients had complications such as hypotension, hypertension, arrhythmia, hypoxemia, or bronchospasm, corresponding measures were taken. Tachycardia was considered to be a heart rate of >100 bpm and hypertension a systolic pressure >180 mm Hg. The physical symptoms of insufficient anesthesia depth were tears, perspiration, and a rosy complexion of the patient. At this time, the inhalation concentration of sevoflurane was increased and 0.5 µg/kg fentanyl administered. *Low blood pressure* was defined as an MABP of below 20% of the baseline level. When this situation occurred, the rate of intravenous infusion of a combination of vasopressor drugs was increased; *bradycardia* was considered as a heart rate of <60 bpm and was treated with 0.01 mg/kg atropine administered intravenously. All patients received a unified standard of anesthesia and surgical procedures. Preoperative sedation scores, heart rate, MABP after induction, and changes after tracheal catheterization of the airway were evaluated and recorded in the different groups of patients. After anesthesia was terminated, patients were transferred to the waking room until there were no adverse events such as nausea, vomiting, respiratory discomfort, hemodynamic instability (hypotension/hypertension or tachycardia/bradycardia), or adverse reactions such as dizziness or blurred vision.

### Sample Size

The number of patients studied was based on our initial pilot studies, and after referral to previously published papers, it was established that it was necessary to include at least 23 patients in each group to ensure a power of 0.80 for the detection of clinically meaningful reductions of 20% in heart rate and MABP. We anticipated a 10% dropout rate, so

the final planned cohort size was 90 patients, which permitted a type I error of  $\alpha = 0.05$ , a type II error of  $\beta = 0.5$ , and a power of 0.8.

### Statistical Analysis

The results were analyzed using Excel (Microsoft, Redmond, Washington), SPSS version 21 (SPSS Inc), Stata version 12.0 (StataCorp, College Station, Texas). Continuous variables are reported as means (SD). Any statistically significant differences between groups were assessed using ANOVA, the  $\chi^2$  test, and mixed linear model as required.  $P < 0.05$  was deemed statistically significant.

### RESULTS

The 90 patients scheduled for surgery were allocated into the 3 groups (30 patients per group). The groups had similar demographic characteristics, with no differences with regard to sex, age, weight, anesthesia scores (American Society of Anesthesiologists scale score of I or II), or types of surgery (Table I).

First, we measured and compared the sedation scores that were increased to level 2 after 1 hour of receiving pregabalin among the 3 groups. It was clear that the sedation score in the LDP and HDP groups were significantly higher than that in the control group, but the difference between the sedation scores in the LDP versus the HDP group was not significant (Figure 1A). In addition, the total operation time was not significantly different among the 3 groups (data not shown).

### Effects of Combinations of Opioids on Pain After Endotracheal Intubation

There were no significant differences in applications of fentanyl (71.4 [53.9] µg, 78.1 [17.83] µg, and 73.8 [20.77] µg;  $P = 0.754$ ) or sufentanil (33.62 [10.51] µg, 30.17 [10.3] µg, and 30.67 [12.23] µg;  $P = 0.429$ ) between the control, LDP, and HDP groups, respectively. In contrast, the mean visual analog scale scores at 1 hour after the end of surgery were significantly lower after limb and spinal surgery in the HDP group compared to that in the LDP group, as well as after abdominal surgery in the LDP group (Figure 1B).

At 1 hour after premedication, the mean heart rate in the HDP group was significantly lower than those in the control and LDP groups (both,  $P < 0.05$ ). After 1 minute of laryngoscopy and intubation in the

Table I. Patient's demographic and clinical data.

Characteristic	Control (n = 30)	LDP (n = 30)	HDP (n = 30)	P*
Age, mean (SD), y	48.57 (13.11)	45.70 (14.70)	50.23 (13.49)	0.440
Height, mean (SD), cm	164.95 (7.27)	167.80 (9.24)	165.20 (7.26)	0.499
Weight, mean (SD), kg	63.23 (11.57)	67.00 (9.30)	63.07 (11.90)	0.297
Sex, male/female	12/18	15/15	16/14	0.561
ASA score I/II	14/16	13/17	15/15	0.874
Type of surgery, no. (%)				
Limbs and spinal	13 (43.33)	17 (56.67)	8 (26.67)	0.062
Abdominal	11 (36.67)	8 (26.67)	10 (33.33)	0.700
Craniofacial and neck	6 (20.00)	5 (16.67)	12 (40.00)	0.081

ASA = American Society of Anesthesiologists; HDP = high-dose pregabalin; LDP = low-dose pregabalin.

\* Assessed using  $\chi^2$  test and one-way ANOVA.

control group, the heart rate was immediately increased compared to the heart rate at 1 hour after premedication, but the heart rates in LDP and HDP groups became lower than the values at 1 hour after premedication. Compared to that in the control group, the LDP and HDP groups had dose-dependent and significantly lower heart rates during intubation (Figure 2A).

No significant differences in MABP were measured in the HDP, LDP, or control groups before laryngoscopy and intubation. However, the MABP values in both the LDP and HDP groups were significantly attenuated after intubation, but the between-group difference was not significant (Figure 2B).

For arterial blood pressure, no significant differences were observed prior to or after premedication, but following intubation and laryngoscopy, the attenuations in SBP and DBP in the premedicated (LDP and HDP) groups were statistically significant compared to that in the control group during intubation. This effect was not dose dependent (Figure 3).

### Complications and Adverse Reactions

Hemodynamic complications within 10 minutes of intubation occurred more frequently in the control group (13 events), followed by the LDP group (8 events), and the HDP patients (1 event) (Table II).

None of the 3 groups of patients developed allergy. Of adverse reactions associated with the use of drugs, dizziness occurred in 13% of the LDP group

( $P = 0.038$ ) and in 20% of HDP patients ( $P = 0.010$ ) at 1 hour after taking pregabalin. At 1 hour after the operation, adverse reactions of dizziness, nausea, and vomiting occurred in the 3 groups. One patient in the HDP group had blurred vision, which was alleviated by  $\leq 24$  hours after operation. No obvious differences were detected in the prevalences of dizziness, nausea, or vomiting among the 3 groups at 24 hours after operation (Figure 4).

### DISCUSSION

Several publications have reported that preoperative oral administration of 150-mg pregabalin plays a significant role in maintaining hemodynamic stability during endotracheal intubation,<sup>23–26</sup> which is in agreement with our findings, but in this study the effect of a 300-mg pregabalin dose as a preoperative medication has been evaluated for the first time in Chinese patients. Postintubation stress response in patients with cardiovascular or endocrine system disease, such as ischemic heart disease, cerebral aneurysm or aortic dissection can lead to disastrous consequences. Shribman et al.<sup>27</sup> reported that laryngoscopy alone or combined with tracheal intubation increased arterial blood pressure and raised circulating catecholamine levels, while intubation significantly increased heart rate. Hassan et al.<sup>28</sup> and Reid et al.<sup>29</sup> documented a high prevalence of acute left ventricular failure, myocardial ischemia, cardiac arrhythmias, and cerebrovascular accidents after intubation in patients with hypertension. Aronson and Fontes<sup>30</sup> suggested

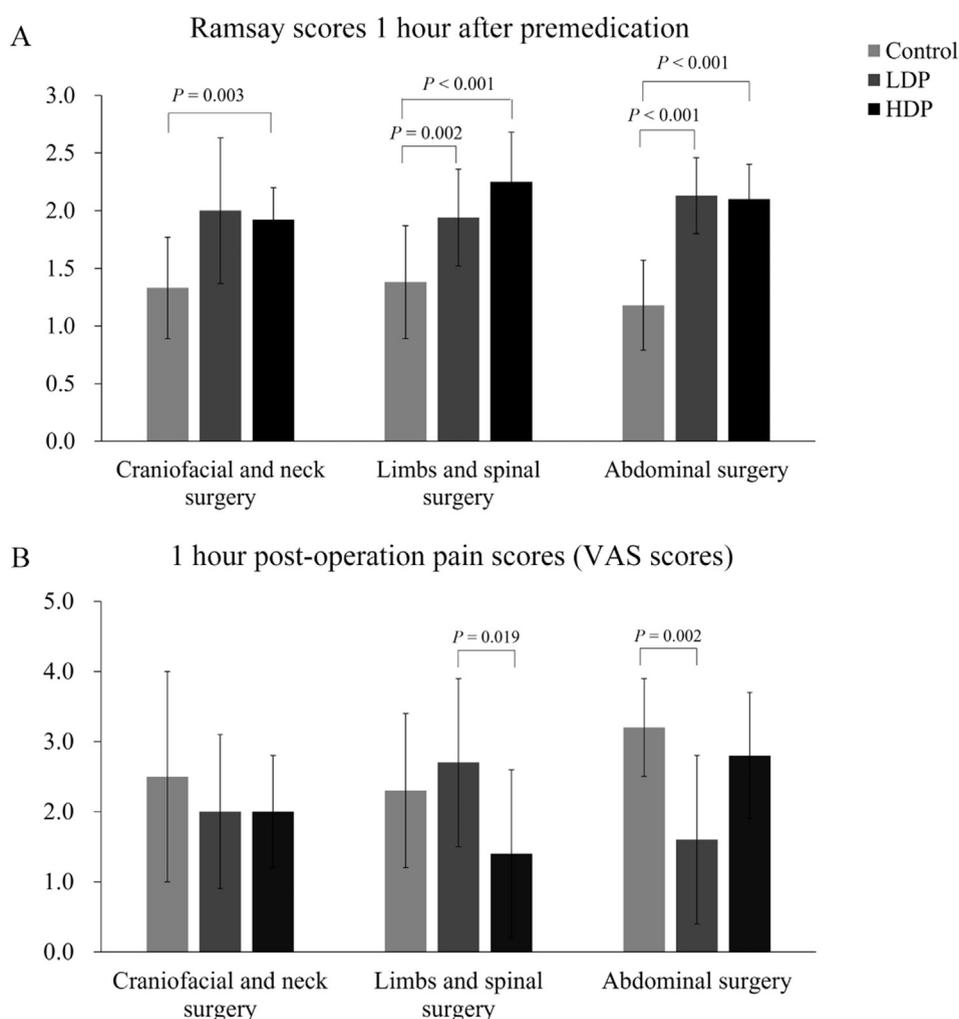


Figure 1. A Comparison of the Ramsay scores after 1 hour of premedication and B VAS scores of patients one hour after indicated operations. Note: The statistical differences between the groups were assessed using Student's t test.

that if pulse pressure is raised by as little as 10 mm Hg in both normotensive and hypertensive persons, there will be an associated 20% or more increased risk for developing renal failure, adverse cardiac events, and/or cerebral stroke. Our findings revealed that the heart rate and hemodynamic complications within 10 minutes after intubation were lower after preoperative pregabalin medication in a dose-dependent manner, while the mean arterial pressure was reduced to a similar extent in both the HDP and LDP groups. Similarly, the fluctuation range of blood pressures was significantly reduced in the LDP and HDP groups to a

similar extent compared to control patients. These findings are consistent with those from previous studies on intubation reaction in patients who received 150-mg pregabalin.<sup>23–25,31,32</sup>

In the literature, several meta-analyses have noted that preoperative pregabalin medication reduced postoperative pain.<sup>33–35</sup> However, another meta-analysis reported that the pain-reduction effects were more obvious in ophthalmologic, otorhinolaryngologic, thoracic, and abdominal surgeries than in gynecologic or orthopedic surgery,<sup>36</sup> which is in agreement with our findings that pain scores were significantly reduced

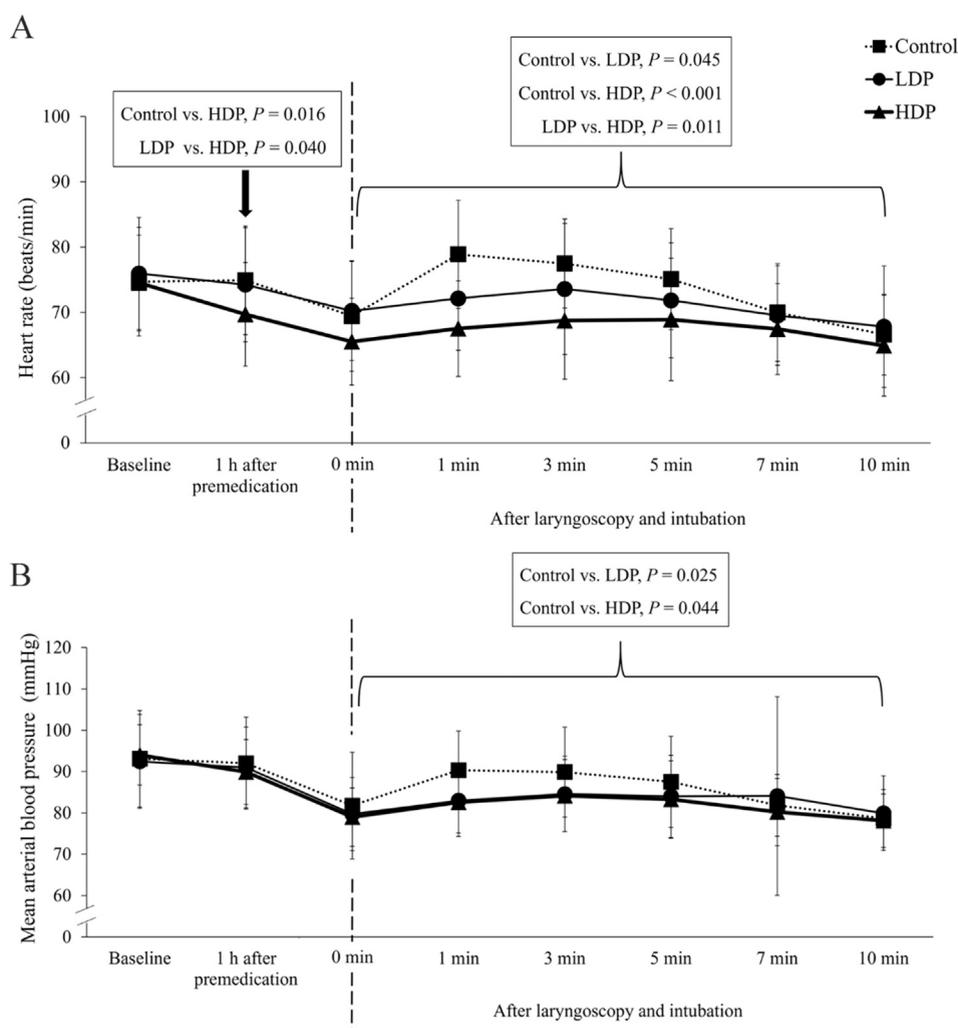


Figure 2. A Heart rate and B mean arterial pressure changes during anesthesia. Note: The statistical differences between the groups were assessed using Student's t test and a mixed linear model.

mainly in abdominal surgery. In our study, no significant difference was found between the opioid dosage and the VAS score 1 hour after surgery. The study by YaDeau et al.<sup>26</sup> also showed that pregabalin did not significantly improve perioperative pain in patients undergoing knee arthroplasty. Because the present study was aimed at determining the stress response of intubation, no corresponding follow-up study was conducted in patients with chronic pain.

In contrast, the degrees of sedation at 1 hour after premedication in the LDP and HDP groups were higher than in the control patients in all 3 surgery

categories with dose dependency in patients who underwent limb and spinal surgery. Therefore, based on the current 150-mg pregabalin dose, we further consider the use of 300 mg to provide enough sedation and to reduce fluctuations in heart rate and blood pressure when intubating with the aid of a laryngoscope.

The main adverse reactions of pregabalin therapy included allergy, dizziness, nausea, vomiting, and blurred vision. One hour after taking pregabalin, the LDP (13%) and HDP (20%) group patients all had the adverse event of dizziness. One hour after

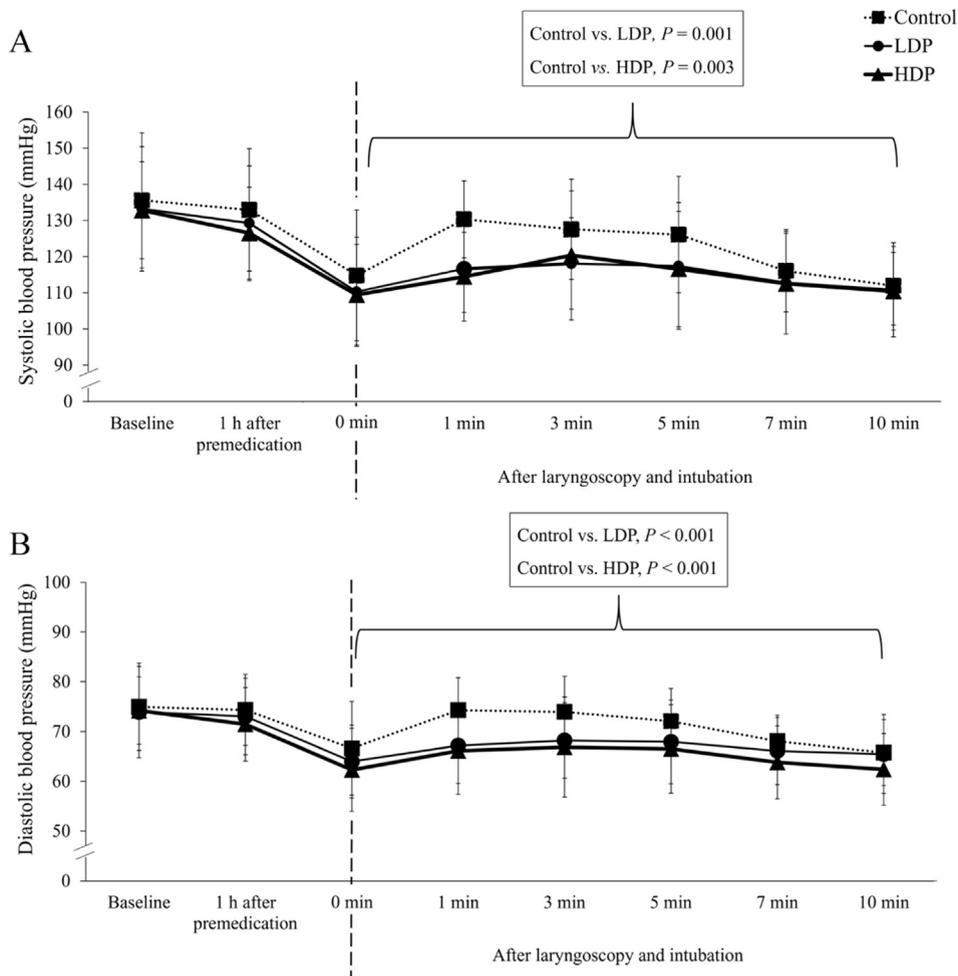


Figure 3. Changes of A systolic and B diastolic blood pressures during anesthesia. Statistical differences between the groups were assessed using a mixed linear model.

surgery, considering the interference of inhaled anesthetics and opioid drugs, dizziness, nausea, and vomiting were observed in all 3 groups. The prevalences of dizziness in the LDP group (30%) and HDP group (33%) were higher than in the placebo group (17%), a finding that may have been related to the dose of pregabalin administered.

In addition to pregabalin, many therapeutic drugs and methods have been recommended for the elimination or inhibition of cardiovascular responses induced by endotracheal intubation, including surface anesthesia, intravenous administration of lidocaine, inhalation of narcotic drugs, narcotic analgesics, drugs acting on adrenergic receptors ( $\beta$ -adrenoceptor

Table II. Hemodynamic complications in the 3 groups within 10 minutes of intubation. Data are given as number (%) of patients.

Complication	Control (n = 30)	LDP (n = 30)	HDP (n = 30)
Hypertension	9 (30.00)	4 (13.33)	0
Tachycardia	2 (6.67)	2 (6.67)	0
Hypotension	1 (3.33)	2 (6.67)	1 (3.33)
Bradycardia	1 (3.33)	0	0

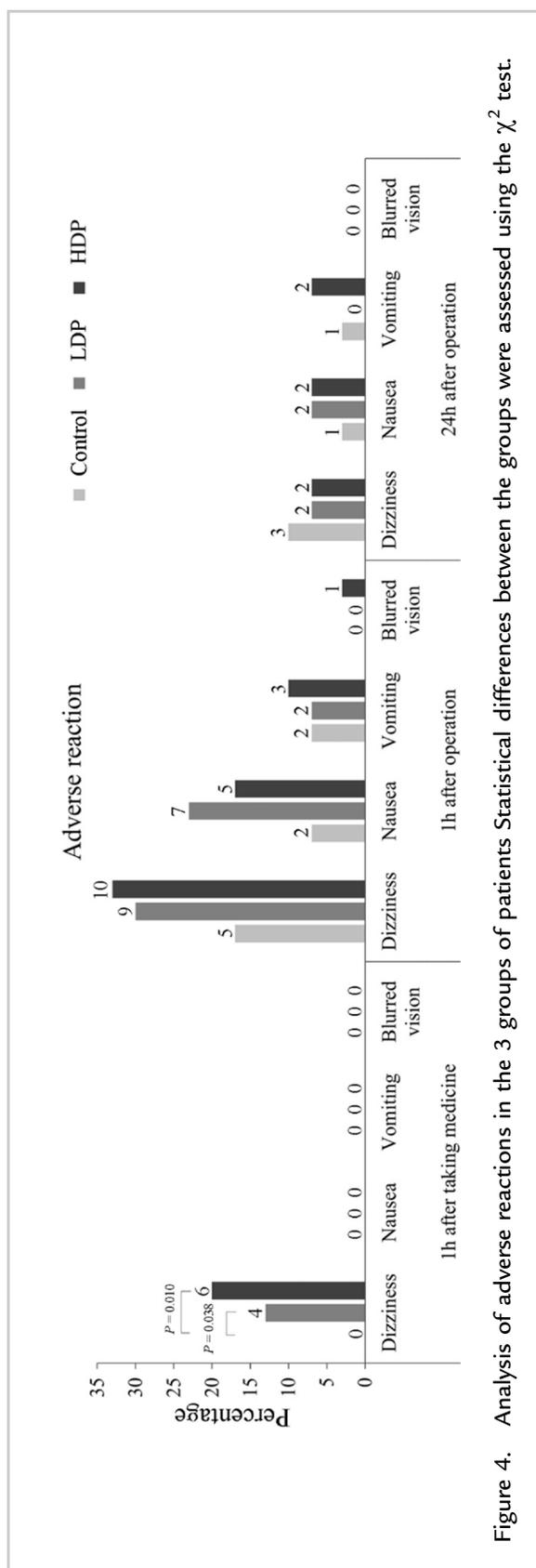


Figure 4. Analysis of adverse reactions in the 3 groups of patients. Statistical differences between the groups were assessed using the  $\chi^2$  test.

antagonists,  $\alpha_2$ -adrenoceptor agonists,  $\alpha_1$ -adrenoceptor antagonists), vasoactive drugs (nitroglycerin, calcium channel blockers, sodium nitroprusside), or a laryngeal mask. However, the reality is that none of these drugs or methods were treatments that were effective.

Pregabalin is a newly synthesized 3-isobutyl substituent of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid. It can bind to the  $\alpha_2\text{-}\delta$  subunit of the presynaptic membrane calcium channel, resulting in a decreased release of a number of neurotransmitters including glutamic acid, norepinephrine, 5-serotonin, dopamine, and substance P. It is a lipophilic analogue of  $\gamma$ -aminobutyric acid, replacing the 3' site of  $\gamma$ -aminobutyric acid, which makes it easier for it to diffuse through the blood brain barrier.<sup>3,15,16</sup> Studies in healthy volunteers found that pregabalin was absorbed quickly enough to peak within an hour.<sup>17–20</sup> The mean bioavailability was over 90% and was not dose dependent, so the patient's response can be predicted. Pregabalin has been proved effective for a variety of types of neuropathic pain, incisions, inflammatory damage, and formaldehyde-induced damage.<sup>14,37,38</sup> It can also be used to treat anxiety or to regulate sleep<sup>20</sup> but at present pregabalin is mainly used to treat postherpetic neuralgia.

In our study, we used high-dose pregabalin for the first time in Chinese patients to observe the cardiovascular responses during endotracheal intubation under general anesthesia. Although no advantage was found regarding the analgesic effect of pregabalin, and the prevalence of dizziness in the 300-mg pregabalin patient group was higher than that in the 150-mg group, 300-mg preoperative pregabalin could effectively reduce hemodynamic complications and reduce the heart rate within 10 minutes of intubation to a higher extent than the 150-mg dose.

## CONCLUSIONS

Both the 150- and 300-mg doses of pregabalin can effectively attenuate cardiovascular responses in patients undergoing endotracheal intubation under general anesthesia. The 300-mg pregabalin group had more stable heart rates and less hemodynamic complications, but this dose also enhanced the corresponding adverse event of dizziness. These advantages and disadvantages should be considered in the clinic before prescribing a 300-mg dose of pregabalin.

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W. Chen and H. Huang contributed equally to this work. W. Chen contributed conceptualization, funding acquisition, supervision, and writing, review, and editing of the manuscript. H. Huang conducted the formal analysis and contributed to the write of the manuscript. C. Yang contributed data curation. X. Hu contributed data curation. F. Bao contributed data curation. H. Jiang contributed supervision.

## CONFLICTS OF INTEREST

The author have indicated that they have no conflicts of interest with regard to the content of this article.

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